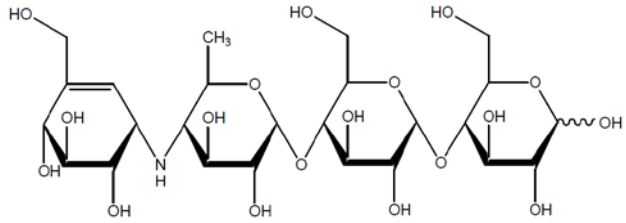
[Appendix 3]

Monographs, Part I
(Related to Article 2 Subparagraph 3)

Acarbose
아카르보스



$C_{25}H_{43}NO_{18}$: 645.60

(2*R*,3*R*,4*R*,5*S*,6*R*)-5-{[(2*R*,3*R*,4*R*,5*S*,6*R*)-5-{[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4-dihydroxy-6-methyl-5-{[(1S,4S,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-en-1-yl]amino}oxan-2-yl]oxy}-3,4-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy}-6-(hydroxy-methyl)oxane-2,3,4-triol [*56180-94-0*]

Acarbose is created by a number of strains of *Actinoplanes utahensis*.

Acarbose contains NLT 95.0% and NMT 102. 0% acarbose ($C_{25}H_{43}NO_{18}$), calculated on the anhydrous basis.

Description Acarbose occurs as a white or yellow non-crystalline powder.
It is hygroscopic.
It is very soluble in water, soluble in methanol and practically insoluble in dichloromethane.

Identification (1) Determine the infrared spectra of Acarbose and acarbose RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The major peak of the test solution under the Assay has the same retention time as the major peak of the standard solution.

Optical rotation $[\alpha]_D^{20}$: Between +168° and + 183° (0.1 g calculated on the anhydrous basis, 10 mL of water, 100 mm).

pH Dissolve Acarbose in water to make 50 mg/mL; the pH of the solution is between 5.5 and 7.5.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Acarbose according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).
(2) ***Related substances***—Weigh accurately 0.2 g of Acarbose, dissolve in water, add water to make 10 mL, and use this solution as the test solution. Pipet 1.0 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Pipet 10 μL each of the test solution and the standard solution and perform the test as directed under the Liquid Chromatography according to the following conditions. Measure the peak area *A*i of the peak area of each related substance from the test solution and the peak area *A*s of acarbose from the standard solution to determine the amount of related substances, related substance I{*O*-4,6-dideoxy-4-[[(1*S*,4R,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino]-α-D-glucopyranosil-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-arabino-hex-2-europyranose} is NMT 0.6%, related substance II {(1*R*,4*R*,5*S*,6*R*)-4,5,6-trihydroxy-2-(hydroxymethyll)cyclohex-2-enyl4-*O*-[4,6-dideoxy-4-[[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino]-α-D-glucopyranosil]-α-D-glucopyranoside} is NMT 0.5%, related substance III{α-D-glucopyranosil 4-*O*-[4,6-dideoxy-4-[[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino]-α-D-glucopyranosil]-α-D-glucopyranoside} is NMT 1.5%, related substance IV{4-*O*-[4,6-dideoxy-4-[[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino]-α-D-glucopyranosil]-D-glucopyranose} is NMT 1.0%, related substance V{*O*-4,6-dideoxy-4-[[(1*S*,4*R*,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino]-α-D-glucopyranosil-(1→4)-*O*-α-D-glucopyranosil-(1→4)-*O*-α-D-glucopyranosil-(1→4)-D-arabino-hex-2-europyranose (4-*O*-α-acarbosyl-D-frutcopyranose)} is NMT 0.2%, related substance VI{*O*-4,6-dideoxy-4-[[(1S,4R,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino]-α-D-glucopyranosil-(1→4)-*O*-α-D-glucopyranosil-(1→4)-*O*-α-D-glucopyranosil-(1→4)-D-glucopyranose (4-*O*-α-acarbosyl-D-glucopyranose)} is NMT 0.3%, related substance VII{α-D-glucopyranosil*O*-4,6-dideoxy-4-[[(1S,4R,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino]-α-D-glucopyranosil-(1→4)-*O*-α-D-glucopyranosil-(1→4)-*O*-α-D-glucopyranoside(α-D-glucopyranosil α-acarbosyde)} is NMT 0.3%, related substance VIII{*O*-4,6-dideoxy-4-[[(1S,4R,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enyl]amino]-α-D-glucopyranosil-(1→4)-*O*-6-deoxy-α-D-glucopyranosil-(1→4)-D-glucopyranose} is NMT 0.2%, other individual related substances are NMT 0.2%, and total amount of related substances is NMT 3.0%. The peak areas of related substances II, IV, V, VI and VII are calculated by dividing the area obtained by the automatic integration method by the correction factor, 1.6, 1.33, 0.8, 0.8 and 0.8, respectively.

$$\text{Content (\%) of each related substance} = \frac{A_i}{A_S}$$

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed under the operating conditions in the Assay.

System suitability

Relative retention time: The relative retention times of related substances I, II, III, IV, V, VI, VII and VIII are about 0.9, 0.8, 1.2, 0.5, 1.7, 1.9, 2.2 and 0.6, respectively.

Water NMT 4.0% (0.300 g, volumetric titration, direct titration).

Residue on ignition NMT 0.2% (1.0 g).

Assay Weigh accurately about 200 mg of acarbose, dissolve in water, and add water to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of acarbose RS, add 5 mL of water, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of acarbose in each solution.

$$\text{Amount (mg) of acarbose } (C_{25}H_{43}NO_{18}) = \frac{A_T}{A_S} \times C \times 10$$

C: Concentration (μg/mL) of acarbose in the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 25 cm in length, packed with aminopropylsilyl silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

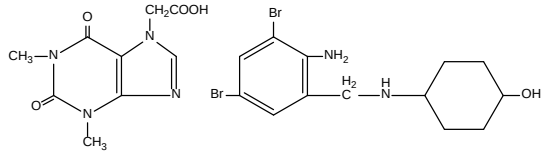
Mobile phase: A mixture of acetonitrile and phosphate buffer solution (750 : 250).

Flow rate: 1.0 mL/min

Phosphate buffer solution: Dissolve 0.6 g of potassium dihydrogen phosphate and 0.35 g of sodium monohydrogen phosphate in 900 mL of water, and then add water to make 1000 mL.

Packaging and storage Preserve in tight containers.

Acebrophylline
아세브로필린



$C_{22}H_{28}Br_2N_6O_5$: 616.30

1,2,3,6-Tetrahydro-1,3-dimethyl-2,6-dioxo-7*H*-purine-7-acetic acid with trans-4-[[(2-amino-3,5-dibromophenyl)methyl]amino]cyclohexanol, [*96989-76-3*]

Acebrophylline, when dried, contains NLT 98.0% and NMT 101.0% of acebrophylline ($C_{22}H_{28}Br_2N_6O_5$: 616.30), NLT 60.12% and NMT 62.57% of ambroxol ($C_{13}H_{18}Br_2N_4O_2$: 378.11) and NLT 37.87% and NMT 39.42% of theophylline-7-acetic acid ($C_9H_{10}N_4O_4$: 238.20).

Description Acebrophylline occurs as a white to pale white powder.
It is sparingly soluble in water and slightly soluble in ethanol(95).

Identification (1) Determine the infrared spectra of Acebrophylline and acebrophylline RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve 0.1 g of Acebrophylline in water to make 100 mL. Take 2 mL of this solution and add water to make 100 mL. Determine the absorption spectra of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima at the wavelengths of around 306 nm, 242 nm and 273 nm.

(3) Weigh 0.2 g each of Acebrophylline and acebrophylline RS, dissolve in 10 mL of a mixture of ethanol and water (1: 1), and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel 60 F_{254} for thin-layer chromatography (with a fluorescent indicator). Develop the plate with a mixture of ethyl acetate, methanol, acetic acid(100) and water (15 : 5 : 5 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots from the test solution and the standard solution are the same in R_f value.

(4) The retention time of major peak of the test solution and the standard solution for Assay is the same.

Melting point Between 216 and 220 ºC.

pH Between 5.0 and 6.0 (1% aqueous solution).

Purity (1) ***Free ambroxol***—Weight 1.0 g of Acebrophylline, transfer to a flask with a glass stopper, add 50 mL of toluene, and stir for 30 minutes. Add 30 mL of toluene, filter this solution after stirring for 30 minutes, and concentrate the filtrate at below 40 ˚C under reduced pressure. Dissolve the residue in 10 mL of ethanol(95) and use this solution as the test solution. Separately, weigh 50 mg of ambroxol RS, dissolve in ethanol(95) to make 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed

under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel 60 F_{254} with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol-acetic acid(100)-water (2 : 1 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Apply ultraviolet light (main wavelength: 254 nm) to the plate; the spots other than the principal spots obtained from the test solution are not larger or more intense than the spots from the standard solution (0.5%).

(2) ***cis ambroxol***—Weigh accurately about 0.5 g of Acebrophylline, dissolve in 100 mL of the mobile phase, and use this solution as the test solution. Separately, weigh accurately about 5 mg of *cis* ambroxol RS and add the mobile phase to make exactly 100 mL. Pipet 10 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the amount of related substances; the amount is NMT 0.1%.

$$\text{Content (\%) of cis ambroxol} = (A_T / A_S) \times (W_S / W_T) \times (1 / 10) \times 100$$

A_T: Peak area of *cis* ambroxol in the test solution

A_S: Peak area of *cis* ambroxol in the standard solution

10: Dilution factor

W_S: Amount (mg) of *cis* ambroxol RS taken

W_T: Amount (mg) of Acebrophylline taken

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 244 nm).

Column: A stainless steel column about 4 mm in internal diameter and 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 23 g of phosphoric acid in the 1000 mL of water and add 180 mL of acetonitrile to 820 mL of this solution.

Flow rate: 1.3 mL/min

Loss on drying NMT 1.0% (2 g, 105 ℃, constant mass).

Assay (1) ***Acebrophylline*—**Weigh accurately about 0.4 g of Acebrophylline, dissolve in 50 mL of water, and titrate with 0.1 mol/L potassium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L potassium hydroxide VS
= 61.63 mg of $C_{22}H_{28}Br_2N_6O_5$

(2) ***Ambroxol and theophylline-7-acetic acid*—**Weigh accurately about 0.1 g each of Acebrophylline and acebrophylline RS, dissolve in water to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with exactly 20 mL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_{T1}, A_{T2}, A_{S1} and A_{S2} of ambroxol and theophylline-7-acetic acid, respectively.

$$\text{Amount (mg) of ambroxol } (C_{13}H_{18}Br_2N_4O_2) = \text{Amount (mg) of acebrophylline RS} \times (A_{T1} / A_{S1}) \times (61.35 / 100)$$

$$\text{Amount (mg) of theophylline-7-acetic acid } (C_9H_{10}N_4O_4) = \text{Amount (mg) of acebrophylline RS} \times (A_{T2} / A_{S2}) \times (38.65 / 100)$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 244 nm).

Column: A stainless steel column about 4 mm in internal diameter and 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 1 g of ammonium tetraborate in 1000 mL of water and add 570 mL of acetonitrile to 430 mL of this solution.

Flow rate: 1.2 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution under the above operating conditions; theophylline-7-acetic acid and ambroxol are eluted in this order.

Packaging and storage Preserve in tight containers.

Acebrophylline Capsules
아세브로필린 캡슐

Acebrophylline Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of acebrophylline ($C_{22}H_{28}Br_2N_6O_5$: 616.30).

Method of preparation Prepare as directed under Capsules, with Acebrophylline.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the content of NLT 20 Acebrophylline Capsules. Weigh accurately the

amount equivalent to about 0.1 g of acebrophylline ($C_{22}H_{28}Br_2N_6O_5$: 616.30) and add 50% ethanol to make exactly 100 mL. Use this solution as the test solution. Separately, weigh accurately about 0.1 g of acebrophylline RS, add 50% ethanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of ambroxol in each solution.

Amount (mg) of acebrophylline ($C_{22}H_{28}Br_2N_6O_5$)
= Amount (mg) of acebrophylline RS × (A_T / A_S) × (61.35 / 100) × 1.63

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 244 nm).

Column: A stainless steel column about 4 mm in internal diameter and 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 1 g of ammonium carbonate in 1000 mL of water, and add 570 mL of acetonitrile to 430 mL of this solution.

Flow rate: 1.0 mL/min

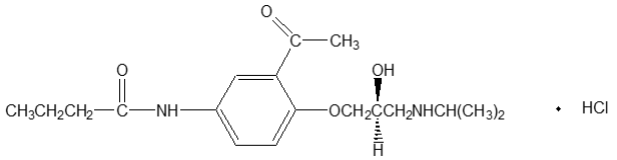
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; theophylline-7-acetic acid and ambroxol are eluted in this order with the resolution between these peaks being NLT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above conditions; the relative standard deviation of the peak areas of theophylline-7-acetic acid and ambroxol are NMT 2.0%.

Packaging and storage Preserve in tight containers.

Acebutolol Hydrochloride
아세부톨롤염산염



and enantiomer

$C_{18}H_{28}N_2O_4 \cdot HCl$: 372.89

N-[3-Acetyl-4-[2-hydroxy-3-(propan-2-yl-amino)propoxy]phenyl]butanamide monohydrochloride [*34381-68-5*]

Acebutolol Hydrochloride, when dried, contains NLT 98.0% and NMT 102.0% of acebutolol hydrochloride ($C_{18}H_{28}N_2O_4 \cdot HCl$).

Description Acebutolol Hydrochloride occurs as white to pale yellowish white crystals or a crystalline powder.
It is freely soluble in water, methanol, ethanol(95) or acetic acid(100) and practically insoluble in ether.
An aqueous solution of Acebutolol Hydrochloride (1 in 20) shows no optical rotation.

Identification (1) Determine the absorption spectra of solutions of Acebutolol Hydrochloride and acebutolol hydrochloride RS in 0.01 mol/L hydrochloric acid TS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectrum of Acebutolol Hydrochloride and acebutolol hydrochloride RS as directed in the potassium bromide disk method under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Acebutolol Hydrochloride (1 in 100) responds to the Qualitative Analysis for chloride.

Melting point Between 141 and 145 ºC.

Purity (1) ***Heavy metals*—**Proceed with 1.0 g of Acetylspiramycin according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic*—**Prepare the test solution with 1.0 g of Acebutolol Hydrochloride according to Method 3 and perform the test (NMT 2 ppm).

(3) ***Related substances*—**Dissolve 40 mg of Acebutolol Hydrochloride in 2 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution and add methanol to make exactly 25 mL. Pipet 1 mL of this solution, add methanol to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of water, 1-butanol and acetic acid(100) (5 : 4 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Observe the plate under ultraviolet light (main wavelength: 365 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 1.0% (0.5 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.2% (1 g).

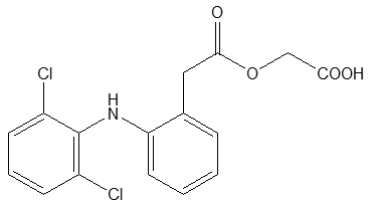
Assay Weigh accurately about 0.25 g of Acebutolol Hydrochloride, previously dried, dissolve in 20 mL of acetic acid(100), add 80 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration

under Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 37.289 mg of $C_{18}H_{28}N_2O_4 \cdot HCl$

Packaging and storage Preserve in tight containers.

Aceclofenac
아세클로페낙



$C_{16}H_{13}Cl_2NO_4$: 354.19
2-{2-[2-(2,6-Dichloroanilino)phenyl]acetyl} oxyacetic acid [*89796-99-6*]

Aceclofenac, when dried, contains NLT 99.0% and NMT 101.0% of aceclofenac ($C_{16}H_{13}Cl_2NO_4$).

Description Aceclofenac occurs as a white crystalline powder.
It is freely soluble in of ammonium peroxydisulfate or acetone, soluble in methanol or ethanol(95), and practically insoluble in water.

Identification (1) Dissolve 10 mg of Aceclofenac in 10 mL of ethanol(95), and add 0.2 mL of a mixture of freshly prepared potassium ferricyanide solution (6 in 1000) and iron(III) chloride solution (9 in 1000) (1 : 1) to 1 mL of this solution. Allow to stand in the dark for five minutes, add 3 mL of the hydrochloric acid solution (10 in 1000), allow to stand in the dark again for 15 minutes; the solution exhibits a blue color and a precipitate is produced.

(2) Dissolve 50 mg of Aceclofenac in 100 mL of methanol, and to 2 mL of this solution, add methanol to make 50 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy at the wavelength of 220 nm - 230 nm); it exhibits a maximum absorption at the wavelength of 275 nm. The specific absorbance at this absorption maximum wavelength is between 320 nm and 350 nm.

(3) Determine the infrared spectra of Aceclofenac and aceclofenac RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Aceclofenac according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Weigh accurately 0.1 g of Aceclofenac, dissolve in 50 mL of the mobile phase, and use this solution as the test solution. Dissolve an amount of diclofenac sodium RS, equivalent to 5 ml of diclofenac, in 50 mL of the mobile phase, and use this solution as the standard solution (1). To 2 mL of the standard solution (1), add the mobile phase to make exactly 50 mL, and use this solution as the standard solution (2). To 5 mL of the standard solution (1), add 0.25 mL of the test solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution (3). Perform the test with 10 μL each of the test solution and the standard solution (2) as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of these solutions; any peak area other than the major peak from the test solution is not greater than the major peak area from the standard solution (2) (0.2%). The sum of all peak areas other than the major peak from the test solution is not greater than 2.5 times the major peak area from the standard solution (2) (0.5%). When determining the peak areas from the test solution, disregard any peak areas NMT 0.2 times the major peak area from the standard solution (2).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 275 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with butylsilyl silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Add sodium hydroxide TS to the a mixture of acetic acid(100) (12 in 10000), acetonitrile and tetrahydrofuran (550 : 225 : 225) and adjust the pH to 3.5.

Flow rate: 1 mL/min

System suitability

Detection sensitivity: Adjust the detection sensitivity so that the peak heights of aceclofenac and diclofenac obtained from the standard solution (3) are about 50% of the full scale.

System performance: Proceed with 10 μL each of the standard solution (3) under the above operating conditions; aceclofenac and diclofenac are eluted in this order with the resolution between these peaks being NLT 8.0.

Time span of measurement: About 10 times the retention time of aceclofenac.

Loss on drying NMT 0.5% (1.0 g, between 100 and 105 °C, constant mass).

Residue on ignition NMT 0.1% (1.0 g).

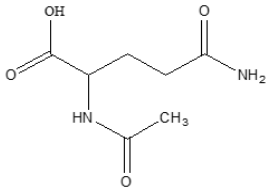
Assay Weigh accurately about 0.3 g of Aceclofenac, previously dried, dissolve in 40 mL of methanol, and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test

in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 35.419 mg of $C_{16}H_{13}Cl_2NO_4$

Packaging and storage Preserve in light-resistant, well-closed containers.

Aceglutamide
아세글루타미드



$C_7H_{12}N_2O_4$: 188.18

N-Acetyl-L-glutamine, [*2490-97-3*]

Aceglutamide, when dried, contains NLT 98.0% and NMT 101.0% of aceglutamide ($C_7H_{12}N_2O_4$).

Description Aceglutamide occurs as a white crystalline powder.
It is odorless.

Melting point About 199 °C.

Identification (1) Add 5 mL of 1 mol/L sodium hydroxide to 0.1 g of Aceglutamide, and heat the mixture; it gives an ammonia odor and changes a wet red litmus paper to blue.

(2) Determine the infrared spectra of Aceglutamide and aceglutamide RS, previously dried for 24 hours in a desiccator with phosphorus pentoxide in vacuum, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -11° and -13° (2% aqueous solution).

Purity (1) ***Free amino acids***—Weigh accurately 20 mg of Aceglutamide, dissolve in 5 mL of water, and transfer this solution to a test tube. To the test tube, add 0.5 mL of 1.0% ninhydrin TS and mix, and let it stand for exactly 5 minutes on a steam bath. Observe the solution; it does not exhibit a blue color.

(2) ***Chloride***—Weigh 1 g of Aceglutamide, dissolve in water to make 40 mL, and perform the test as directed under the Chloride. Prepare the control solution with 0.1 mL of 0.02 mol/L hydrochloric acid VS (NMT 0.007%).

(3) ***Sulfate***—Weigh 2.5 g of Aceglutamide, dissolve in water to make 40.0 mL, and perform the test as directed under the Sulfate. Prepare the control solution with 0.15 mL of 0.01 mol/L sulfuric acid VS (NMT 0.006%).

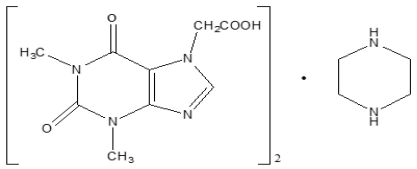
Loss on drying NMT 1.0% (1.0 g, 105 °C, 2 hours).

Assay Weigh accurately about 0.25 g of Aceglutamide, previously dried, dissolve in 50 mL of water, add 0.5 mL of 1% phenolphthalein ethanol TS as an indicator, and titrate with 0.1 mol/L sodium hydroxide VS. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 18.82 mg of $C_7H_{12}N_2O_4$

Packaging and storage Preserve in tight containers.

Acepifylline
아세피필린



$C_{22}H_{30}N_{10}O_8$: 562.54

1,2,3,6-Tetrahydro-1,3-dimethyl-2,6-dioxo-7*H*-purine-7-acetic acid piperazine, [*18833-13-1*]

Acepifylline, when dried, contains NLT 75.0% and NMT 78.0% of acepifylline ($C_9H_{10}N_4O_4$: 238.20) and NLT 22.0% and NMT 25.0% of anhydrous piperazine ($C_4H_{10}N_2$: 86.14).

Description Acepifylline occurs as a white powder. It is odorless, and has a bitter taste.
It is freely soluble in water and sparingly soluble in ethanol(95).
The pH of an aqueous solution of Acepifylline (1 in 10) is between 6.5 and 7.0.

Identification (1) Dissolve 0.25 g of Acepifylline in 25 mL of water, take 10 mL of this solution, and add 30 mL of saturated solution of picric acid; a yellow precipitate develops (piperazine).

(2) Dissolve 0.25 g of Acepifylline in 25 mL of water, take 10 mL of this solution, add 10 mL of diluted citric acid (3 in 100) and 10 mL of ammonium reineckate TS, and cool with ice; a red fine precipitate develops.

(3) Weigh 10 mg of Acepifylline, dissolve in 2 mL of 2 mol/L acetic acid, and use this solution as the test solution. Weigh about 20 mg of acepifylline RS, dissolve in 2 mL of 2 mol/L acetic acid, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a

mixture of methanol and ammonia water (20 : 3) as the developing solvent, and air-dry the plate. Spray evenly hexachloroplatinate-potassium iodide TS on the plate; the R_f value and the color of the spots obtained from the test solution and the standard solution are the same.

(4) Weigh 25 mg of Acepifylline, dissolve by adding 10 mL of 0.1 mol/L hydrochloric acid, add water to make 100 mL, and determine the absorption spectrum of the solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelength between 271 nm and 275 nm.

Purity (1) ***Clarity and color of solution*** —To 5 mL of the aqueous solution of Acepifylline (1 in 10), add 1 mL of strong ammonia water, put 1 mL of silver nitrate TS, and shake to mix; no gelatinous mass is formed.

(2) ***Heavy metals*** —Proceed with 1.0 g of Acepifylline according to Method 3 under the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic*** —Proceed with 0.2 g of Acepifylline according to Method 3 under the Arsenic and perform the test (NMT 10 ppm).

Loss on drying NMT 2.5% (1 g, 105 °C, 3 hours).

Residue on ignition NMT 0.15% (1 g).

Assay (1) ***Acepifylline***—Weigh accurately about 0.25 g of Acepifylline, previously dried, dissolve by adding 1 mL of water, and add 20 mL of ethanol(99.5) (neutralized with 0.1 mol/L potassium hydroxide-ethanol VS). Add 2 to 3 drops of thymolphthalein TS to this solution, and titrate with 0.1 mol/L potassium hydroxide-ethanol VS until the color of the solution changes to blue. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L potassium hydroxide-ethanol VS
= 23.82 mg of $C_9H_{10}N_4O_4$

(2) ***Piperazine***—Weigh accurately about 0.15 g of Acepifylline, previously dried, dissolve by adding 30 mL of acetic acid(100) for nonaqueous titration, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 4.307 mg of $C_4H_{10}N_2$

Packaging and storage Preserve in tight containers.

Acepifylline Tablets
아세피필린 정

Acepifylline Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of acepifylline ($C_{22}H_{30}N_{10}O_8$: 562.54).

Method of preparation Prepare Acepifylline Tablets as directed under Tablets, with Acepifylline.

Identification (1) ***Acepifylline—***Weigh an amount of Acepifylline Tablets, equivalent to about 20 mg of acepifylline according to the labeled amount. Add 10 mL of water and 2 mL of dilute hydrochloric acid, shake occasionally to mix in iced water, add 5 mL of bromine TS, and evaporate to dryness on a steam bath; a yellow precipitate is formed. Expose the precipitate to ammonia vapor; it turns violet.

(2) ***Piperazine—***Weigh an amount of Acepifylline Tablets, equivalent to about 20 mg of acepifylline, according to the labeled amount, add water to make 50 mL, and use this solution as the test solution.

(i) Take 10 mL of the test solution, and add 30 mL of saturated solution of picric acid; a yellow precipitate is formed.

(ii) Take 10 mL of the test solution, add 5 mL of diluted citric acid solution (3 in 100) and 5 mL of ammonium reineckate TS, and cool in iced water; a fine red precipitate is formed.

Dissolution Perform the test with 1 tablet of Acepifylline Tablets at 50 revolutions per minute according to Method 2, using 900 mL of water as the dissolution medium. Take the dissolved solution 30 minutes after starting the Dissolution, and filter. Pipet 5 mL of this solution, add water to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately about 70 mg of acepifylline RS, and dissolve in water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Take exactly 10 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of acepifylline of each solution. Meets the requirements if the dissolution rate of Acepifylline Tablets in 30 minutes is NLT 85%.

Dissolution rate (%) with respect to the labeled amount of acepifylline ($C_{22}H_{30}N_{10}O_8$)
$= W_S \times (A_T / A_S) \times (1 / C) \times 360$

W_S: Amount (mg) of acepifylline RS
C: Labeled amount (mg) of acepifylline ($C_{22}H_{30}N_{10}O_8$) per tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 273 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of acetate buffer solution (pH 3.5) and acetonitrile (9 : 1).

Flow rate: 0.8 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of acepifylline is NMT 2.0%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Acepifylline Tablets, and powder them. Weigh accurately an amount equivalent to about 5 mg of acepifylline ($C_{22}H_{30}N_{10}O_8$), dissolve in water to make exactly 100 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 50 mg of acepifylline RS, dissolve in water, and make exactly 100 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Pipet 10 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography, and determine the peak areas, A_T and A_S, of the test solution and the standard solution.

Amount (mg) of acepifylline ($C_{22}H_{30}N_{10}O_8$)
= Amount (mg) of acepifylline RS × (A_T / A_S) × (1 / 10)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 273 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetate buffer solution (pH 3.5) and acetonitrile (9 : 1).

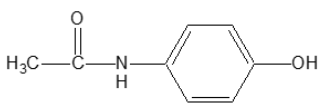
Flow rate: 0.8 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above conditions, the relative standard deviation of the peak areas of acepifylline is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Acetaminophen
아세트아미노펜



Paracetamol $C_8H_9NO_2$: 151.16

N-(4-Hydroxyphenyl)acetamide [*103-90-2*]

Acetaminophen contains NLT 98.0% and NMT 101.0% of acetaminophen ($C_8H_9NO_2$), calculated on the dried basis.

Description Acetaminophen occurs as white crystals or a crystalline powder.
It is freely soluble in methanol or ethanol(95), sparingly soluble in water and very slightly soluble in ether.
It dissolves in sodium hydroxide TS.

Identification Determine the infrared spectra of Acetaminophen and acetaminophen RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit the same intensities of absorption at the same wavenumbers.

Melting point Between 169 and 172 ℃.

Purity (1) ***Chloride***—Dissolve 4.0 g of Acetaminophen in 100 mL of water by heating, cool in iced water by shaking to mix, and allow to stand until it reaches ordinary temperature. Add water to make 100 mL and filter. To 25 mL of the filtrate, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid (NMT 0.014%).

(2) ***Sulfate***—To 25 mL of the filtrate obtained in (1), add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid (NMT 0.019%).

(3) ***Heavy metals***—Proceed with 2.0 g of Acetaminophen according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Proceed with 1.0 g of Acetaminophen according to Method 3 and perform the test (NMT 2 ppm).

(5) ***Related substances***—Dissolve 50 mg of Acetaminophen in 1 mL of methanol, add the mobile phase to make 50 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the total area of peaks other than acetaminophen from the test solution is not greater than the peak area of acetaminophen from the standard solution.

(6) ***4-Aminophenol***—Weigh accurately about 2.5 g of Acetaminophen, dissolve in methanol to make exactly 100 mL and use this solution as the test solution. Separately, weigh accurately about 5.0 mg of 4-aminophenol RS and add methanol to make exactly 100 mL. Take exactly 5 mL of this solution, add methanol to make exactly 200 mL, and use this solution as the standard solution.

Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions; the amount of 4-aminophenol with the relative retention time to acetaminophen of 0.6 is NMT 0.005%.

$$\text{Content (\%) of 4-aminophenol} = (A_T/A_S) \times (C_S/C_T) \times 100$$

A_T: Peak area of 4-aminophenol in the test solution

A_S: Peak area of 4-aminophenol in the standard solution

C_S: Concentration (mg/mL) of 4-aminophenol in the standard solution

C_T: Concentration (mg/mL) of acetaminophen in the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 10 cm in length, packed with octylsilyl silica gel for liquid chromatography (about 3.5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: Control the gradient elution or stepwise by mixing the mobile phase A, B as directed under the following table.

Mobile phase A: Dissolve 1.7 g of potassium dihydrogen phosphate and 1.8 g of anhydrous sodium monohydrogen phosphate in water to make exactly 1000 mL.

Mobile phase B: Methanol

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0.0 → 3.0	99	1
3.0 → 7.0	99 → 19	1 → 81
7.0 → 7.1	19 → 99	81 → 1
7.1 → 10.0	99	1

Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times according to the above conditions with 5 μL each of the standard solution; the relative standard deviation of the peak area is NMT 5.0%.

Loss on drying NMT 0.3% (0.5 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 20 mg each of Acetaminophen and acetaminophen RS, previously dried, dissolve in 2 mL of methanol, add water to make exactly 100 mL. Pipet 3 mL of these solutions, add water to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, using water as the blank, at the wavelength of 244 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of acetaminophen } (C_8H_9NO_2) = \text{Amount (mg) of acetaminophen RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in light-resistant, tight containers.

Acetaminophen Tablets
아세트아미노펜 정

Paracetamol Tablets

Acetaminophen Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of acetaminophen ($C_8H_9NO_2$: 151.17).

Method of preparation Prepare as directed under Tablets, with Acetaminophen.

Identification (1) The retention times of the major peaks from the test solution and the standard solution obtained under the Assay are the same.

(2) Weigh an amount of Acetaminophen Tablets, previously powdered, equivalent to 50 mg of acetaminophen according to the labeled amount, add 50 mL of methanol, shake to mix, and filter. Use the filtrate as the test solution. Separately, weigh 5 mg of acetaminophen RS, add methanol to make 5 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of methylene chloride and methanol (4 : 1) to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the principal spot of the test solution exhibits an R_f value corresponding to that of the standard solution.

Purity ***Related substances***—Weigh accurately the mass of NLT 10 tablets of Acetaminophen Tablets and powder. Dissolve an amount of acetaminophen ($C_8H_9NO_2$) equivalent to about 350 mg in diluent to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 21.0 mg each of acetaminophen RS and 4-aminophenol RS and dissolve in diluent to make exactly 100 mL, respectively. Pipet 5 mL each of these solutions exactly, combine into a 200-mL volumetric flask, add diluent to make exactly 200 mL, and use this solution as the standard solution. Perform the test

with 25 mL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, measure the peak areas of each solution by automatic integration method; the amount of 4-aminophenol and each related substance is NMT 0.15%, and the amount of all related substances other than acetaminophen is NMT 0.60%.

$$\text{Content (\%) of 4-aminophenol} = (A_T/A_S) \times (C_S/C_T) \times 100$$

A_T: Peak area of 4-aminophenol obtained from the test solution

A_S: Peak area of 4-aminophenol obtained from the standard solution

C_S: Concentration (mg/mL) of 4-aminophenol obtained from the standard solution

C_T: Concentration (mg/mL) of acetaminophen obtained from the test solution

$$\text{Amount of related substances (\%)} = (A_T/A_S) \times (C_S/C_T) \times 100$$

A_T: Peak area of each related substance obtained from the test solution

A_S: Peak area of acetaminophen obtained from the standard solution

C_S: Concentration (mg/mL) of acetaminophen in the standard solution

C_T: Concentration (mg/mL) of acetaminophen in the test solution

Diluent—A mixture of buffer solution and methanol (95 : 5).

Buffer solution—Weigh accurately 1.9 g of ammonium formate, dissolve in water to make 1000 mL, and add 1 mL of formic acid.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 272 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 3 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Control the gradient elution or stepwise by mixing the mobile phase A, B and C as directed under the following table.

Mobile phase A: Dissolve 3.1 g of ammonium acetate in water to make 1000 mL and add 1 mL of trifluoroacetic acid.

Mobile phase B: A mixture of acetonitrile, methanol and water (10 : 75 : 15).

Mobile phase C: Dissolve 3.1 g of ammonium acetate in mobile phase B to make 1000 mL and add 1 mL of trifluoroacetic acid.

Time (min)	Mobile phase A (%)	Mobile phase C (%)
0.0 → 5.0	97 → 70	3 → 30
5.0 → 10.0	70 → 10	30 → 90
10.0 → 11.0	10	90

Flow rate: 0.9 mL/min

System suitability

Test for required detectability: Weigh accurately about 7.0 mg of 4-aminophenol RS and dissolve in diluent to make exactly 100 mL. Pipet 1 mL of this solution exactly, add diluent to make exactly 20 mL, pipet 1 mL of this solution again, and add diluent to make exactly 20 mL. Perform the test with 25 μL each of this solution; the signal-to-noise ratio of 4-aminophenol is NLT 10.

System repeatability: Repeat the test 6 times with 25 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of acetaminophen and 4-aminophenol is NMT 5.0%.

Dissolution Perform the test with 1 tablet of Acetaminophen Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of phosphate buffer solution, pH 5.8, as the dissolution medium. Take the dissolved solution 30 minutes after starting the test, filter, dilute the filtrate with the dissolution medium if necessary, and use this solution as the test solution. Separately, weigh accurately a suitable amount of acetaminophen RS, previously dried in a desiccator (silica gel) for 18 hours, and dissolve in the dissolution medium to the same concentration as the test solution. Use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance at the absorbance maximum wavelength of about 243 nm.

Meets the requirements if the dissolution rate of Acetaminophen Tablet in 30 minutes is NLT 80%.

Phosphate buffer solution, pH 5.8—To 50 mL of 0.2 mol/L potassium dihydrogen phosphate TS, add 3.6 mL of 0.2 mol/L sodium hydroxide TS and water to make 200 mL.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately and powder NLT 20 tablets of Acetaminophen Tablets. Weigh accurately an amount of the powder, equivalent to about 0.1 g of acetaminophen ($C_8H_9NO_2$), add 100 mL of the mobile phase, shake to mix for 10 minutes, then shake vigorously for 5 minutes, and add the mobile phase to make exactly 200 mL. Pipet 5 mL of this solution, add the mobile phase to make 250 mL, and filter through a membrane filter with a pore size not exceeding 0.5 μm. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution.

Separately, weigh accurately about 20 mg of acetaminophen RS, previously dried at 105 ºC for 2 hours, and dissolve in the mobile phase to make exactly 100 mL. Pipet 5 mL of the solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with each 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak areas, A_T and A_S, of acetaminophen from the solutions.

$$\text{Amount (mg) of acetaminophen } (C_8H_9NO_2) = \text{Amount (mg) of acetaminophen RS} \times \frac{A_T}{A_S} \times 5$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 243 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 5 to 10 μm in particle diameter).

Mobile phase: A mixture of water and methanol (3 : 1).

Flow rate: 1.5 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; the symmetry factor is NMT 2.0.

System repeatability: Repeat the test 6 times according to the above conditions with 10 μL each of the standard solution; the relative standard deviation of the peak area is NMT 2.0%

Packaging and storage Preserve in tight containers.

Acetaminophen and DL-Methionine Tablets
아세트아미노펜·DL-메티오닌 정

Acetaminophen and DL-Methionine Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of acetaminophen ($C_8H_9NO_2$: 151.16) and NLT 90.0% and NMT 130.0% of the labeled amount of DL-methionine ($C_5H_{11}NO_2S$: 149.21).

Method of preparation Prepare as directed under Tablets, with Acetaminophen and DL-Methionine

Identification The retention times of major peaks from the test solution and standard solution prepared as directed under the Assay are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Acetaminophen*—**Weigh accurately NLT 20 tablets of Acetaminophen and DL-Methionine Tablets and powder. Weigh accurately an amount of the powder, equivalent to about 30 mg of acetaminophen ($C_8H_9NO_2$), dissolve in ethanol(95) to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately 0.15 g of acetaminophen RS, dissolve in ethanol(95) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with each 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak areas, A_T and A_S, of acetaminophen from the test solution and the standard solution.

$$\text{Amount (mg) of acetaminophen } (C_8H_9NO_2) = \text{Amount (mg) of acetaminophen RS} \times (A_T / A_S) \times (1 / 5)$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 275 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Mobile phase: A mixture of 0.0025 mol/L sodium octanesulfonate and methanol (17 : 3).

Flow rate: 1.0 mL/min

System suitability

System repeatability: Perform the test 6 times with each 10 μL of the standard solution according to the above operating conditions; the relative standard deviation of the acetaminophen peak area is NMT 2.0%.

(2) ***DL-Methionine*—**Weigh accurately 20 tablets of Acetaminophen and DL-Methionine Tablets, power, and perform the test as directed under the Identification and Assay for Amino Acids.

Packaging and storage Preserve in light-resistant, tight containers.

Acetaminophen, Pseudoephedrine Hydrochloride and Chlorpheniramine Maleate Tablets
아세트아미노펜·슈도에페드린염산염·클로르페니라민말레산염 정

Acetaminophen, Pseudoephedrine Hydrochloride and Chlorpheniramine Maleate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of acetaminophen ($C_8H_9NO_2$: 151.16), pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$: 201.69) and chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$: 390.86).

Method of preparation Prepare as directed under Tablets, with Acetaminophen, Pseudoephedrine Hydrochlo-

ride and Chlorpheniramine Maleate.

Identification The retention times of major peaks obtained from the test solution and the standard solution prepared as directed under the Assay are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Acetaminophen, Pseudoephedrine Hydrochloride and Chlorpheniramine Maleate Tablets, and powder. Weigh accurately an amount of Acetaminophen, Pseudoephedrine Hydrochloride and Chlorpheniramine Maleate Tablets, equivalent to about 500 mg of acetaminophen ($C_8H_9NO_2$) [about 30 mg of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$), about 2 mg of chlorpheniramine maleate ($C_{16}H_{19}Cl\ N_2 \cdot C_4H_4O_4$)], add water to make exactly 100 mL, sonicate for 5 minutes, and filter through a membrane filter with a pore size of 0.45 μm. Discard the first 10 mL of the filtrate, take exactly 10 mL of the subsequent filtrate, add water to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of acetaminophen RS, transfer to a 100-mL volumetric flask, add about 30 mg of pseudoephedrine hydrochloride RS to the flask, and add water to make exactly 100 mL. Pipet 10 mL of the solution, add about 20 mg of chlorpheniramine maleate RS, and add water to make exactly 100 mL. Pipet 1 mL of the solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with each 20 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_{T1}, A_{T2}, A_{T3}, A_{S1}, A_{S2} and A_{S3}, of each solution.

Amount (mg) of acetaminophen ($C_8H_9NO_2$)
= Amount (mg) of acetaminophen RS
$$\times \frac{A_{T1}}{A_{S1}} \times 10$$

Amount (mg) of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$)
= Amount (mg) of pseudoephedrine hydrochloride RS
$$\times \frac{A_{T2}}{A_{S2}}$$

Amount (mg) of chlorpheniramine maleate RS ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$)
= Amount (mg) of chlorpheniramine maleate RS
$$\times \frac{A_{T3}}{A_{S3}} \times \frac{1}{10}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: Mix 900 mL of 0.1% trifluoroacetic acid and 100 mL of 0.1% trifluoroacetic acid in methanol.

Mobile phase B: Mix 100 mL of 0.1% trifluoroacetic acid and 900 mL of 0.1% trifluoroacetic acid in methanol.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0.0 - 3.0	95	5
3.0 - 15.0	95 → 30	5 → 70
15.0 - 16.0	30 → 0	70 → 100
16.0 - 16.1	0 → 95	100 → 5
16.1 - 26.0	95	5

Flow rate: 1.0 mL/min

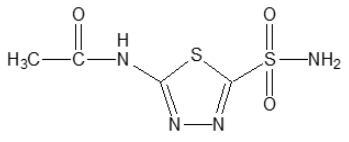
System suitability

System performance: Perform the test with 20 μL of the standard solution according to the above operating conditions; acetaminophen, pseudoephedrine hydrochloride and chlorpheniramine maleate are eluted in this order with the resolution between the peaks of acetaminophen and pseudoephedrine hydrochloride being NLT 4.3.

System repeatability: Perform the test 6 times with each 20 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of acetaminophen, pseudoephedrine hydrochloride and chlorpheniramine maleate is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Acetazolamide
아세타졸아미드



$C_4H_6N_4O_3S_2$: 222.25

5-Acetamido-1,3,4-thiadiazole-2-sulfonamide [*59-66-5*]

Acetazolamide contains NLT 98.0% and NMT 102.0% of acetazolamide ($C_4H_6N_4O_2S_2$), calculated on the dried basis.

Description Acetazolamide occurs as a white to pale yellowish white crystalline powder, is odorless and has a slightly bitter taste.
It is slightly soluble in ethanol(95), very slightly soluble in water, and practically insoluble in ether.

Melting point—About 255 °C (with decomposition).

Identification (1) Dissolve 0.1 g of Acetazolamide in 5 mL of sodium hydroxide TS, and add 5 mL of a solution prepared by dissolving 0.1 g of hydroxylamine hydrochloride and 50 mg of copper(II) sulfate pentahydrate in 10 mL of water; the resulting solution exhibits a pale yellow color and this color slowly darkens when heated for another 5 minutes.

(2) Add 2 mL of dilute hydrochloric acid to 20 mg of Acetazolamide, boil for 10 minutes, cool, and add 8 mL of water; the resulting solution responds to the Qualitative Analysis for primary aromatic amines.

(3) To 0.2 g of Acetazolamide, add 0.5 g of granular zinc and 5 mL of diluted hydrochloric acid (1 in 2); the gas produced changes the color of moistened lead acetate paper into black.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Acetazolamide in 10 mL of sodium hydroxide TS; the solution is clear, and is colorless to pale yellow.

(2) ***Chloride***—Dissolve 1.5 g of Acetazolamide in 75 mL of water and warm at 70 ℃ for 20 minutes with occasional shaking. After cooling, filter the solution, and add 6 mL of dilute nitric acid and water to 25 mL of to the filtrate to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.20 mL of 0.01 mol/L hydrochloric acid (NMT 0.014%).

(3) ***Sulfate—***Take 25 mL of the filtrate obtained from (2), add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid (NMT 0.038%).

(4) ***Heavy metals—***Proceed with 1.0 g of Acetazolamide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(5) ***Silver reducing substances—***Wet Acetazolamide with 5 mL of aldehyde-free ethanol, add 125 mL of water and 10 mL of nitric acid, and add again exactly 5 mL of 0.1 mol/L silver nitrate solution. Stir to mix for 30 minutes, protected against light, filter through a glass filter (G 3), wash the residue on the filter with 10 mL of water twice, and combine the washings with the filtrate. Add 5 mL of ammonium iron(III) sulfate TS and titrate with 0.1 mol/L ammonium thiocyanate VS; the volume consumed is NLT 4.8 mL.

(6) ***Selenium***—Weigh 0.2 g of Acetazolamide and combust as directed under the Oxygen Flask Combustion with 25 mL of diluted nitric acid (1 in 30) as an absorbent. Proceed the combustion with a combustion flask with a volume of 1000 mL, wash the stopper and the inner wall of the flask with 10 mL of water, and transfer the solution in the combustion flask into a 150-mL beaker with about 20 mL of water. Heat gently to boiling, boil for 10 minutes, cool to room temperature, and use this solution as the test solution. Separately, pipet 6.0 mL of the standard selenium stock solution, add 25 mL of diluted nitric acid (1 in 30) and 25 mL of water, and use this solution as the standard solution. Add diluted ammonia water(28) (1 in 2) to each of the test and standard solutions, adjust the pH to 0.2, respectively, and dilute with water to make 60 mL. transfer into a separatory funnel with 10 mL of water, and then, wash the separatory funnel with 10 mL of water. Add 0.2 g of hydroxylamine hydrochloride, dissolve by stirring, add 5.0 mL of 2,3-diaminonaphthalene TS, and put a stopper on the funnel. Stir to mix, and then allow to stand at room temperature for 100 minutes. Add 5.0 mL of cyclohexane, shake well for two minutes, and allow to stand. If the layer is separated, remove the water layer, centrifuge cyclohexane extract to remove water, and take the cyclohexane layer. With these solutions, perform the test as directed under the Ultraviolet-visible Spectroscopy, using a solution prepared in the same manner by adding 25 mL of water to 25 mL of diluted nitric acid (1 in 30) as the control solution. Determine the absorption at the absorption maximum wavelength of around 380 nm; the absorption of the solution from the test solution is not larger than the absorption from the standard solution (NMT 30 ppm).

(7) ***Related substances***—Dissolve 100 mg of Acetazolamide in a mixture of acetone and methanol (1:1) to make 10 mL, and use this solution as the test solution. Pipet 2 mL of the test solution, add a mixture of acetone and methanol (1 : 1) to make 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of 1-propanol and 1 mol/L ammonia water (88 : 12) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelengths: 254 nm and 366 nm); the spots other than the principal spot obtained from the test solution are not larger or more intense than those from the standard solution (NMT 2.0%).

Loss on drying NMT 0.5% (0.5 g, 105 ℃, 3 hours).

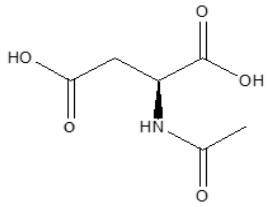
Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately about 0.15 g of Acetazolamide, add 400 mL of water, dissolve by heating on a steam bath, cool it down, and add water to make exactly 1000 mL. Take exactly 5 mL of this solution, add 10 mL of 1 mol/L hydrochloric acid TS, add water to make exactly 100 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance, *A*, at the absorbance maximum wavelength of about 265 nm.

Amount (mg) of acetazolamide ($C_4H_6N_4O_3S_2$)
$$= \frac{A}{474} \times 200000$$

Packaging and storage Preserve in light-resistant, well-closed containers.

N-Acetyl-L-aspartic Acid
N-아세틸-L-아스파르트산



$C_6H_9NO_5$: 175.14
N-Acetyl-L-aspartic acid, [997-55-7]

N-Acetyl-L-aspartic Acid, when dried, contains NLT 97.0% and NMT 101.0% of N-acetyl-L-aspartic acid ($C_6H_9NO_5$).

Description N-Acetyl-L-aspartic Acid occurs as a white crystalline powder.
It is odorless.
Its aqueous solution is acidic.
It is freely soluble in water and insoluble in ethanol(95) and most organic solvents.

Identification Dissolve 1 g of N-Acetyl-L-aspartic Acid in water to make 100 mL, and use this solution as the test solution. Dissolve 1 g of N-acetyl-L-aspartic acid RS in water to make 100 mL, and use this solution as the standard solution. With the test solution and the standard solution, perform the test as directed under the Paper Chromatography. Spot the test solution and the standard solution on the paper for chromatography. Next, develop the paper with a mixture of phenol and water (4 : 1) as the developing solvent, and air-dry the filter paper. Spray 0.01% congo red solution on the paper; the test solution and the standard solution exhibit blood blue spots on a red background at the same R_f value.

Melting point Between 140 and 141 ºC.

Purity (1) ***Sulfate***—Transfer 1 g of N-Acetyl-L-aspartic Acid into a Nessler test tube, add water to make 50 mL, and use this solution as the test solution. Prepare the control solution with 2.0 mL of 0.005 mol/L sulfuric acid VS (NMT 0.1%).

(2) ***Chloride***—Transfer 1 g of N-Acetyl-L-aspartic Acid into a Nessler test tube, add water to make 50 mL, and use this solution as the test solution. Prepare the control solution with 2.8 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.1%).

(3) ***Heavy metals***—To 10 mL of 5% aqueous solution of N-Acetyl-L-aspartic Acid, add 2 mL of hydrogen sulfide TS; the resulting solution does not change to brown.

(4) ***Iron***—Transfer 0.4 g of N-Acetyl-L-aspartic Acid into a Nessler test tube, add 45 mL of water, add 5 mL of 0.1 mol/L ammonium thiocyanate, and dissolve (test solution). Separately, dissolve 86.5 mg of ammonium ferrous sulfate in 10 mL of 0.25 mol/L sulfuric acid, and add water to make 1000 mL. Transfer the resulting solution into a Nessler test tube, add 45 mL of water and 5 mL of 0.1 mol/L ammonium thiocyanate, and use this solution as the control solution. The color of the test solution is not more intense than that of the control solution.

Loss on drying NMT 0.5% (105 ºC, four hours, constant mass).

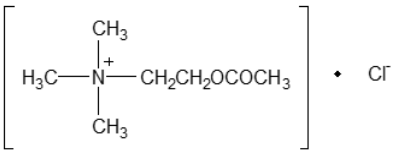
Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.2 g of N-Acetyl-L-aspartic Acid, previously dried, dissolve in 40 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS using phenolphthalein as an indicator. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 8.757 mg of $C_6H_9NO_5$

Packaging and storage Preserve in light-resistant, tight containers.

Acetylcholine Chloride for Injection
주사용 아세틸콜린염화물



$C_7H_{16}ClNO_2$: 181.66

Acetylcholine Chloride for Injection is a preparation for injection which is dissolved before use. Acetylcholine Chloride for Injection contains NLT 98.0% and NMT 102.0% of acetylcholine chloride ($C_7H_{16}ClNO_2$) and NLT 19.3% and NMT 19.8% of chlorine (Cl: 35.45), calculated on the dried basis. Acetylcholine Chloride for Injection contains NLT 93.0% and NMT 107.0% of the labeled amount of acetylcholine chloride ($C_7H_{16}ClNO_2$).

Method of preparation Prepare as directed under Injections.

Description Acetylcholine Chloride for Injection occurs as white crystals or a crystalline powder.

It is very soluble in water and freely soluble in ethanol(95).
It is highly hygroscopic.

Identification (1) Determine the infrared spectra of Acetylcholine Chloride for Injection and acetylcholine chloride for injection RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Acetylcholine Chloride for Injection (1 in 10) responds to the Qualitative Analysis (2) for chloride.

Melting point Between 149 and 152 ℃. Dry Acetylcholine Chloride for Injection and a capillary tube at 105 ℃ for 3 hours, seal the capillary tube filled with Acetylcholine Chloride for Injection, and measure the melting point.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Ipratropium Bromide Hydrate in 10 mL of water; the solution is clear and colorless.

(2) ***Acid***—Dissolve 1.0 g of Acetylcholine Chloride for Injection in 10 mL of freshly boiled and cooled water, add 1 drop of bromthymol blue TS, and use this solution as the test solution. To the test solution, add 0.30 mL of 0.01 mol/L sodium hydroxide VS; the solution is blue.

(3) ***Heavy metals*—**Proceed with 2.0g of Acetylcholine Chloride for Injection according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

Loss on drying NMT 1.0% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Acetylcholine chloride*—**Weigh accurately the contents of NLT 10 units of Acetylcholine Chloride for Injections. Weigh accurately about 0.5 g of the contents, dissolve in 15 mL of water, then add exactly 40 mL of 0.1 mol/L sodium hydroxide VS, stopper loosely and heat on a steam bath for 30 minutes. Cool quickly and titrate the excess sodium hydroxide with 0.05 mol/L sulfuric acid VS (indicator: 3 drops of phenolphthalein TS). Perform a blank test in the same manner and make any necessary correction.

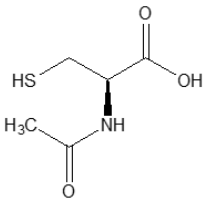
Each mL of 0.1 mol/L sodium hydroxide VS
= 18.166 mg of $C_7H_{16}ClNO_2$

(2) ***Chlorine*—**Titrate the solution, which has been titrated in (1), with 0.1 mol/L silver nitrate VS (indicator: 3 drops of fluorescein sodium TS).

Each mL of 0.1 mol/L silver nitrate VS
= 3.5453 mg of Cl

Packaging and storage Preserve in hermetic containers.

Acetylcysteine
아세틸시스테인



$C_5H_9NO_3S$: 163.20
(2R)-2-Acetamido-3-sulfanylpropanoic acid [*616-91-1*]

Acetylcysteine, when dried, contains NLT 98.0% and NMT 102.0% of acetylcysteine ($C_5H_9NO_3S$).

Description Acetylcysteine occurs as a white crystalline powder.
It is freely soluble in water or ethanol(95) and practically insoluble in dichloromethane.

Identification Determine the infrared spectra of Acetylcysteine and acetylcysteine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between + 21° and + 27°. Weigh accurately 1.25 g of Acetylcysteine, calculated on the dried basis, dissolve in 1 mL of ethylenediaminetetraacetic acid disodium salt solution (1 in 100) and 7.5 mL of sodium hydroxide solution (1 in 25), and add pH 7.0 phosphate buffer solution, pH 7.0 to make 25 mL. Determine the optical rotation of this solution.

pH 7.0 phosphate buffer solution—Transfer 50 mL of 1 mol/L potassium dihydrogen phosphate TS and 29.5 mL of 1 mol/L sodium hydroxide solution into a volumetric flask to mix, add water, adjust the pH to 7.0, and add water again to make 100 mL.

pH Dissolve 1.0 g of Acetylcysteine in 100 mL of freshly boiled and cooled water; the pH of this solution is between 2.0 and 2.8.

Purity ***Heavy metals*—**Proceed with 2.0 g of Acetylcys-

teine according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

Loss on drying NMT 0.1% (1 g, in vacuum, NMT 0.67 kPa, 70 ℃, 4 hours).

Residue on ignition NMT 0.5% (2 g, 600 ℃).

Assay Weigh accurately about 1.0 g of Acetylcysteine, previously dried, and dissolve by adding freshly prepared sodium metabisulfite (1 in 2000) to make exactly 100 mL. Pipet 10 mL of this solution, add exactly 10 mL of the internal standard solution, put sodium metabisulfite solution (1 in 2000) to make exactly 200 mL, and use this solution as the test solution. Separately, weigh accurately about 1.0 g of acetylcysteine RS, and dissolve by adding sodium metabisulfite solution (1 in 2000) to make exactly 100 mL. Pipet 10 mL of this solution, add exactly 10 mL of the internal standard solution, put sodium metabisulfite solution (1 in 2000) to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of acetylcysteine to the internal standard, respectively.

$$\text{Amount (mg) of acetylcysteine } (C_5H_9NO_3S) = \text{Amount (mg) of acetylcysteine RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Dissolve 1 g of *dl*-phenylalanine in freshly prepared sodium metabisulfite (1 in 2000) to make 200 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: pH 3.0 potassium dihydrogen phosphate solution (68 in 10000).

Flow rate: 1.5 mL/min

System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; acetylcysteine and *dl*-phenylalanine are eluted in this order with the resolution being NLT 6.0.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution according to the above conditions; the relative standard deviation is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Acetylcysteine capsules
아세틸시스테인 캡슐

Acetylcysteine Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of acetylcysteine ($C_5H_9NO_3S$: 163.20).

Method of preparation Prepare as directed under Capsules, with Acetylcysteine.

Identification The retention time and the ultraviolet absorption spectrum at 190 nm to 300 nm of the major peaks obtained from the test solution and the reference standard from the Assay are the same.

Dissolution Perform the test with 1 Acetylcysteine Capsule at 100 revolutions per minute according to Method 1 under the Dissolution, using 900 mL of water as the dissolution medium. Take the dissolved solution 30 minutes after starting the dissolution test and filter it. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add water to make exactly *V'* mL so that each mL contains about 20 μg of acetylcysteine according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 20 mg of acetylcysteine RS, and dissolve in water to make 100 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. However, keep the temperature of the solution at 5 ℃ during the procedure. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of acetylcysteine ($C_5H_9NO_3S$) in each solution. Meets the requirements if the dissolution rate of Acetylcysteine Capsules in 30 minutes is NLT 75%.

$$\text{Dissolution rate (\%) of the labeled amount of acetylcysteine } (C_5H_9NO_3S) = W_S \times (V'/V) \times (A_T/A_S) \times (1/C) \times 90$$

W_S: Amount (mg) of acetylcysteine RS

C: Labeled amount (mg) of acetylcysteine ($C_5H_9NO_3S$) per capsule

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Sample temperature: A constant temperature of about 5 ℃.

Mobile phase: 0.05 mol/L potassium dihydrogen phosphate TS (pH 3.0).

Flow rate: 1.0 mL/min

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the content of NLT 20 Acetylcysteine Capsules. Weigh accurately an amount equivalent to about 1.0 g of acetylcysteine ($C_5H_9NO_3S$), add sodium bisulfite solution (1 in 2000), and shake to dissolve. Add sodium bisulfite solution (1 in 2000) to make exactly 100 mL and filter. Take 10.0 mL of the filtrate and 10.0 mL of the internal standard solution and dilute it with a sodium bisulfite solution (1 in 2000) to make exactly 200 mL. Use this solution as the test solution. Separately, weigh accurately about 1.0 g of the acetylcysteine RS, proceed in the same way as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of the peak areas of acetylcysteine to that of internal standard, respectively.

Amount (mg) of acetylcysteine ($C_5H_9NO_3S$)
= Amount (mg) of acetylcysteine RS × (Q_T / Q_S)

Internal standard solution—Dissolve 1 g of DL-phenylalanine in 200 mL of sodium bisulfite solution (1 in 2000) prepared before use.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm). However, use a photo-diode array detector (190 nm to 300 nm) when performing the Identification.

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography.

Mobile phase: Phosphate buffer solution, pH 3.0.

Flow rate: 1.5 mL/min

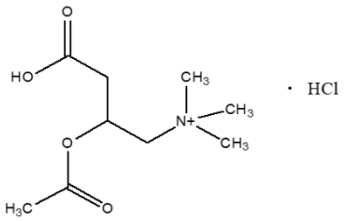
System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; the resolution of acetylcysteine and DL-phenylalanine are NLT 6.0.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of acetylcysteine RS is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Acetyl-L-carnitine Hydrochloride
아세틸-L-카르니틴염산염



$C_9H_{17}NO_4 \cdot HCl$: 239.70

(2*R*)-2-Acetyloxy-3-carboxy-*N*,*N*,*N*-trimethyl-1-propanaminium chloride (1:1), [*5080-50-2*]

Acetyl-L-carnitine Hydrochloride contains NLT 97.0% and NMT 102.0% of acetyl-L-carnitine hydrochloride ($C_9H_{17}NO_4 \cdot HCl$), calculated on the anhydrous basis.

Description Acetyl-L-carnitine Hydrochloride occurs as a white fine crystalline powder.
It has a characteristic odor.
It is very soluble in water, soluble in methanol or ethanol(95) and practically insoluble in acetone or ether.

Identification Determine the infrared spectra of Acetyl-L-carnitine Hydrochloride and acetyl-L-carnitine hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Clarity and color of solution***—An 1% aqueous solution of Acetyl-L-carnitine Hydrochloride is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Acetyl-L-carnitine Hydrochloride according to Method 1 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Weigh accurately about 0.1 g of Acetyl-L-carnitine Hydrochloride, dissolve in the mobile phase to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of L-carnitine hydrochloride RS, dissolve in the mobile phase to make 100 mL, and use this solution as the standard solution of L-carnitine hydrochloride. Separately, weigh accurately about 10 mg of crotonoylbetaine hydrochloride RS and dissolve in the mobile phase to make 100 mL. Pipet 5.0 mL of this solution, add the mobile phase to make 25 mL, and use this solution as the standard solution of the crotonoylbetaine hydrochloride. Perform the test with 25 μL each of the test solution, the standard solution of L-carnitine hydrochloride and the standard solution of the crotonoylbetaine hydrochlorideas directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method and calculate the amount of related substances; the amounts of L-carnitine hydrochloride and crotonoylbetaine hydrochloride are NMT 1.0% and NMT 0.2%, respectively.

Content (%) of related substances

$$= 100 \times \frac{C_S}{C_T} \times \frac{A_i}{A_S}$$

C_s: Concentration (mg/mL) of each related substance in the standard solution

C_T: Concentration (mg/mL) of Acetyl-L-carnitine Hydrochloride in the test solution

A_i: Peak area of each related substance obtained from the test solution

A_s: Peak area of each related substance obtained from the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with aminopropylsilanized silica gel for liquid chromatography (5 μmto10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and 0.05 mol/L potassium dihydrogen phosphate TS, pH 4.7 (65 : 35).

Flow rate: 1.0 mL/min

pH Between 2.3 and 2.6 (1% aqueous solution).

Optical rotation $[\alpha]_D^{20}$: Between -26.5° and -28.0° (0.1 g, water, 100 mL, 100 mm).

Water NMT 1.0% (1 g, volumetric titration, direct titration).

Assay Weigh accurately about 40 mg each of Acetyl-L-carnitine Hydrochloride and acetyl-L-carnitine hydrochloride RS, and add the mobile phase to make 50 mL. Pipet 1.0 mL of these solutions, add the mobile phase to make 10 mL, filter through 0.45 μm filters, and use the filtrate as the test solution and the standard solution, respectively. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of acetyl-L-carnitine hydrochloride in each solution.

Amount (mg) of acetyl-L-carnitine hydrochloride ($C_9H_{17}NO_4$·HCl)
= Amount (mg) of acetyl-L-carnitine hydrochloride RS $\times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with aminopropylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and 0.05 mol/L potassium dihydrogen phosphate TS, pH 4.7 (65 : 35).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in light-resistant, tight containers.

Acetyl-L-carnitine Hydrochloride Tablets
아세틸-L-카르니틴염산염 정

Acetyl-L-carnitine Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of acetyl-L-carnitine hydrochloride ($C_9H_{17}NO_4$·HCl : 239.70).

Method of preparation Prepare Acetyl-L-carnitine Hydrochloride Tablets as directed under Tablets, with Acetyl-L-carnitine Hydrochloride.

Identification The retention time of major peak of the test solution and the standard solution for Assay is the same.

Dissolution Take one tablet of Acetyl-L-carnitine Hydrochloride Tablets, and perform the test at 100 revolutions per minute according to Method 2 using 900 mL of phosphate buffer solution, pH 7.5 as the dissolution medium. Take the medium 120 minutes after starting the dissolution test to filter, discard the first 10 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately about 0.2 g of acetyl-L-carnitine hydrochloride RS, dissolve in phosphate buffer solution, pH 7.5 to have the same concentration as the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the operating conditions under the Assay. It meets the requirements if the dissolution rate of Acetyl-L-carnitine Hydrochloride Tablets in 120 minutes is NLT 90%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Acetyl-L-carnitine Hydrochloride Tablets, and powder. Weigh accurately an amount equivalent to about 0.1 g of acetyl-L-carnitine hydrochloride ($C_9H_{17}NO_4$·HCl), add water to make exactly 100 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 0.1 g of acetyl-L-carnitine hydrochloride RS, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of acetyl-L-carnitine hydrochloride in each solution.

Amount (mg) of acetyl-L-carnitine hydrochloride ($C_9H_{17}NO_4$·HCl)

= Amount (mg) of acetyl-L-carnitine hydrochloride RS

$$\times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and 30 cm in length, packed with aminopropylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

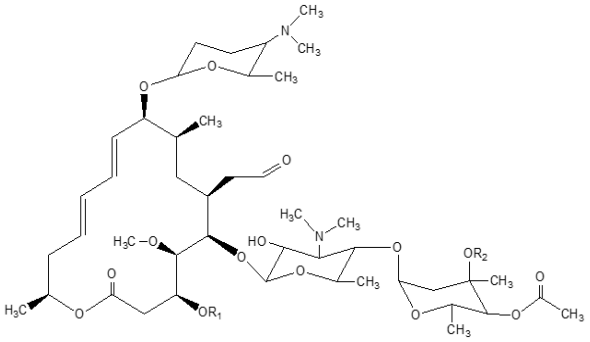
Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of acetonitrile and 0.05 mol/L potassium dihydrogen phosphate (pH 4.7) (65 : 35).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in well-closed containers.

Acetylspiramycin
아세틸스피라마이신



Acetylspiramycin II : R_1=$COCH_3$ R_2=H
$C_{47}H_{78}N_2O_{16}$: 927.13

Acetylspiramycin III : R_2=$COCH_2CH_3$ R_2=H
$C_{48}H_{80}N_2O_{16}$: 941.16

Acetylspiramycin IV : R_1=$COCH_3$ R_2=$COCH_3$
$C_{49}H_{80}N_2O_{17}$: 969.17

Acetylspiramycin V : R_1=$COCH_2CH_3$ R_2=$COCH_3$
$C_{50}H_{82}N_2O_{17}$: 983.19

Acetylspiramycin VI : R_1=H R_2=H
$C_{45}H_{76}N_2O_{15}$: 885.09

acetylspiramycin II:
(4*R*,5*S*,6*R*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-4-Acetyloxy-10-{[(2*R*,5*S*,6*R*)-5-(dimethylamino)-6-methyltetrahydro-2H-pyran-2-yl]oxy}-9,16-dimethyl-5-methoxy-2-oxo-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-6-yl 3,6-dideoxy-4-O-(4-O-acetyl-6-deoxy-3-C-methyl-α-L-ribo-hexopyranosyl)-3-(di-methyl-amino)-α-D-glucopyranoside

acetylspiramycin III:
(4*R*,5*S*,6*R*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-10-{[(2R,5S,6R)-5-(Dimethylamino)-6-methyltetrahydro-2H-pyran-2-yl]oxy}9,16-dimethyl-5-methoxy-2-oxo-7-(2-oxoethyl)-4-(propanoyl-oxy)oxacyclohexadeca-11,13-dien-6-yl 3,6-dideoxy-4-O-(4-O-acetyl-6-deoxy-3-C-methyl-α-L-ribo-hexopyranosyl)-3-(dimethylamino)-α-D-glucopyranoside

acetylspiramycin IV:
(4*R*,5*S*,6*R*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-4-Acetyloxy-10-{[(2R,5S,6R)-5-(dimethylamino)-6-methyltetrahydro-2H-pyran-2-yl]oxy}-9,16-dimethyl-5-methoxy-2-oxo-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-6-yl 3,6-dideoxy-4-O-(3,4-di-O-acetyl-6-deoxy-3-C-methyl-α-L-ribo-hexopyranosyl)-3-(dimethylamino)-α-D-glucopyranoside

acetylspiramycin V: (4*R*,5*S*,6*R*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-10-{[(2R,5S,6R)-5-(Dimethylamino)-6-methyltetrahydro-2H-pyran-2-yl]oxy}-9,16-dimethyl-5-methoxy-2-oxo-7-(2-oxoethyl)-4-(propanoyloxy)oxacyclohexadeca-11,13-dien-6-yl 3,6-dideoxy-4-O-(3,4-di-O-acetyl-6-deoxy-3-C-methyl-α-L-ribo-hexopyranosyl)-3-(dimethylamino)-α-D-glucopyranoside

acetylspiramycin VI:
(4*R*,5*S*,6*R*,7*R*,9*R*,10*R*,11E,13E,16*R*)-10-{[(2*R*,5*S*,6*R*)-5-(Dimethylamino)-6-methyltetrahydro-2H-pyran-2-yl]oxy}-4-hydroxy-9,16-dimethyl-5-methoxy-2-oxo-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-6-yl 3,6-dideoxy-4-O-(4-O-acetyl-6-deoxy-3-C-methyl-α-L-ribo-hexopyranosyl)-3-(dimethylamino)-α-D-glucopyranoside

Acetylspiramycin is a mixture derivative of macrolide substances having antibacterial activity produced by the growth of S*treptomyces ambofaciens.*

Acetylspiramycin contains NLT 900 μg and NMT 1450 μg (potency) of acetylspiramycin per mg, calculated on the dried basis. The potency of Acetylspiramycin is expressed as the amount of acetylspiramycin II ($C_{47}H_{78}N_2O_{16}$: 927.13) in terms of the mass (potency) of acetylspiramycin, and 1 mg (potency) of acetylspiramycin is equivalent to 0.7225 mg of acetylspiramycin II ($C_{47}H_{78}N_2O_{16}$).

Description Acetylspiramycin occurs as a white to pale yellowish white powder.
It is very soluble in methanol or acetonitrile, freely soluble in ethanol(99.5) and practically insoluble in water.

Identification (1) Determine the absorption spectra of solutions of Acetylspiramycin and acetylspiramycin RS in methanol (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Acetylspiramycin and acetylspiramycin RS as directed in the potassium bromide disk method under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Content ratio Dissolve 25 mg of Acetylspiramycin in 25 mL of the mobile phase and use this solution as the test solution. Perform the test with 5 μL of the test solution as directed under the Liquid Chromatography according to the following conditions, and determine peak areas, A_{II}, A_{III}, A_{IV}, A_V, A_{VI} and A_{VII}, of acetylspiramycin

III, acetylspiramycin IV, acetylspiramycin V, acetylspiramycin VI and acetylspiramycin VII, and calculate the ratios of A_{II} and A_{IV}, and the ratio of the sum of A_{III} and A_V to the sum of the peak areas; the ratios of A_{II}, A_{IV} and the sum of A_{III} and A_V are between 30% and 45%, between 30% and 45%, and NMT 25%, respectively. The relative retention time of acetylspiramycin III, acetylspiramycin IV, acetylspiramycin V, acetylspiramycin VI and acetylspiramycin VII to that of acetylspiramycin II is 1.3, 1.7, 2.3, 0.85 and 1.4, respectively.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 231 nm).

Column: A stainless steel column about 6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of acetonitrile, 0.02 mol/L potassium dihydrogen phosphate TS and dibasic potassium phosphate (87 in 25000) (26 : 7 : 7).

Flow rate: Adjust the flow rate so that the retention time of acetylspiramycin II is about 10 minutes.

System suitability

System performance: Dissolve 25 mg of acetonitrile II RS in the mobile phase to make 100 mL. Proceed with 5 μL of this solution under the above operating conditions; the number of theoretical plates and symmetry factor of the peak of acetonitrile II are NLT 14500 and NMT 2.0, respectively.

System repeatability: Repeat the test 6 times with 5 μL each of the test solutions according to the above conditions; the relative standard deviation of the peak area of acetonitrile II is NMT 2.0%.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Acetylspiramycin according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Proceed with 2.0 g of Acetylspiramycin according to Method 3 and perform the test (NMT 1 ppm).

Loss on drying NMT 3.0% (1 g, in vacuum, phosphorus pentoxide, 60 ℃, 3 hours).

Residue on ignition NMT 0.5% (1 g).

Assay ***Cylinder plate method*** (1) Medium: Agar media for seed and base layer-Use the medium in (i) (2) (a) ① ⓐ under the Microbial Assays for Antibiotics.

(2) Test organism: Use *Bacillus subtilis* ATCC 6633 as the test organism.

(3) Weigh accurately an amount of Acetylspiramycin, equivalent to about 50 mg (potency), dissolve in 20 mL of methanol, and add 0.1 mol/L phosphate buffer solution, pH 8.0, for antibiotics to make exactly 50 mL. Take accurately an appropriate amount of this solution, dilute it with 0.1 mol/L phosphate buffer solution, pH 8.0, for antibiotics to make solutions containing 80 μg (potency) and 20 μg (potency) per mL, and use these solutions as the high concentration test solution and low concentration test solution, respectively. Weigh accurately about 50 mg (potency) of acetylspiramycin II RS, dissolve in 20 mL of methanol, add 0.1 mol/L phosphate buffer solution, pH 8.0, for antibiotics to make exactly 50 mL, and use this solution as the standard stock solution. Store the standard stock solution at below 5 °C and use it within 3 days. Pipet an appropriate amount of this standard stock solution and dilute with 0.1 mol/L phosphate buffer solution, pH 8.0 for antibiotics to make solutions containing 80 μg (potency) and 20 μg (potency) per mL, and use these solutions as the high concentration standard solution and the low concentration standard solution, respectively. With these solutions, perform the test according to (i)(8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in tight containers.

Acetylspiramycin Tablets
아세틸스피라마이신 정

Acetylspiramycin Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of acetylspiramycin.

Method of preparation Prepare Acetylspiramycin Tablets as directed under Tablets, with Acetylspiramycin.

Identification (1) To 20 mg (potency) of Acetylspiramycin Tablets, dissolve in 2 mL of diluted methanol (1 in 2), and add 1 to 2 drops of Mayer's TS; a yellow to yellowish white precipitate is formed.

(2) Dissolve 20 mg (potency) of Acetylspiramycin Tablets in 2 mL of diluted methanol (1 in 2), and add 1 to 2 drops of iodine TS; a brown precipitate is formed.

(3) Weigh 10 mg (potency) of Acetylspiramycin Tablets, and dissolve in diluted methanol (1 in 5) to make exactly 1000 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 230 nm and 234 nm.

(4) Weigh an appropriate amount of Acetylspiramycin Tablets and acetylspiramycin RS, respectively, dissolve in chloroform to make solutions containing 200 μg (potency) per mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography, and develop the plate with the mixture of methanol and ethyl acetate (1 : 1) as the developing solvent. Spray evenly diluted sulfuric acid (1 in 10) on the

thin-layer chromatographic plate, heat at 110 ℃ to 120 ℃ for about 10 minutes, and compare the purplish brown spots of the test solution and standard solution; the R_f values are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Loss on drying NMT 5.0% (0.1 g, 0.7 kPa, 60 ℃, 3 hours).

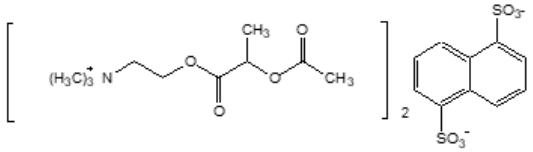
Assay ***Cylinder plate method*—**(1) Medium: Agar media for seed and base layer Use the medium in (i) (2) (a) ① ⓐ under the Microbial Assays for Antibiotics.

(2) Test organism: Use *Bacillus subtilis* ATCC 6633 as the test organism.

(3) Weigh accurately the mass of NLT 20 tablets of Acetylspiramycin Tablets, and powder them. Weigh accurately about 0.25 g (potency) according to the labeled potency, add methanol, shake vigorously to mix, and make exactly 100 mL. Filter or centrifuge, if necessary. Take exactly an appropriate amount of this solution, dilute with 0.1 mol/L phosphate buffer solution, pH 8.0, to make solutions so that each mL contains 80.0 μg and 20.0 μg (potency) per mL, respectively, and use these solutions as the high concentration test solution and the low concentration test solution, respectively. Separately, weigh accurately about 50 mg (potency) of acetylspiramycin RS, dissolve in 20 mL of methanol, add 0.1 mol/L phosphate buffer solution (pH 8.0) to prepare a standard stock solution containing 1 mg (potency) per mL. Keep the standard stock solution below 5 ℃ and use it within 3 days. For assay, pipet an appropriate amount of the standard stock solution, dilute with 0.1 mol/L phosphate buffer solution (pH 8.0) to obtain solutions containing 80.0 μg and 20.0 μg (potency) per mL, and use these solutions as the high-concentration standard solution and the low-concentration standard solution, respectively. With these solutions, perform the test according to (i) (8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in tight containers.

Aclatonium Napadisilate
아클라토늄나파디실산염



$C_{30}H_{46}N_2O_{14}S_2$: 722.82

2-[2-(Acetyloxy)-1-oxopropoxy]-*N*,*N*,*N*-trimethylethanaminium 1,5-naphthalenedisulfonate (2:1), [*55077-30-0*]

Aclatonium Napadisilate, when dried, contains NLT 98.0% and NMT 101.1% of aclatonium napadisilate ($C_{30}H_{46}N_2O_{14}S$).

Description Aclatonium Napadisilate occurs as white tablets or a crystalline powder. It is odorless or has a slight characteristic odor and a bitter taste.
It is very soluble in water, freely soluble in methanol and practically insoluble in ethanol(95) or ether.
An aqueous solution of Aclatonium Napadisilate (1 in 10) shows no optical rotation.

Identification (1) Add 1 mL of hydroxylamine hydochloride solution (1 in 10) and 2 mL of sodium hydroxide TS to aqueous solution of Aclatonium Napadisilate, mix, and add 2 mL of dilute hydrochloric acid and 0.5 mL of dilute ferric chloride TS; the solution exhibits a reddish purple color.

(2) Add 2 g of sodium hydroxide to 5 mL of aqueous solution (1 in 10) of Aclatonium Napadisilate, and heat; the solution emits an amine odor and the gas changes the red litmus paper to blue.

(3) Determine the absorbance spectra of an aqueous solution (1 in 25000) of Aclatonium Napadisilate as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 275 nm and 279 nm, between 285 nm and 289 nm, between 296 nm and 300 nm and between 317 nm and 321 nm. Determine the absorbance spectra of an aqueous solution (1 in 20000) of Aclatonium Napadisilate as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 224 nm and 228 nm.

(4) Add 1 mL of barium chloride TS to 5 mL of the aqueous solution of Aclatonium Napadisilate (1 in 10), shake to mix, and allow it to stand; a white precipitate is formed.

Melting point Between 188 and 192 ℃.

Purity (1) ***Clarity and color of solution*—**Dissolve 1 g of Aclatonium Napadisilate in 5 mL of water; the solution is colorless and clear.

(2) ***Chloride*—**Perform the test with 2.0 g of Aclatonium Napadisilate as directed under the Chloride. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid (NMT 0.007%).

(3) ***Heavy metals*—**Proceed with 2.0g of Aclatonium Napadisilate according to Method 1, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic*—**Perform the test with 1.0 g of Aclatonium Napadisilate according to Method 1 under the Arsenic (NMT 2 ppm).

(5) ***Related substances*—**Weigh 0.5 g of Aclatonium Napadisilate, add methanol to make 10 mL, and use this solution as the test solution. Prepare before use. Separately, weigh 50 mg of Aclatonium Napadisilate, dissolve in 5 mL methanol, add 4 mL of dilute sodium hy-

droxide TS, and heat on a steam bath for 30 minutes with a reflux condenser. Cool it, add methanol to make 200 mL, and use this solution as the standard solution. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of cellulose for thin-layer chromatography. Develop the plate with a mixture of 1-butanol, water and acetic acid (5 : 4 : 1) to a distance of about 10 cm, and air-dry the plate. Spray evenly Dragendorff's TS on the plate; the spots from the test solution corresponding to the positions of the spots from the standard solution are not more intense than the spots from the standard solution.

Loss on drying NMT 1.0% (1 g, 105℃, 3 hours).

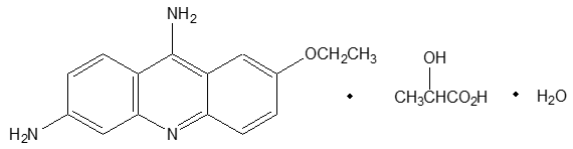
Residue on ignition NMT 0.10% (1 g).

Assay Weigh accurately about 0.25 g of Aclatonium Napadisilate, previously dried, dissolve in 25 mL of methanol, add exactly 20 mL of 0.1 mol/L sodium hydroxide solution, and heat on a steam bath for 30 minutes with a reflux condenser. Stopper and rapidly cool, and then titrate the excess sodium hydroxide solution with 0.1 mol/L hydrochloric acid VS (indicator: 3 drops of phenolphthalein TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 18.07 mg of $C_{30}H_{46}N_2O_{14}S_2$

Packaging and storage Preserve in tight containers.

Acrinol Hydrate
아크리놀수화물



Ethacridine Lactate $C_{15}H_{15}N_3O \cdot C_3H_6O_3 \cdot H_2O$: 361.39
7-Ethoxyacridine-3,9-diamine 2-hydroxypropanoate monohydrate [*1837-57-6*]

Acrinol Hydrate contains NLT 98.5% and NMT 101.0% of acrinol ($C_{15}H_{15}N_3O \cdot C_3H_6O_3$: 348.38), calculated on the anhydrous basis.

Description Acrinol Hydrate occurs as a yellow crystalline powder.
It is sparingly soluble in water, methanol or ethanol(99.5).
The pH of the aqueous solution (1 in 100) of Acrinol Hydrate is between 5.5 and 7.0.

Melting point—About 245 °C (with decomposition).

Identification (1) Determine the absorption spectra of aqueous solutions of Acrinol Hydrate and acrinol hydrate RS (3 in 250000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Acrinol Hydrate and acrinol hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) Add 5 mL of dilute sulfuric acid to 5 mL of aqueous solution of Acrinol Hydrate (1 in 100), shake well to mix, allow to stand at room temperature for 5 minutes, and then filter; the filtrate responds to the Qualitative Analysis for lactate.

Purity (1) ***Chloride***—Add 80 mL of water to 1.0 g of Acrinol Hydrate, warm on a steam bath to dissolve, and cool. Add 10 mL of sodium hydroxide TS and water to make 100 mL, shake well to mix, allow to stand for 30 minutes. Filter the solution, take 40 mL of the filtrate, add 7 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. For the control solution, add 4 mL of sodium hydroxide TS, 7 mL of dilute nitric acid and water to 0.30 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.026%).

(2) ***Heavy metals*—**Proceed with 1.0 g of Acrinol Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Volatile fatty acids***—Add 20 mL of water and 5 mL of dilute sulfuric acid to 0.5 g of Acrinol Hydrate, shake well to mix, filter, and warm; no odor of volatile fatty acids is perceptible.

(4) ***Related substances***—Dissolve 10 mg of Acrinol Hydrate in 25 mL of mobile phase and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution (1). Pipet 1 mL of the standard solution (1), add the mobile phase to make exactly 10 mL, and use this solution as the standard solution (2). Perform the test with 10 μL each of the test solution, the standard solution (1) and the standard solution (2) as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by automatic integration method; the peak area other than the peak of acrinol from the test solution is not greater than 3 times the peak area of acrinol from the standard solution (2). Also, the sum of the peak areas other than acrinol from the test solution is not greater than the peak area of acrinol from standard solution (1).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 268 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 7.8 g of sodium dihydrogen phosphate dihydrate in 900 mL of water, adjust the pH to 2.8 with phosphoric acid, and add water to make 1000 mL. Add 300 mL of acetonitrile for liquid chromatography to 700 mL of this solution, and then dissolve 1.0 g of sodium octanesulfonate.

Flow rate: Adjust the flow rate so that the retention time of acrinol is about 15 minutes.

System suitability

Test for required detectability: Confirm that the peak area of acrinol from 10 μL of the standard solution (2) is equivalent to 7 to 13% of the peak area of acrinol obtained from the standard solution (1).

System performance: Proceed with 10 μL of the standard solution (2) according to above operating conditions; the number of theoretical plates and symmetry factor of acrinol are NLT 5000 and NMT 2.0, respectively.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution (1) according to the above conditions; the relative standard deviation of the peak area for acrinol is NMT 1.5%.

Time span of measurement: About 3 times the retention time of acrinol after the solvent peak.

Water Between 4.5% and 5.5% (0.2 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.27 g of Acrinol Hydrate, dissolve in 5 mL of formic acid, add 60 mL of a mixture of acetic anhydride and acetic acid(100) (1 : 1), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 34.34 mg of $C_{15}H_{15}N_3O \cdot C_3H_6O_3 \cdot H_2O$

Packaging and storage Preserve in light-resistant, tight containers.

Acrinol, Berberine Chloride and Scopolia Extract Capsules
아크리놀·베르베린염화물·스코폴리아엑스 캡슐

Acrinol, Berberine Chloride and Scopolia Extract Capsules contain 90.0% to 110.0% of acrinol hydrate ($C_{15}H_{15}N_3O \cdot C_3H_6O_3 \cdot H_2O$: 361.39) and berberine chloride ($C_{20}H_{18}ClNO_4$: 371.81), and contain 0.90% to 1.09% of the total alkaloids [hyoscyamine ($C_{17}H_{23}NO_3$: 289.37) and scopolamine ($C_{17}H_{21}NO_4$: 303.35)] in scopolia extract.

Method of preparation Prepare as directed under Capsules, with Acrinol Hydrate, Berberine Chloride and Scopolia Extract.

Identification (1) ***Acrinol hydrate and berberine chloride*—**Weigh an amount of Acrinol, Berberine Chloride and Scopolia Extract Capsules, equivalent to 20 mg of acrinol hydrate (an amount equivalent to 30 mg of berberine chloride) according to the labeled amount, add 20 mL of water, shake well to mix, and centrifuge. Use the clear supernatant as the test solution. Weigh 20 mg of acrinol hydrate RS and 30 mg of berberine chloride RS, respectively, add 20 mL of water, shake to dissolve, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on a thin-layer chromatographic plate made using silica gel for thin-layer chromatography. Develop the plate with a mixture of 1-butanol, water and acetic acid(100) (7 : 1 : 1) as the developing solvent, and air-dry the plate. Spray evenly hexachloroplatinic(IV) acid-potassium iodide TS on the plate; the colors and the Rf values obtained from the test solution and the standard solution are the same.

(2) ***Scopolia extract*—**Weigh an amount of Acrinol, Berberine Chloride and Scopolia Extract Capsules equivalent to 2.0 g of scopolia rhizome, add 20 mL of methanol, attach a reflux condenser, and reflux it for 30 minutes. After cooling, filter, wash the residue twice with 10 mL of methanol, combine the filtrate and the washings, and concentrate in vacuum. Dissolve the residue in 25 mL of sulfuric acid (1 in 50), filter, and transfer the filtrate to a separatory funnel. Add 10 mL of ether, and shake well to mix. Take the water layer, add ammonia TS to make it slightly alkaline, add 30 mL of chloroform, and shake to mix. Add 2.0 g of anhydrous sodium sulfate to the chloroform layer, shake to mix, and filter when the solution is clear. Concentrate the filtrate in vacuum, dissolve the residue in 1 mL of ethanol(95), and use this solution as the test solution. Separately, proceed in the same manner as in the preparation of the test solution with 2.0 g of Scopolia Rhizome, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of chloroform, methanol, acetone and ammonia water(28) (73 : 15 : 10 : 2) as the developing solvent, and heat the plate at 105 ℃ for 10 minutes. Spray Dragendorff's TS on the plate; the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Acrinol hydrate and berberine chloride*—** Weigh accurately the contents of NLT 20 Acrinol, Berberine Chloride and Scopolia Extract Capsules, and powder. Weigh accurately an amount equivalent to about 20 mg of acrinol hydrate ($C_{15}H_{15}N_3O \cdot C_3H_6O_3 \cdot H_2O$) [an amount equivalent to about 30 mg of berberine chloride ($C_{20}H_{18}ClNO_4$)], dissolve in the mobile phase to make exactly 50 mL, and filter. Pipet 5 mL of the filtrate, add exactly 25 mL of the internal standard solution, add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of acrinol hydrate and about 30 mg of berberine chloride hydrate RS (previously measure water), respectively, and dissolve in the mobile phase to make exactly 50 mL. Pipet 5 mL of this solution, add exactly 25 mL of the internal standard solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 15 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas of acrinol hydrate, berberine chloride and internal standard in each solution by the automatic integration method, and calculate the ratio of the peak areas, Q_{T1}, Q_{S1}, Q_{T2} and Q_{S2}, of the acrinol hydrate and berberine chloride to that of the internal standard in each solution.

Amount (mg) of acrinol hydrate ($C_{15}H_{15}N_3O \cdot C_3H_6O_3 \cdot H_2O$) = Amount (mg) of acrinol hydrate RS × (Q_{T1} / Q_{S1})

Amount (mg) of berberine chloride ($C_{20}H_{18}ClNO_4$) = Amount (mg) of berberine chloride RS × (Q_{T2} / Q_{S2})

Internal standard solution—Weigh accurately about 50 mg of atenolol, and dissolve in the mobile phase to make 50 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Column temperature: Ordinary temperature

Mobile phase: A mixture of methanol and 0.02 mol/L ammonium monohydrogen phosphate (9 : 1).

Flow rate: 2.0 mL/min

(2) ***Total alkaloid in scopolia extract [hyoscyamine and scopolamine]*—**Weigh accurately the contents of NLT 20 Acrinol, Berberine Chloride and Scopolia Extract Capsules, and weigh accurately an amount equivalent to about 0.4 mg of total alkaloids [hyoscyamine and scopolamine] in scopolia extract. Put it in a centrifugal test tube with a stopper, add 15 mL of ammonia TS, and shake to mix. Add 25 mL of ether, cover it with the stopper, and shake for 15 minutes. Centrifuge, and separate the ether layer. For the water layer, repeat this procedure twice using 25 mL of ether. Combine all the extracts and evaporate ether on a steam bath. Dissolve the residue in exactly 5 mL of the mobile phase, add exactly 3 mL of the internal standard solution, and add the mobile phase again to make exactly 25 mL. Filter this solution through filter paper with a pore size of NMT 0.8 μm, discard the first 2 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately about 25 mg of atropine sulfate RS (previously determine the loss on drying), dissolve in the mobile phase to make exactly 25 mL, and use this solution as the standard stock solution (1). In addition, weigh accurately about 25 mg of scopolamine hydrobromide RS (previously determine the loss on drying), dissolve in the mobile phase to make exactly 25 mL, and use this solution as the standard stock solution (2). Take exactly 5 mL of the standard stock solution (1) and 1 mL of the standard stock solution (2), add exactly 3 mL of the internal standard solution, add the mobile phase again to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area ratios, Q_{TS} and Q_{SA}, of hyoscyamine (atropine), and the peak area ratios, Q_{TS} and Q_{SS}, of scopolamine to the peak area of the internal standard in each solution. Then, calculate the amounts of hyoscyamine and scopolamine using the following formula, and use their sum as the total amount of alkaloids.

Amount (mg) of hyoscyamine ($C_{17}H_{23}NO_3$) = Amount (mg) of atropine sulfate RS, calculated on the dried basis × (Q_{TS} / $Q_{SA)}$ × (1 / 5) × 0.8551

Amount (mg) of scopolamine ($C_{17}H_{21}NO_4$) = Amount (mg) of scopolamine hydrobromide RS, calculated on the dried basis × (Q_{TS} / $Q_{SS)}$ × (1 / 25) × 0.7894

Internal standard solution—Mobile phase of brucine (1 in 2500).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of a solution, prepared by dissolving 6.8 g of potassium dihydrogen phosphate in 900 mL of water, adding 10 mL of triethylamine, adding phosphoric acid to adjust the pH to 3.5, and add water to make 1000 mL, and acetonitrile (9 : 1).

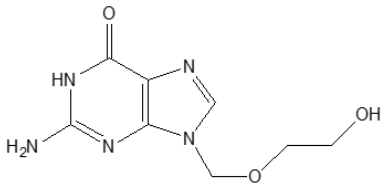
Flow rate: Adjust the flow rate so that the retention time of scopolamine is about 8 minutes.

Selection of column: Proceed with 10 μL of the standard solution according to the above conditions; scopolamine, atropine, and the internal standard are eluted in

this order, and each peak is completely separated.

Packaging and storage Preserve in well-closed containers.

Acyclovir
아시클로버



$C_8H_{11}N_5O_3$: 225.21

2-Amino-1,9-dihydro-9-((2-hydroxyethoxy) methyl)-6H-purin-6-one [*59277-89-3*]

Acyclovir contains NLT 98.0% and NMT 101.0% of acyclovir ($C_8H_{11}N_5O_3$), calculated on the anhydrous basis.

Description Acyclovir occurs as a white crystalline powder.
It is freely soluble in dimethylsulfoxide, slightly soluble in water, and very slightly soluble in ethanol(95).
It dissolves in dilute hydrochloric acid.

Identification (1) Determine the infrared spectra of Acyclovir and acyclovir RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention times of the major peaks obtained from the test solution and the standard solution in the Assay are the same.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Acyclovir in 20 mL of dilute sodium hydroxide TS; the solution is clear and the color is not more intense than the following control solution.
Control solution—To 2.5 mL of Matching Fluid for Color F, add diluted dilute hydrochloric acid (1 in 10) to make 100 mL.

(2) ***Heavy metals***—Proceed with 1.0 g of Acyclovir according to Method 2 under the Heavy Metals and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Use the test solution obtained in the Assay as the test solution. Separately, weigh accurately about 25 mg of guanine RS, dissolve in 50 mL of dilute sodium hydroxide TS, and add the mobile phase to make exactly 100 mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas of guanine of each solution, A_T and A_S, and calculate the amount of guanine by the following equation; it is NMT 0.7%. Determine each peak area from the test solution by the automatic integration method, and calculate the amount of each related substance other than acyclovir and guanine by the percentage peak area method: it is NMT 0.2%. Furthermore, the sum of the amount of each related substance determined by the percentage peak area method and the amount of guanine calculated above is NMT 1.5%.

$$\text{Content (\%) of guanine} = \frac{W_S}{W_T} \times \frac{A_T}{A_S} \times \frac{2}{5}$$

W_S: Amount (mg) of guanine RS taken
W_T: Amount (mg) of Acyclovir taken

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed under the operating conditions in the Assay.

System suitability

System performance: Proceed as directed under the system suitability in the Assay.

Test for required detectability: Pipet 1 mL of the test solution, add the mobile phase to make exactly 100 mL, and use this solution as the system suitability solution. Pipet 1 mL of the system suitability solution and add the mobile phase to make exactly 10 mL. Confirm that the peak area of acyclovir obtained with 10 μL of this solution is equivalent to 7% to 13% of that with 10 mL of the system suitability solution.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of acyclovir is NMT 2.0%.

Time span of measurement: About 8 times the retention time of acyclovir after the solvent peak.

Water NMT 6.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1.0 g).

Assay Weigh accurately about 20 mg each of Aciclovir and aciclovir RS (previously determine the water in the same manner as Aciclovir), dissolve each in 1 mL of dilute sodium hydroxide TS, add the mobile phase to make exactly 20 mL each, and use these solutions as the test solution and the standard solution, respectively. Perform the test with exactly 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of acyclovir in each solution.

$$\text{Amount (mg) of acyclovir } (C_8H_{11}N_5O_3)$$

= Amount (mg) of acyclovir RS, as calculated on the anhydrous basis $\times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 20 °C.

Mobile phase: Dissolve 1.0 g of sodium 1-decanesulfonate and 6.0 g of sodium dihydrogen phosphate dihydrate in 1000 mL of water, and adjust the pH to 3.0 with phosphoric acid. To this solution, add 40 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of acyclovir is about 3 minutes.

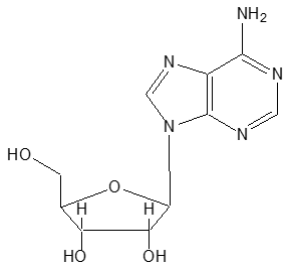
System suitability

System performance: Dissolve 0.1 g of Acyclovir in 5 mL of dilute sodium hydroxide TS, add 2 mL of a solution of guanine in dilute sodium hydroxide TS (1 in 4000), and add the mobile phase to make 100 mL. Proceed with 10 μL of this solution under the above operating conditions; acyclovir and guanine are eluted in this order with the resolution being NLT 17.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of acyclovir is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Adenosine
아데노신



$C_{10}H_{13}N_5O_4$: 267.24

(2*R*,3*R*,4*S*,5*R*)-2-(6-Amino-9*H*-purin-9-yl)-5-(hydroxymethyl)oxolane-3,4-diol [*58-61-7*]

Adenosine contains NLT 99.0% and not more 101.0% of adenosine ($C_{10}H_{13}N_5O_4$), calculated on the dried basis.

Description Adenosine occurs as a colorless crystalline powder and produces adenine and D-ribose by hydrolysis. It is freely soluble in cold water, sparingly soluble in warm water and slightly soluble in ethanol(95).

Identification Determine the infrared spectra of Adenosine and Adenosine RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 233 and 238 ℃.

Optical rotation $[\alpha]_D^{20}$: Between -68° and -72° (after drying, 0.4 g, sodium hydroxide solution (1 in 10), 20 mL, 100 mm).

Purity (1) ***Acidity or alkalinity***—Suspend 1 g of Adenosine in 20 mL of water, shake it for 30 seconds and filter. To 10 mL of the filtrate, add 0.1 mL of Bromocresol purple TS, then add 0.01 mol/L of sodium hydroxide solution until it turns bluish purple; the volume of sodium hydroxide solution consumed is NMT 0.3 mL. To 10 mL of the filtrate, add 0.1 mL of Bromocresol purple TS, then add 0.01 mol/L of hydrochloric acid until it turns yellow; the volume of hydrochloric acid consumed is NMT 0.1 mL.

(2) ***Chloride***—Suspend 0.2 g of Adenosine in 10 mL of water, shake it for 30 seconds, and filter. Use the filtrate as the test solution. Add water to 1.0 mL of 0.0231% sodium chloride solution to make exactly 100 mL, and use this solution as the control solution. Add 1 mL of nitric acid and 1 mL of silver nitrate TS to 10 mL of the test solution and the control solution, respectively, add water to make 40 mL, mix well, and allow to stand for 5 minutes while protected from light. Compare both solutions against a black background; the test solution is not more turbid than the control solution (NMT 0.007%).

(3) ***Sulfate***—Suspend 0.75 g of Adenosine in 15 mL of water, shake it for 30 seconds, and filter. Use the filtrate as the test solution. Add 0.15 mL of 0.01 mol/L sulfuric acid to 15 mL of water and use this solution as the control solution. Add 2 mL of barium chloride TS and 1 mL of 3 mol/L hydrochloric acid to the test solution and the control solution, respectively, add water to make 30 mL, mix well, and allow to stand for 5 minutes; the test solution is not more turbid than the control solution (NMT 0.02%).

(4) ***Ammonia***—Suspend 0.5 g of Adenosine in 10 mL of water. Stir for 30 seconds, pass through a coarse filter. Add water to the filtrate to make 15 mL and use this solution as the test solution. Add water to 0.1 mL of 0.0314% ammonium chloride solution to make exactly 100 mL. To 2.0 mL of this solution, add 13 mL of water and use this solution as the control solution. Add 0.3 mL of Nessler's TS to the test solution and the control solution, respectively, stopper them and allow to stand for about 5 minutes; the yellow color of the test solution is not more intense than that of the control solution (NMT 0.0004%).

(5) ***Heavy metals***—Proceed with 1.0 g of Adenosine

according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(6) ***Related substances***—Weigh accurately about 25 mg of Adenosine, dissolve in the mobile phase to make exactly 25 mL, and use this solution as the test solution. Perform the test with 20 μL of the test solution as directed under the percentage peak area method under the Liquid Chromatography according to the following conditions; the amounts of guanosine, inosine and uridine are NMT 0.1%, respectively, the amount of adenine is NMT 0.2%, and the total amount of substances is NMT 0.5%, all of which are obtained from the test solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of sulfate buffer solution and sodium azide solution (1 in 10000) (60 : 40).

Flow rate: 1.5 mL/min

System suitability

System performance: Weigh 20 mg of adenosine and 20 mg of inosine and dissolve in the mobile phase to make 100 mL. Proceed with 20 μL of this solution under the above operating conditions; the resolution between the peaks of adenosine and inosine is NLT 9.0, and the symmetry factor is NLT 2.5.

System repeatability: Weigh 20 mg of adenosine and 20 mg of inosine and dissolve in the mobile phase to make 100 mL. Repeat the test 5 times with 20 μL each of these solutions under the above operating conditions; the relative standard deviation of the peak area is NMT 2.0%.

Time span of measurement: About 2 times the retention time of the major peak obtained from the test solution.

Sulfate buffer solution—Dissolve 6.8 g of potassium hydrogen sulfate and 3.4 g of tetrabutylammonium hydrogen sulfate in water to make 1000 mL. Adjust the pH to 6.5 with 2 mol/L potassium hydroxide TS.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

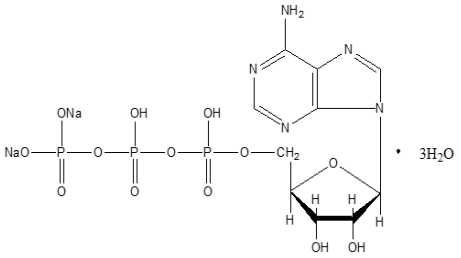
Residue on ignition NMT 0.1%. (1 g).

Assay Weigh accurately about 0.5 g of Adenosine, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 26.724 mg of $C_{10}H_{13}N_5O_4$

Packaging and storage Preserve in tight containers.

Adenosine Disodium Triphosphate Trihydrate
아데노신트리포스페이트이나트륨삼수화물



$C_{10}H_{14}N_5O_{13}P_3Na_2 \cdot 3H_2O$: 605.22

5'-(Tetrahydrogen triphosphate) adenosine disodium salt trihydrate, [*987-65-5, anhydride*]

Adenosine Disodium Triphosphate Trihydrate contains NLT 97.0% of adenosine disodium triphosphate ($C_{10}H_{14}N_5O_{13}P_3Na_2$: 551.14), calculated on the anhydrous basis.

Description Adenosine Disodium Triphosphate Trihydrate occurs as a white crystalline powder, which is odorless and has a slightly acidic taste.
It is freely soluble in water and practically insoluble in ethanol or in ether.

Identification (1) To 3 mL aqueous solution of Adenosine Disodium Triphosphate Trihydrate (3 in 1000), add 0.2 mL of a solution of orcinol in ethanol (1 in 10), add 3 mL of ammonium ferric sulfate solution (1 in 1000), then warm on a steam bath for 10 minutes; the resulting solution exhibits a green color.

(2) An aqueous solution of Adenosine Disodium Triphosphate Trihydrate (1 in 100) responds to the Qualitative Analysis for sodium salt.

(3) An aqueous solution of Adenosine Disodium Triphosphate Trihydrate (1 in 100) responds to the Qualitative Analysis for phosphate.

(4) Determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy with a solution of Adenosine Disodium Triphosphate Trihydrate in 0.1 mol/L phosphate buffer solution (pH 7.0) (1 in 80000); it exhibits the maximum absorption at the wavenumber of about 260 nm. Absorbances at the wavelengths of 250 nm, 260 nm and 280 nm are calculated as follows:

E250/E260 = 0.80 ± 0.2
E280/E260 = 0.15 ± 0.2

pH Dissolve 5 g of Adenosine Disodium Triphosphate Trihydrate in water to make 1000 mL; the pH of this solution is between 2.5 and 3.5.

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g

of Adenosine Disodium Triphosphate Trihydrate in 20 mL of water; the resulting solution is clear and colorless.

(2) ***Heavy metals***—Weigh 1.0 g of Adenosine Disodium Triphosphate Trihydrate and perform the test according to Method 2 as directed under the Heavy Metals. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Perform the test with Adenosine Disodium Triphosphate Trihydrate according to Section (2) as directed under the Assay; the total amount of related substances other than adenosine disodium triphosphate is NMT 3.0%.

$$\text{Amount of related substances (\%)} = \frac{0.671 \times T_1 + 0.855 \times T_2 + T_X}{0.671 \times T_1 + 0.855 \times T_2 + T_3 + T_X}$$

Water Put 50 mL of a mixture of ethylene glycol for water determination and methanol for water determination (3 : 2) in a dried titration flask, add Karl Fischer TS to the extent slightly exceeding, then titrate to the endpoint with water and the standard methanol VS. Next, weigh accurately 0.1 g of Adenosine Disodium Triphosphate Trihydrate, place quickly into a titration flask, add a known excess volume of Karl Fischer TS, and shake well to mix for 30 minutes. Titrate it while shaking; the water content is between 6.0% and 12.0%.

Assay (1) ***Total amount of nucleotides***—Weigh accurately about 0.1 of Adenosine Disodium Triphosphate Trihydrate, dissolve in 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 200 mL. Pipet 5 mL of this solution and add 0.1 mol/mL phosphate buffer solution (pH 7.0) to make exactly 200 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance of this solution, *A*, at wavelength of 259 nm.

$$\text{Total amount (mg) of nucleotides} = \frac{A}{27.94} \times 8000$$

(2) ***Mass ratio of adenosine disodium triphosphate***—Weigh accurately about 0.2 g of Adenosine Disodium Triphosphate Trihydrate, add the mobile phase, dissolve it to make exactly 50 mL. Use this solution as the test solution. Perform the test with 10 μL of the test solution as directed under the Liquid Chromatography according to the following conditions, and calculate the mass ratio of adenosine disodium triphosphate equivalent to the total amount of nucleotides according to the following equation with the peak area T_1 of adenosine monophosphate, the peak area T_2 of adenosine diphosphate, the peak area T_3 of adenosine triphosphate, and the peak area T_X of other related substances.

$$\text{Mass ratio of adenosine disodium triphosphate equivalent to the total amount of nucleotides} = \frac{T_3}{0.671 \times T_1 + 0.855 \times T_2 + T_3 + T_X}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 259 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 5 cm in length, packed with totally porous spherical silica gel of 3 μm in particle diameter, chemically bonded to a weak base ion exchanger.

Column temperature: A constant temperature of about 35 °C.

Mobile phase: Adjust the pH of 0.25 mol/L sodium monohydrogen phosphate TS to 7.0 with 0.25 mol/L potassium dihydrogen phosphate TS.

Flow rate: Adjust the flow rate so that the retention time of adenosine triphosphate is about 10 minutes.

Selection of column: Weigh 40 mg of adenosine monophosphate, 0.1 mg of adenosine 5'-diphosphate sodium and 0.3 g of adenosine disodium triphosphate, respectively, and dissolve in the mobile phase to make 1000 mL. Proceed with 10 μL of this solution under the above operating conditions. At this time, use a column from which adenosine monophosphate, adenosine 5'-diphosphate sodium, adenosine disodium triphosphate are eluted in this order with the resolution between these peaks being NLT 3.

Time span of measurement: About 2 times the retention time of adenosine disodium triphosphate.

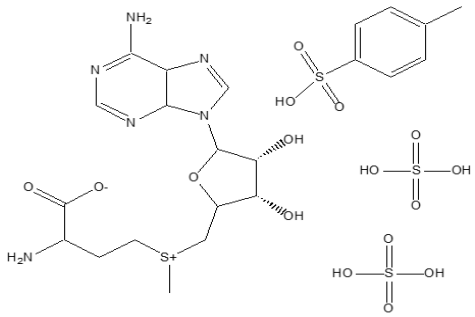
$$\text{Amount (mg) of adenosine disodium triphosphate} = f_T \times f_R$$

f_T: Total amount (mg) of nucleotides obtained from the Procedure (1).

f_R: Mass ratio of adenosine disodium triphosphate obtained from the Procedure (2).

Packaging and storage Preserve in tight containers in a cold place.

S-Adenosyl-L-methionine Sulfate Tosilate
S-아데노실-L-메티오닌황산토실산염



$C_{15}H_{22}N_6O_5S \cdot 2(H_2SO_4) \cdot C_7H_8SO_3$: 766.78

5'-[[(3*S*)-3-Amino-3-carboxypropyl]methylsulfonio]-5'-

deoxy-adenosine disulfate 4-methylbenzenesulfonate, [*97540-22-2*]

S-Adenosyl-L-methionine Sulfate Tosilate contains NLT 49.5% and NMT 54.7% of S-adenosyl-L-methionine ($C_{15}H_{22}N_6O_5S$: 398.44), NLT 24.3% and NMT 26.7% of sulfuric acid (H_2SO_4: 98.08), and NLT 21.3% and NMT 23.5% of p-tosylic acid ($C_7H_7SO_3H$: 172.20).

Method of preparation If there is any possibility of alkyl (methyl, ethyl, isopropyl, etc.) toluenesulfonate esters to be included as impurities in the manufacturing process of *S*-Adenosyl-L-methionine Sulfate Tosilate, precautions must be taken in controlling the starting materials, manufacturing process and intermediates to minimize the residue of impurities in consideration of risk assessment results. If necessary, the manufacturing process may be verified by the test data proving that no quality risk exists in the final drug substance.

Description *S*-Adenosyl-L-methionine Sulfate Tosilate occurs as a white crystalline powder and is water-absorbing.
It is freely soluble in water, and practically insoluble in organic solvents.

Identification (1) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

(2) Weigh 125 mg of *S*-Adenosyl-L-methionine Sulfate Tosilate, dissolve in 5 mL of water, and use this solution as the test solution. Weigh 70 mg of *S*-adenosyl-L-methionine RS and dissolve in 5 mL of water. Separately, dissolve 37 mg of p-tosylic acid RS in 5 mL of water. Use these solutions as the standard solutions. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of *n*-butanol, acetic acid(100) and water (60 : 25 : 15) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet rays; the R*f* value and color of the spots obtained from the test solution and the standard solution are the same.

Purity Dissolve 125 mg of *S*-Adenosyl-L-methionine Sulfate Tosilate in 5 mL of water, and use this solution as the test solution. Weigh 62.5 mg of methylthioadenosine RS, dissolve in water to make 500 mL, and use this solution as the standard solution. Weigh 62.5 mg of homoserine RS, dissolve in water to make 500 mL, and use this solution as the standard solution. Weigh 62.5 mg of adenine RS, dissolve in water to make 500 mL, and use this solution as the standard solution. Weigh 115.5 mg of 2-anmino-4-butyrolactone-hydrobromic acid RS, dissolve in water to make 500 mL, and use this solution as the standard solution. Weigh 62.5 mg of adenosine RS, dissolve in water to make 500.0 mL, and use this solution as the standard solution. With 2 μL each of these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of *n*-butanol, acetic acid(100) and water (60 : 25 : 15) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet rays to identify spots, then spray (methyladenosine, adenine, adenosine) 0.2% methanolic ninhydrin solution, and heat at 110 °C for 10 minutes; the Rf value and color of the spots obtained from the test solution and the standard solution are the same.

Water NMT 2.0% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.5% (1 g).

Assay (1) ***S-adenosyl-L-methionine***—Weigh accurately about 50 mg of S-Adenosyl-L-methionine Sulfate Tosilate, dissolve by adding the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of *S*-adenosyl-L-methionine RS, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Take exactly 5 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas A_T and A_S of *S*-adenosyl-L-methionine for each solution.

Amount (mg) of *S*-adenosyl-L-methionine ($C_{15}H_{22}N_6O_5S$)
= Amount (mg) of *S*-adenosyl-L-methionine RS
× (A_T/ A_S)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 260 nm).

Column: A stainless steel column, 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 5 μm to 10 μm in particle diameter).

Mobile phase A: A mixture of a solution in which formic acid is added to 0.2 mol/L ammonium formate to adjust the pH to 4.0 and methanol (9 : 1).

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 5 μL of each standard solution under the above operating conditions; the number of theoretical plates for *S*-adenosyl-L-methionine is NLT 15000.

System repeatability: Repeat the test 6 times with 5 μL of each standard solution according to the above operating conditions; the relative standard deviation of the peak area for *S*-adenosyl-L-methionine is NMT 2.0%.

(2) ***p-tosylic acid***—Weigh accurately about 250 mg

of *S*-Adenosyl-L-methionine Sulfate Tosilate, transfer to a separatory funnel, dissolve in 10 mL of water, and elute it to a column filled with 50W × 8 (H form, 100 to 200 mesh) of the ion-exchange resin, diatomaceous earth up to about 10 cm in height in a glass column (1 cm in internal diameter, 20 cm in length). Put each 10 mL of water into the separatory funnel, elute three times, and collect the effluent. Add water to the effluent to make exactly to 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of *p*-tosylic acid RS, add water to make 100 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Liquid Chromatography under the same conditions as in the Assay of S-adenosyl-L-methionine, and determine the peak areas, A_T and A_S of each solution.

Amount (mg) of *p*-tosylic acid ($C_7H_7SO_3H$)
= Amount (mg) of *p*-tosylic acid RS$\times \frac{A_T}{A_S} \times \frac{1}{2}$

(3) ***Sulfuric acid***—Take 25.0 mL of the test solution under the Assay of *p*-tosylic acid in (2) and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1mol/L sodium hydroxide VS
= 4.904 mg of H_2SO_4

Packaging and storage Preserve in tight containers.

S-Adenosyl-L-methionine Sulfate Tosilate Tablets
S-아데노실-L-메티오닌황산토실산염 정

S-Adenosyl-L-methionine Sulfate Tosilate Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of *S*-adenosyl-L-methionine ($C_{15}H_{22}N_6O_5S$: 398.44).

Method of preparation Prepare as directed under Tablets, with *S*-Adenosyl-L-methionine Sulfate Tosilate.

Identification (1) ***S-Adenosyl-L-methionine*—**The retention times of the major peaks from the test solution and the standard solution are the same.

(2) ***p-Tosilic acid*—**Weigh an amount of *S*-Adenosyl-L-methionine Sulfate Tosilate Tablets according to the labeled amount, equivalent to about 310 mg of S-adenosyl-L-methionine sulfate tosilate, and transfer to a separatory funnel. Dissolve in a small amount of water and elute the column prepared by packing a glass column with an internal diameter of 1 cm and a length of 20 cm with ion exchange resin diatomaceous earth 50W×8 (H form, 100 to 200 mesh) up to about 10 cm in height. Elute the separatory funnel with a small amount of water to obtain 50 mL of eluate and use the solution as the test solution. Separately, dissolve about 60 mg of *p*-tosilic acid RS to make 50 mL and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Liquid Chromatography according to the operating conditions described in the Assay under *S*-Adenosyl-L-Methionine; the retention times of the major peaks from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately 20 tablets of *S*-Adenosyl-L-methionine Sulfate Tosilate Tablets and make into powder. Weigh accurately an amount of the powder, equivalent to 50 mg of *S*-adenosyl-L-methionine ($C_{15}H_{22}N_6O_5S$), add the mobile phase to make exactly 100 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately 10 mg of *S*-adenosyl-L-methionine RS, add the mobile phase to make exactly 20 mL, and use this solution as the standard solution. Perform the test with each 5 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak areas, A_T and A_S, of *S*-adenosyl-L-methionine for each solution.

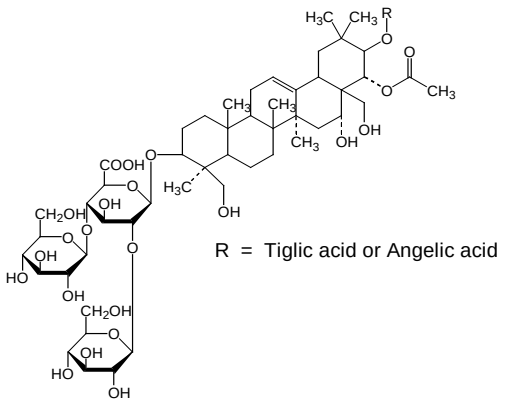
Amount (mg) of *S*-adenosyl-L-methionine ($C_{15}H_{22}N_6O_5S$)
= Amount (mg) of *S*-adenosyl-L-methionine RS
× (A_T / A_S) × 5

Operating conditions

For the detector, column, mobile phase, flow rate, and system suitability, proceed as directed under the Assay (1) under *S*-Adenosyl-L-Methione Sulfate Tosilate.

Packaging and storage Preserve in tight containers.

Aescin
무정형에스신



$C_{55}H_{86}O_{24}\cdot 2H_2O$: 1167.29
3-(4-*O*-β-glucopyranosyl-2-*O*-β-*D*-xylopyranosyl-β-*D*-glucopyranuronoside), 3-hydroxy-2-methylbutyrate escigenin acetate, [*6805-41-0*]

Aescin is prepared from crystalline aescin, a triterpene glycoside mixture isolated from *Aesculus hippocastanum* (horse chestnuts), by a special process, and it contains NLT 97.0% and NMT 100.0% of aescin ($C_{55}H_{86}O_{24}$: 1131.26), calculated on the anhydrous basis.

Description Aescin occurs as an amorphous white powder and has a pungent bitter taste.
The X-ray diffraction pattern of the amorphous form of Aescin does not exhibit a crystal lattice structure in contrast to the crystalline aescin.
It is freely soluble in methanol or in water, soluble in ethanol and practically insoluble in acetone, in ether, in chloroform or in petroleum ether.

Identification Dissolve 0.1 g of Aescin in methanol to make 10 mL and use this solution as the test solution. Separately, dissolve 0.1 g of aescin RS in methanol to make 10 mL and use this solution as the standard solution. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, propanol, and water (9 : 7 : 4) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray a solution of 20% antimony trichloride in chloroform on the plate and heat it at 105 ℃ for 15 minutes; the R_f values and color of the spots obtained from the test and standard solutions are the same.

Melting point Between 223 and 226 °C.

Optical rotation $[\alpha]_D^{20}$: Between -26° and -28° (0.5 g, calculated on the anhydrous basis, methanol, 10 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—To 0.2 g of Aescin, add 10 mL of water and stir at 20 ℃ for 20 minutes; the resulting solution is clear. Immediately, transfer this solution into a test tube and allow it to stand in a thermostat at 20 ± 1 ℃; the resulting solution remains clear for at least 60 minutes.

(2) ***Heavy metals***—Proceed with 2.0 g of Aescin as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

Water NMT 3.5%.

Residue on ignition NMT 0.1% (2 g).

Assay Weigh accurately about 0.325 g of Aescin, dissolve in 15 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 113.7 mg of $C_{54}H_{84}O_{23}\cdot 2H_2O$

Packaging and storage Preserve in well-closed containers.

Afloqualone Tablets
아플로쿠알론 정

Afloqualone Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of afloqualone ($C_{16}H_{14}FN_3O$: 283.30).

Method of preparation Prepare as directed under Tablets, with Afloqualone.

Identification (1) Weigh an amount of Afloqualone Tablets, equivalent to 10 mg of afloqualone, according to the labeled amount. Add 10 mL of anhydrous ethanol, shake to mix, dissolve, and filter. To 2 mL of the filtrate, add 1 mL of dilute hydrochloric acid and 4 mL of water; the solution responds to the Qualitative Analysis for primary aromatic amine.

(2) Weigh an amount of Afloqualone Tablets equivalent to 10 mg of afloqualone, add 10 mL of anhydrous ethanol, shake well to mix, and filter. Examine the filtrate under ultraviolet light (360 nm); the solution exhibits a blue fluorescence.

(3) ***Purity***—Perform the test as directed under the Thin Layer Chromatography for the related substances; the R_f values of the spots obtained from the test solution and the standard solution D are the same.

Purity ***Related substances*—**Perform the test while protected from light. Weigh an amount of Afloqualone Tablets equivalent to 50 mg of afloqualone, and add 5.0 mL of a mixture of anhydrous ethanol and chloroform (1 : 1). After shaking well to mix, centrifuge at 3000 rpm for 10 minutes, and use the clear supernatant as the test solution. Separately, weigh accurately about 1.0 mg, 2.0 mg and 3.0 mg of afloqualone RS, respectively, dissolve in a mixture of anhydrous ethanol and chloroform (1 : 1) to make exactly 100 mL, and use these solutions as the standard solutions A, B and C. Again, weigh 50 mg of afloqualone RS, dissolve in 5.0 mL of a mixture of anhydrous ethanol and chloroform (1 : 1), and use this solution as the standard solution D. Spot 10 μL each of the test solution and the standard solutions A, B, C and D on a thin-layer chromatographic plate made using silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of hexane and ethyl acetate (1 : 1) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots appearing in the test solution are a single spot, or

the total amount of spots is NMT 0.3% for afloqualone as compared to those obtained from the standard solutions A, B and C, even if other spots appear.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the contents of NLT 20 tablets of Azathioprine Tablets, and powder. Weigh accurately an amount equivalent to about 25 mg of afloqualone ($C_{16}H_{14}FN_3O$), and add methanol to make exactly 100 mL. Pipet 5 mL of this solution, add 5 mL of the internal standard solution, add methanol to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg of afloqualone RS, and add methanol to make 100 mL. Pipet 5 mL of this solution, add 5 mL of the internal standard solution, add methanol to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each internal standard and afloqualone, and calculate the ratio of peak area, Q_T and Q_S, of afloqualone to the peak area of the internal standard in each solution.

$$\text{Amount (mg) of afloqualone } (C_{16}H_{14}FN_3O) = \text{Amount (mg) of afloqualone RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of anhydrous caffeine in methanol (1 in 4000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with porous silica gel for liquid chromatography (10 μm in particle diameter).

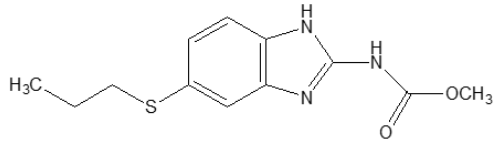
Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of methanol and water (45 : 55).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in light-resistant, tight containers.

Albendazole
알벤다졸



$C_{12}H_{15}N_3O_2S$: 265.33

Methyl *N*-(6-propylsulfanyl-1*H*-benzimidazol-2-yl)carbamate [*54965-21-8*]

Albendazole, when dried, contains NLT 98.0% and NMT 102.0% of Albendazole.

Description Albendazole occurs as a white to pale yellow powder.

It is freely soluble in anhydrous formic acid, very slightly soluble in ether or methylene chloride and practically insoluble in water or in ethanol(95).

Identification (1) Perform the test as directed under the testing for related substances; the principal spots from the test solution and the standard solution show the same R_f value.

(2) Determine the infrared spectra of Albendazole and albendazole RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity ***Related substances***—Dissolve 50 mg of Albendazole in 3 mL of acetic acid(100), add acetic acid(100) to make 5 mL, and use this solution as the test solution. Separately, weigh accurately a suitable portion of albendazole RS, dissolve in the acetic acid(100) so that the solution contains 5 mg of albendazole per mL, and use this solution as the standard solution (1). Pipet 1.0 mL of the standard solution, dilute with acetic acid(100) to make exactly 100 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solutions (1) and (2) on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of chloroform, acetic acid(100) and ether (60 : 10 : 10) as the developing solvent to a distance of about 15 cm. and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); any spots other than the principal spot from the test solution are not larger and more intense than the principal spot from the standard solution (2). (NMT 0.5%)

Loss on drying NMT 0.5% (105 ℃, 4 hours).

Residue on ignition NMT 0.2% (1.0 g).

Assay Weigh accurately about 0.25 g of Albendazole, previously dried, and dissolve in 100 mL of acetic acid(100), and warm if necessary. After cooling, add 1 drop of solvent blue 19 in acetic acid(100) (1 in 200), and titrate with 0.1 mol/L perchloric acid VS. The endpoint of the titration is when the solution exhibits a purple color. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS

= 26.533 mg of $C_{12}H_{15}N_3O_2S$

Packaging and storage Preserve in well-closed containers.

Albumin Tannate
알부민탄닌산염

Tannarubin

Albumin Tannate is a compound of tannic acid and protein.

The label states the origin of the protein of Albumin Tannate.

Description Albumin Tannate occurs as a pale brown powder. It is odorless or has a faint, characteristic odor.
It is practically insoluble in water or ethanol(95).
It dissolves in sodium hydroxide TS with turbidity.

Identification (1) To 0.1 g of Albumin Tannate, add 10 mL of ethanol(95), and heat on a steam bath for 3 minutes while shaking. After cooling, filter and add 1 drop of iron(III) chloride TS to 5 mL of the filtrate; the solution exhibits a bluish purple to black blue color. And allow to stand; blackish blue precipitates are produced.

(2) To 0.1 g of Albumin Tannate, add 5 mL of nitric acid; an orange yellow color develops.

Purity (1) ***Acid***—To 1.0 g of Albumin Tannate, add 50 mL of water, shake for 5 minutes, and filter. To 25 mL of the filtrate, add 1.0 mL of 0.1 mol/L sodium hydroxide TS and 2 drops of phenolphthalein TS; a red color develops.

(2) ***Fats***—To 2.0 g of Albumin Tannate, add 20 mL of petroleum benzine, shake vigorously for 15 minutes, and filter. Evaporate 10 mL of the filtrate on a steam bath; the residue is NMT 50 mg.

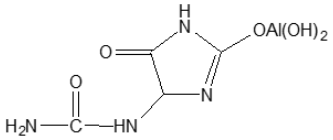
Loss on drying NMT 6.0% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 1.0% (0.5 g).

Digestive power To 1.00 g of Albumin Tannate, add 0.25 g of saccharated pepsin and 100 mL of water, shake well to mix, and allow to stand for 20 minutes at 40 ± 1 ºC on a steam bath. Add 1.0 mL of dilute hydrochloric acid, shake to mix, and allow to stand for 3 hours at 40 ± 1 ºC on a steam bath. Cool rapidly to ordinary temperature and filter. Wash the residue with 10 mL of water three times and dry in a desiccator (silica gel) for 18 hours and then dry at 105 ºC for 5 hours; the amount is 0.50 g to 0.58 g.

Packaging and storage Preserve in light-resistant, tight containers.

Aldioxa
알디옥사



Dihydroxialuminum Allantoinate $C_4H_7AlN_4O_5$: 218.10
Aluminium hydroxide 4-(carbamoylamino)-5-oxo-4,5-dihydro-1*H*-imidazol-2-olate (1:2:1) [*5579-81-7*]

Aldioxa is a condensation product of allantoin and aluminum hydroxide.

Aldioxa, when dried, contains NLT 65.3% and NMT 74.3% of allantoin ($C_4H_6N_4O_3$: 158.12) and NLT 11.1% and NMT 13.0% of aluminum (Al: 26.98).

Description Aldioxa occurs as a white powder. It is odorless and tasteless.
It is practically insoluble in water, ethanol(95) or ether.
It dissolves in dilute hydrochloric acid or dilute nitric acid.

Melting point—About 230 ℃ (with decomposition).

Identification (1) To 0.2 g of Aldioxa, add 10 mL of dilute hydrochloric acid, boil for 5 minutes, and add 10 mL of phenylhydrazinium hydrochloride (1 in 100). After cooling, add 0.5 mL of potassium hexacyanoferrate(III), mix well, add 1 mL of hydrochloric acid, and shake well to mix; the resulting solution exhibits a red color.

(2) To 0.2 g of Aldioxa, add 10 mL of dilute hydrochloric acid, dissolve by warming, and cool; the resulting solution responds to the Qualitative Analysis for aluminum salt.

Purity (1) ***Chloride***—To 0.01 g of Aldioxa, add 6 mL of dilute nitric acid, and dissolve by boiling for 5 minutes while shaking to mix. After cooling, add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid (NMT 0.142%).

(2) ***Nitrate***—To 0.10 g of Aldioxa, carefully add 5 mL of water and 5 mL of sulfuric acid, and dissolve by shaking well to mix. After cooling, superimpose 2 mL of iron(II) sulfate TS; no brown band appears at the interface.

(3) ***Sulfate***—To 0.20 g of Aldioxa, add 6 mL of dilute hydrochloric acid, and dissolve by boiling for 5 minutes while shaking to mix. After cooling, add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.240%).

(4) ***Heavy metals***—To 1.0 g of Aldioxa, add 3 mL of hydrochloric acid and 3 mL of water, heat gently to boiling while shaking to mix, and evaporate to dryness on a water bath. Add 30 mL of water to the residue, warm while shaking to mix, cool, and filter. To the filtrate, add

2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by evaporating to dryness 3 mL of hydrochloric acid and 3 mL of water, and adding 2.0 mL of lead standard solution, 2 mL of dilute acetic acid and water to make 50 mL (NMT 20 ppm).

(5) ***Arsenic***—Proceed with 1.0 g of Aldioxa according to Method 2 and perform the test (NMT 2 ppm).

Loss on drying NMT 4.0% (1 g, 105 ℃, 2 hours).

Assay (1) ***Allantoin*—**Weigh accurately 0.1 g of Aldioxa, previously dried, dissolve in 50 mL of dilute sulfuric acid by heating, cool, and add water to make exactly 100 mL. Pipet 10 mL of this solution, and perform the test according to the Nitrogen Determination.

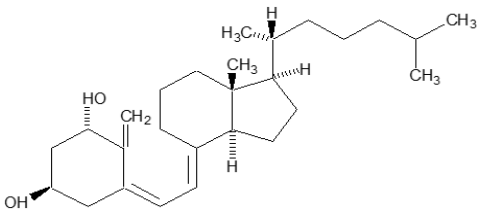
Each mL of 0.005 mol/L sulfuric acid VS
= 0.39529 mg of $C_4H_6N_4O_3$

(2) ***Aluminum*—**Weigh accurately 0.2 g of Aldioxa, previously dried, dissolve in 50 mL of dilute hydrochloric acid by heating gently, cool, and add dilute hydrochloric acid to make exactly 100 mL. Pipet 4 mL of this solution, add water to make exactly 25 mL, and use this solution as the test solution. Separately, pipet an appropriate amount of aluminum standard stock solution, dilute with water to make a solution containing 16.0 μg to 64.0 μg of aluminum (Al: 26.98), and use this solution as the standard solution. Determine the absorbances of the test solution and the standard solution as directed under the Atomic Absorption Spectroscopy according to the following conditions, and calculate the content of aluminum in the test solution using the calibration curve obtained from the absorbances of the standard solution.

Gas: Nitrous oxide–acetylene
Lamp: Aluminum hollow cathode lamp
Wavelength: 309.2 nm.

Packaging and storage Preserve in well-closed containers.

Alfacalcidol
알파칼시돌



$C_{27}H_{44}O_2$: 400.64

(1*R*,3*S*,5*Z*)-5-[(2*E*)-2-[(1*R*,3a*S*,7a*R*)-7a-Methyl-1-[(2*R*)-6-methylheptan-2-yl]-2,3,3a,5,6,7-hexa-hydro-1*H*-inden-4-ylidene]ethylidene]-4-methylidene-cyclohexane-1,3-diol [*41294-56-8*]

Alfacalcidol contains NLT 97.0% and NMT 102.0% of Alfacalcidol ($C_{27}H_{44}O_2$).

Description Alfacalcidol occurs as white crystals.
It is freely soluble in ethanol(95), soluble in fatty oils and practically insoluble in water.
It is easily affected by air, heat or light.
It reversibly isomerizes to pre-alfacalcidol in solution, and both compounds contribute to the isomerization activity.

Identification (1) Determine the infrared spectra of Alfacalcidol and alfacalcidol RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Purity ***Related substances***—Calculate the amount of related substances other than pre-alfacalcidol eluted within twice the retention time of alfacalcidol with the peak areas obtained from the test solution by the percentage peak area method under the Assay; the amount of each related substance is NMT 0.5%, and the total area of these peaks is NMT 1.0%. However, exclude any peaks smaller than 0.1%.

Assay Perform the test as rapidly as possible while protected from light and air. Weigh accurately about 1.0 mg of Alfacalcidol, dissolve in the mobile phase to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately 1.0 mg of alfacalcidol RS, dissolve in the mobile phase without heating to make exactly 10 mL, and use this solution as the standard solution (1). To 1.0 mL of the standard solution (1), add the mobile phase to make exactly 100 mL, and use this solution as the standard solution (2). Heat 2 ml of the standard solution (1) on a steam bath at 80 ºC with a reflux condenser for 2 hours, cool, and use this solution as the standard solution (3). Perform the test with 100 μL each of the test solution and the standard solutions (1) and (2) as directed under the Liquid Chromatography according to the following conditions and determine the peak area, A_T and A_S, of alfacalcidol.

Amount (mg) of alfacalcidol ($C_{27}H_{44}O_2$)
$= \text{Amount (mg) of alfacalcidol RS} \times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 265 nm).

Column: A stainless steel column about 4 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm

in particle diameter).

Mobile phase: A mixture of acetonitrile, water and 9 mol/L ammonia water (800 : 200 : 1).

Flow rate: 2.0 mL/min

System suitability

System performance: Perform the test with 100 μL of the standard solution (3) according to the above operating conditions; the relative retention time of prealfacalcidol to Alfacalcidol is about 1.3 with the resolution being NLT 4.0.

System repeatability: Perform the test six times with 100 μL of the standard solution (3) according to the above operating conditions; the relative standard deviation of the peak area of alfacalcidol is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers at 2 ºC to 8 ºC under nitrogen atmosphere. The contents of an opened container are to be used immediately.

Alfacalcidol capsules
알파칼시돌 캡슐

Alfacalcidol Capsules contain NLT 90.0% and NMT 130.0% of the labeled amount of alfacalcidol ($C_{27}H_{44}O_2$: 400.64).

Method of preparation Prepare as directed under Capsules, with Alfacalcidol.

Identification The retention time of the major peak obtained from the test solution and the standard solution under the Assay and the ultraviolet absorption spectrum between 200 and 400 nm are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the content of NLT 20 Alfacalcidol Capsules. Weigh accurately an amount equivalent to about 10 μg of alfacalcidol ($C_{27}H_{44}O_2$), transfer into a 10-mL volumetric flask, add ethanol to make exactly 10 mL and use this solution as the test solution. Separately, weigh accurately about 5.0 mg of alfacalcidol RS, and dissolve in ethanol to make 50 mL. Pipet 1.0 mL of this solution, transfer into a 100-mL volumetric flask, add ethanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 30 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas or heights, A_T and A_S, of each solution.

Amount (mg) alfacalcidol ($C_{27}H_{44}O_2$)
= Amount (mg) alfacalcidol RS
× A_T / A_S × 1 / 500 × 1000

Operating conditions

Detector: An ultraviolet absorption photometer (264 nm). However, use a photo-diode array detector (200 nm to 400 nm) when performing the Identification.

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 ℃.

Sample temperature: A constant temperature of about 5 ℃.

Mobile phase: A mixture of water, acetonitrile and ammonia water(28) (200 : 800 : 1).

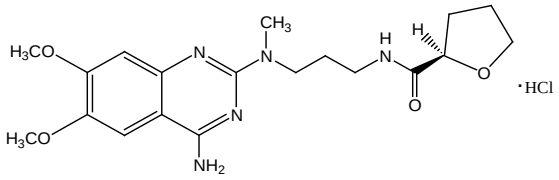
Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 30 μL of the standard solution according to the above conditions; the relative standard deviation of the peak areas of alfacalcidol is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Alfuzosin Hydrochloride
알푸조신염산염



and enantiomer

$C_{19}H_{28}ClN_5O_4$: 425.91

N-{3-[(4-Amino-6,7-dimethoxy-quinazolin-2-yl)methylamino]propyl}tetrahydrofuran-2-carboxamide hydrochloride [*81403-68-1*]

Alfuzosin Hydrochloride contains NLT 98.5% and NMT 101.0% of Alfuzosin Hydrochloride ($C_{19}H_{28}ClN_5O_4$), calculated on the anhydrous basis.

Description Alfuzosin Hydrochloride occurs as a white crystalline powder.
It is freely soluble in water, sparingly solution in ethanol(95) and practically insoluble in dichloromethane.
It is hygroscopic.

Identification (1) Determine the infrared spectra of Alfuzosin Hydrochloride and alfuzosin hydrochloride RS as directed in potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve 0.5 g of Alfuzosin Hydrochloride in 25

mL of water, take 1 mL of the solution, and put 1 mL of water; the resulting solution responds to the Qualitative Analysis (2) for chlorides.

Optical rotation $[\alpha]_D^{20}$: Between -0.10° and + 0.10° (0.2 g calculated on the anhydrous basis, water, 10 mL, 100 mm).

pH Dissolve 0.5 g of Alfuzosin Hydrochloride in water free from carbon dioxide; the pH of the solution ranges between 4.0 and 5.5.

Purity ***Related substances***—Weigh accurately 20.0 mg of Alfuzosin Hydrochloride, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Pipet 1.0 mL of the test solution and add the mobile phase to make exactly 50 mL. Pipet 5.0 mL of this solution, add the mobile phase to make exactly 20 mL, and use this solution as the standard solution (1). Separately, weigh accurately 5 mg of alfuzosin related substance I {*N*-[3-[(4-Amino-6,7-dimethoxyquinolin-2-yl)(methyl)amino] propyl]furan-2-carboxamide} RS, and dissolve in the mobile phase to make 25 mL. Pipet 1 mL of this solution, add 1 mL of the test solution, and then add the mobile phase to make exactly 100 mL. Use this solution as the standard solution (2). Perform the test with exactly 20 μL each of the test and the standard solution (2) as directed under the Liquid Chromatography according to the following conditions and determine each peak area by the automatic integration method; the peak area other than the major peak from the test solution is not greater than 0.6 times the area of the major peak from the standard solution (1) (0.3%); the total area of all peaks other than the major peak is not greater than the area of the major peak from the standard solution (1) (0.5%). Disregard any peak with an area less than 0.025 times the area of the major peak from the standard solution (1).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of sodium perchlorate, acetonitrile and tetrahydrofuran (80 : 20 : 1).

Flow rate: 1.5 mL/min

System suitability

System performance: Perform the test with 20 μL of the standard solution (2) according to the above conditions, and adjust the sensitivity so that the height of the two peaks is NLT 50% of the full scale; the resolution between alfuzosin and alfuzosin related substance I is NLT 3.0.

Sodium perchlorate solution—Mix 5 mL of perchloric acid and 900 mL of water, add 8.5 w/v% sodium hydroxide solution to adjust pH to 3.5, and add water to make 1000 mL.

Water NMT 0.5**%** (0.5 g, volumetric titration, direct titration).

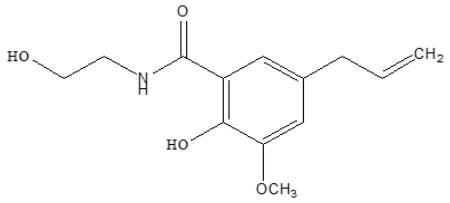
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Alfuzosin Hydrochloride, dissolve in the mixture of 40 mL of acetic acid(100) and 40 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

0.1 mL of 1 mol/L perchloric acid VS
= 42.59 mg of $C_{19}H_{28}ClN_5O_4$

Packaging and storage Preserve in light-resistant, tight containers.

Alibendol
알리벤돌



$C_{13}H_{17}NO_4$: 251.28

2-Hydroxy-*N*-(2-hydroxyethyl)-3-methoxy-5-(2-propenyl)benzamide; 5-Allyl-2-hydroxy-*N*-(2-hydroxyethyl)-*m*-anisamide, [*26750-81-2*]

Alibendol, when dried, contains NLT 98.0% and NMT 101.0% of alibendol ($C_{13}H_{17}NO_4$: 251.28).

Description Alibendol occurs as a white powder.
It is freely soluble in chloroform, alcohol, acetone and sparingly soluble in water.

Melting point—Between 98.5 and 101.5 °C.

Identification (1) Weigh 5 mg of Alibendol, dissolve in 5 mL of ethanol, and add 0.1 mL of 10% ferric chloride solution; the color of the solution turns blue.

(2) Weigh 20 mg of Alibendol, dissolve in 20 mL of ethanol, add 2 mL of a solution of 20% *ρ*-tosylate in ethanol, and allow it to stand on a steam bath at 60 °C for 10 minutes; the resulting solution exhibits a blue fluorescence.

(3) Weigh 0.1 g of Alibendol, dissolve in ethanol to make 10 mL, and use this solution as the test solution. Weigh 0.1 g of alibendol RS, dissolve in ethanol to make 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution

and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Develop the plate with a mixture of toluene, acetone and acetic acid(100) (9 : 1 : 1) as the developing solvent, and air-dry the plate. Examine the plate under iodine vapor and ultraviolet light (main wavelength: 254 nm); the spot of the test solution exhibits an Rf value and color corresponding to that of the standard solution.

(4) Determine the infrared spectra of Alibendol and alibendol RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Absorbance $E_{1cm}^{1\%}$(315 nm): Between 150 and 158 (10 mg, anhydrous ethanol, 2000 mL).

Purity (1) ***Clarity and color of solution***—Take 1 g of Alibendol, and dissolve in 10 mL of ethanol and 10 mL of acetone; the solution is colorless to pale yellow and clear.

(2) ***Ethanolamine***—Transfer 0.1 g of Alibendol to a test tube, add 0.1 mL of ethanol, 2 mL of nitromethane and 2 mL of a solution of 0.05% *ρ*-dimethylaminocinnamaldehyde in nitromethane, allow it to stand in a boiling water bath for 25 minutes, cool, and add nitromethane to make 10 mL. Allow it to stand overnight, and use this solution as the test solution. Separately, take 0.1 mL of a solution of 0.1% ethanolamine in ethanol, proceed in the same manner as in the preparation of the test solution, and use this solution as the control solution. Compare the color of the test solution and the control solution; the color of the test solution is not more intense than the color of the control solution (NMT 0.1%).

(3) ***Related substances***—Weigh 0.1 g of Alibendol, dissolve in ethanol to make 10 mL, and use this solution as the test solution. Weigh 0.1 g of alibendol RS, dissolve in ethanol to make 10 mL, take 1.0 mL of this solution, and add ethanol to make 100 mL. Use this solution as the standard solution. Perform the test as directed under the Thin Layer Chromatography in the Identification; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution (NMT 1.0%).

(4) ***Heavy metals***—Proceed with 1.0 g of Alibendol according to Method 3 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(5) ***Nitrogen***—Weigh accurately about 0.5 g of Alibendol, and perform the test according to Nitrogen Determination (between 5.4% and 5.7%).

Loss on drying NMT 1.0% (0.5 g, in vacuum, 60 ℃, 3 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.15 g of Alibendol, dissolve in 100 mL of methanol, and titrate potentiometrically with a solution of 0.1 mol/L potassium hydroxide in methanol. Perform a blank test in the same manner and make any necessary correction.

Each mL of a solution of 0.1 mol/L potassium hydroxide in methanol
= 25.130 mg of $C_{13}H_{17}NO_4$

Packaging and storage Preserve in well-closed containers.

Alibendol Tablets
알리벤돌 정

Alibendol Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of alibendol ($C_{13}H_{17}NO_4$: 251.28).

Method of preparation Prepare as directed under Tablets, with Alibendol.

Identification (1) Take 1 tablet of Alibendol Tablets, dissolve in 10 mL of ethanol(95), and filter. To 2 mL of this filtrate, add 0.1 mL of 10% iron(III) chloride solution; the color of the solution turns blue. Separately, add 2 mL of 20% *ρ*-tosylic acid-ethanol solution to 2 mL of the above filtrate, and allow it to stand on a steam bath at 60 °C for 10 minutes; the resulting solution exhibits a blue fluorescence.

(2) Weigh an amount of Alibendol Tablets, equivalent to 0.1 g of alibendol, according to the labeled amount, add ethanol(95), dissolve to make 10 mL, and filter. Use the filtrate as the test solution. Weigh 0.1 g of alibendol RS, dissolve in ethanol(95), and make 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made using silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, acetic acid(100) and acetone (9 : 4 : 1) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the colors and the Rf values obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 tablet of Alibendol Tablets at 100 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take and filter the dissolved solution 45 minutes after starting the test, and use this solution as the test solution. Separately, weigh accurately about 11 mg of alibendol RS, add water to make exactly 100 mL, and use this solution as the standard solution. Pipet 10 μL each of the test solution and the standard

solution, perform the test as directed under the Liquid Chromatography, and determine the peak areas of alibendol, A_T and A_S, of each solution. Meets the requirements if the amount dissolved of Alibendol Tablets in 45 minutes is NLT 80%.

Amount dissolved (%) of the labeled amount of alibendol ($C_{13}H_{17}NO_4$)

$$= W_S \times (A_T / A_S) \times (1 / C) \times 900$$

*W*s: Amount (mg) of alibendol RS

C: Labeled amount (mg) of alibendol ($C_{13}H_{17}NO_4$) per tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 316 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of 0.05 mol/L acetate buffer solution (pH 4.0) and methanol (1 : 1).

Flow rate: 1 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak areas of alibendol is NMT 1.0%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the contents of NLT 20 tablets of Alibendol Tablets, and powder. Weigh accurately an amount equivalent to about 100 mg of alibendol ($C_{13}H_{17}NO_4$), add the mobile phase, sonicate for 15 minutes, and add the mobile phase to make exactly 100 mL. Filter this solution, take accurately 2 mL of the filtrate, add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 40 mg of alibendol RS, and dissolve in the mobile phase to make exactly 100 mL. Pipet 10 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Pipet 10 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography, and determine the peak areas, A_T and A_S, of the test solution and the standard solution.

Amount (mg) of alibendol ($C_{13}H_{17}NO_4$)

$$= \text{Amount (mg) of alibendol RS} \times (A_T / A_S)$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 316 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 150 mm in length with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of 0.05 mol/L sodium acetate buffer solution (pH 4.0) and methanol (1 : 1).

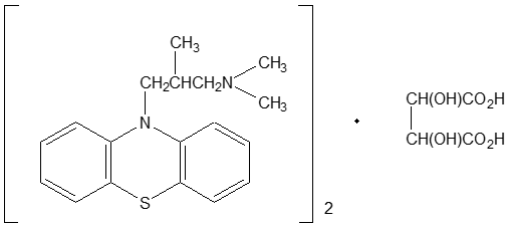
Flow rate: 1 mL/min

System suitability

System repeatability: Perform the test 6 times according to the above conditions with 10 μL of the test solution; the relative standard deviation of the peak areas of alibendol is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Alimemazine Tartrate
알리메마진타르타르산염



Alimemazine Tartrate $(C_{18}H_{22}N_2S)_2 \cdot C_4H_6O_6$: 746.98

bis-(N,N,2-Trimethyl-3-phenothiazin-10-yl)propan-1-amine (2R,3R)-2,3-dihydroxybutanedioate [*4330-99-8*]

Alimemazine Tartrate, when dried, contains NLT 98.0% and NMT 101.0% of alimemazine tartrate [$(C_{18}H_{22}N_2S)_2 \cdot C_4H_6O_6$].

Description Alimemazine Tartrate occurs as a white powder. It is odorless and has a bitter taste.
It is freely soluble in water or acetic acid(100), sparingly soluble in ethanol(95), and practically insoluble in ether.
Dissolve 1.0 g of Alimemazine Tartrate in 50 mL of water; the pH of this solution is between 5.0 and 6.5.
It is gradually colored by light.

Identification (1) To 2 mL of an aqueous solution of Alimemazine Tartrate (1 in 100), add 1 drop of iron(III) chloride TS; the resulting solution exhibits a reddish brown color, and immediately a yellow precipitate forms.

(2) Dissolve 1 g of Alimemazine Tartrate in 5 mL of water, add 3 mL of sodium hydroxide TS, and extract with two 10-mL portions of ether. [Use the water layer for the Identification (4)]. Combine the ether extracts, add 3 g of anhydrous sodium sulfate, shake to mix, and filter. Evaporate the ether by passing air through the filtrate, and dry the residue in vacuum in a desiccator (phosphorus pentoxide) for 16 hours; the melting point is between 66 and 70 °C.

(3) Determine the absorption spectra of solutions of

Alimemazine Tartrate and alimemazine tartrate RS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Neutralize the water layer obtained from (2) with dilute acetic acid; this solution responds to the Qualitative Analysis (1) and (2) for tartrate.

Melting point Between 159 and 163 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Alimemazine Tartrate in 20 mL of water; the resulting solution is colorless and clear.

(2) ***Heavy metals*—**Proceed with 1.0 g of Alimemazine Tartrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Alimemazine Tartrate according to Method 3 and perform the test. Use a solution of magnesium nitrate in ethanol(95) (1 in 5) (NMT 2 ppm).

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

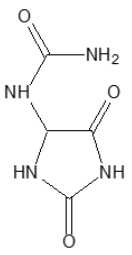
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.8 g of Alimemazine Tartrate, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 mL of 1-naphtholbenzein TS). However, the endpoint of the titration is when this solution changes from red through brown to greenish brown. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 37.349 mg of $(C_{18}H_{22}N_2S)_2 \cdot C_4H_6O_6$

Packaging and storage Preserve in light-resistant, tight containers.

Allantoin
알란토인



$C_4H_6N_4O_3$: 158.12

(2,5-Dioxoimidazolidin-4-yl)urea [*97-59-6*]

Allantoin, when dried, contains NLT 98.5% and NMT 101.0% of allantoin ($C_4H_6N_4O_3$).

Description Allantoin occurs as a white or almost white, crystalline powder.

It is slightly soluble in water and very slightly soluble in ethanol(95).

It dissolves in sodium hydroxide TS.

Melting point—About 225 ℃ (with decomposition).

Identification (1) Dissolve about 20 mg of Allantoin in a mixture of 1 mL of 2 mol/L sodium hydroxide TS and 1 mL of water, heat to boiling, cool, add 1 mL of 2 mol/L hydrochloric acid, and mix. To 0.1 mL of this solution, add 0.1 mL of potassium bromide (1 in 10), 0.1 mL of resorcinol solution (1 in 50), 3 mL of sulfuric acid, and heat on a steam bath for 5 to 10 minutes; the resulting solution exhibits a dark blue color. After cooling, add 10 mL of water; the color turns red.

(2) Determine the infrared spectra of Allantoin and allantoin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) The R_f values of the principal spots obtained from the test solution (2) and from the standard solution (1) are the same.

Optical rotation $[\alpha]_D^{20}$: Between -0.10° and +0.10° (0.2 g, water, 20 mL, 100 mm).

Purity (1) ***Acidity or alkalinity***—Dissolve 50 mg of Allantoin in 10 mL of water, add 0.1 mL of methyl red TS and 0.2 mL of 0.01 mol/L sodium hydroxide TS; the resulting solution exhibits a yellow color. To this solution, add 0.4 mL of 0.01 mol/L hydrochloric acid TS; the color turns red.

(2) ***Potassium permanganate reducing substances***—To 1.0 g of Allantoin, add 10 mL of water, shake to mix for 2 minutes, and filter. To the filtrate, add 1.5 mL of potassium permanganate TS; the resulting solution exhibits a violet color for NLT 10 minutes.

(3) ***Related substances***—Weigh accurately 0.10 g of Allantoin, and dissolve in 5 mL of water by heating, cool, add methanol to make exactly 10 mL, and use this solution as the test solution (1). To 1 mL of the test solution (1), add a mixture of methanol and water (1 : 1) to make exactly 10 mL, and use this solution as the test solution (2). Separately, weigh accurately 10 mg of allantoin RS, dissolve in a mixture of methanol and water (1 : 1) to make exactly 10 mL, and use this solution as the standard solution (1). Weigh accurately 10 mg of urea RS, and dissolve in water to make exactly 10 mL. To 1 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the standard solution (2). Mix 1mL of the standard solution (1) and 1mL of the standard solution (2), and use this solution as the standard solution (3). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 1 μL of the test solution (1), 5 μL each of the test solution (2), the standard solution (1), the standard solution (2), and the stand-

ard solution (3) on the thin-layer chromatographic plate made of cellulose for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, water and acetic acid(100) (60 : 25 : 15) as the developing solvent to a distance of about 10 cm, spray evenly a solution prepared by dissolving 0.1 g of 4-dimethylaminobenzaldehyde in 20 mL of a mixture of methanol and hydrochloric acid (3 : 1), dry the plate with hot air, and observe the plate after 30 minutes; the spots other than the principal spot obtained from the test solution (1) are not more intense than the spots from the standard solution (2) (0.5%). However, this test is valid when the principal spots obtained from the standard solution (3) clearly separate.

Loss on drying NMT 0.1% (2 g, 105 ℃, constant mass).

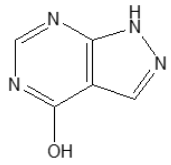
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately 1.2 g of Allantoin, previously dried, dissolve in 40 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Separately, perform a blank test and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 15.812 mg of $C_4H_6N_4O_3$

Packaging and storage Preserve in well-closed containers.

Allopurinol
알로푸리놀



$C_5H_4N_4O$: 136.11
1,2-Dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one [*315-30-0*]

Allopurinol, when dried, contains NLT 98.0% and NMT 101.0% of allopurinol ($C_5H_4N_4O$).

Description Allopurinol occurs as white to pale yellowish white crystals or a crystalline powder.
It is slightly soluble in *N*,*N*-dimethylformamide and very slightly soluble in water and ethanol(99.5).
It dissolves in ammonia TS.

Identification (1) Determine the absorption spectra of solutions of Allopurinol and allopurinol RS (1 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Allopurinol and allopurinol RS, previously dried, as directed in the potassium bromide disk method under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Allopurinol in 10 mL of sodium hydroxide TS; the solution is clear, and the color of the solution is not more intense than that of the Matching Fluid for Color D.

(2) ***Sulfate***—Dissolve 2.0 g of Allopurinol in 100 mL of water, boil for 5 minutes, cool, add water to make 100 mL, and filter. To 25 mL of the filtrate, add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid (NMT 0.038%).

(3) ***Heavy metals***—Proceed with 1.0 g of Allopurinol according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic***—Procced with 1.0 g of Allopurinol according to Method 3 and perform the test (NMT 2 ppm).

(5) ***Hydrazine***—Weigh accurately about 0.25 g of Allopurinol, dissolve in 5.0 mL of a mixture of sodium hydroxide TS and methanol (1 : 1), add 4 mL of benzaldehyde TS, and allow to stand at room temperature for 2.5 hours. Add 5.0 mL of hexane, shake to mix for 1 minute, allow the layers to separate, take the hexane layer, and use this solution as the test solution. Separately, pipet 5.0 mL each of hydrazine TS and a mixture of 2 mol/L sodium hydroxide TS and methanol (1 : 1), proceed in the same manner as in the preparation of the test solution, and use these solutions as the test solution and the blank test solution. Perform the test with 20 μL each of the test solution, the standard solution and the blank test solution as directed under the Liquid Chromatography according to the following conditions; the amount of hydrazine is NMT 10 ppm.

$$\text{Amount (ppm) of hydrazine} = 1000 \times \frac{32.05}{130.12} \times \frac{C_S}{C_T} \times \frac{A_T}{A_S}$$

32.05: Molecular weight of hydrazine
130.12: Molecular weight of hydrazinium sulfate
C_S: Concentration (μg/mL) of hydrazinium sulfate in hydrazine TS
C_T: Concentration (mg/mL) of allopurinol in the test solution
A_T: Peak area of benzalazine obtained from the test solution
A_S: Peak area of benzalazine obtained from the standard solution

Operating conditions
Detector: An ultraviolet absorption photometer (wavelength: 310 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 m in length, packed with nitrated silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of hexane and 2-propanol (95 : 5).

Flow rate: 1.5 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution under the above operating conditions; the relative retention time of benzalazine to benzaldehyde is 0.8 with the resolution between these peaks being NLT 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution; the relative standard deviation of the peak area of benzalazine is NMT 15.0%.

(6) ***Related substances***—Dissolve 50 mg of Allopurinol in 10 mL of ammonia TS, and use this solution as the test solution. Pipet 1 mL of this solution, add ammonia TS to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with ammonia TS-saturated 1-butanol as the developing solvent to a distance of about 10 cm, and air-dry the plate. Observe the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.16 g of Allopurinol, previously dried, and dissolve in 70 mL of *N*,*N*-dimethylformamide by warming. After cooling, titrate with 0.1 mol/L tetramethylammonium hydroxide VS (potentiometric titration under the Titrimetry). Separately, add 12 mL of water to 70 mL of dimethylformamide, and perform a blank test with this solution in the same manner and make any necessary correction.

Each mL of 0.1 mol/L tetramethylammonium hydroxide VS
= 13.611 mg of $C_5H_4N_4O$

Packaging and storage Preserve in tight containers.

Allopurinol Tablets
알로푸리놀 정

Allpurinol Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of allopurinol ($C_5H_4N_4O$: 136.11).

Method of preparation Prepare Allopurinol Tablets as directed under Tablets, with Allopurinol.

Identification The retention times of the major peaks and the ultraviolet absorption spectra between 190 nm and 300 nm obtained from the test solution and the standard solution in the Assay are the same.

Dissolution Perform the test with 1 tablet of Ciprofloxacin Hydrochloride Tablets at 75 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of 0.1 mol/L hydrochloric acid as the dissolution medium. Take the dissolved solution 45 minutes after starting the dissolution test, filter, and add the dissolution medium. After diluting, use this solution as the test solution. Separately, weigh accurately an appropriate amount of allopurinol RS, dissolve in the dissolution medium to make the same concentration with the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy and determine the absorbances at the absorbance maximum wavelength at about 250 nm.
Meets the requirements if the dissolution rate of Allopurinol Tablets in 45 minutes is NLT 75%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Allopurinol Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 50 mg of allopurinol ($C_5H_4N_4O$), add exactly 10 mL of 0.1 mol/L sodium hydroxide VS, shake for 10 minutes and add water to make exactly 50 mL (perform the following assay as soon as possible). After centrifugation, discard 10 mL of the first filtrate, collect exactly 4 mL of the subsequent filtrate, add exactly 2.0 mL of the internal standard solution and the mobile phase to make exactly 200 mL and use this solution as the test solution. Separately, weigh accurately about 50 mg of Allopurinol RS, previously dried at 105 ℃ in vacuum for 5 hours, dissolve in 10 mL of 0.1 mol/L sodium hydroxide VS, mix in shaker for 10 minutes and add water to make exactly 50 mL. To exactly 4 mL of this solution, add exactly 2 mL of the internal standard solution and the mobile phase to make 200 mL and use this solution as the standard solution (prepare freshly when used). Perform the test with 15 μL each of the test solution and the standard solution as directed under Liquid Chromatography according to the following conditions and calculate the ratios, Q_T and Q_S, of the peak area of Allopurinol to that of the internal standard for the

test solution and the standard solution, respectively.

$$\text{Amount (mg) of allopurinol } (C_5H_4N_4O) = \text{Amount (mg) of allopurinol RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of 50 mg of hypoxantin and 10 mL of 0.1 mol/L sodium hydroxide VS, mix in shaker, add water to make exactly 50 mL. Prepare this solution before use.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm). However, use a photo-diode array detector (190 to 300 nm) when the Identification is performed.

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: 0.05 mol/L ammonium dihydrogen phosphate solution.

Flow rate: 1.5 mL/min

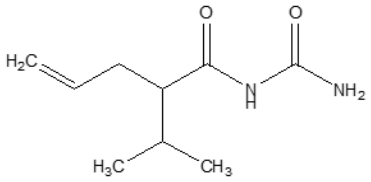
System suitability

System performance: Proceed with 15 μL of the standard solution according to the above conditions; hypoxanthine and allopurinol are eluted in this order with the resolution being NLT 5.

System repeatability: Repeat the test 6 times with 15 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio is NMT 3.0%.

Packaging and storage Preserve in well-closed containers.

Allylisopropylacetylurea
알릴이소프로필아세틸우레아



$C_9H_{16}N_2O_2$: 184.24

N-(Aminocarbonyl)-2-(1-methylethyl)-4-pentenamide; (2-Isopropyl-4-pentenoyl) urea, [*528-92-7*]

Allylisopropylacetylurea, when dried, contains NLT 98.0% and NMT 101.0% of allylisopropylacetylurea ($C_9H_{16}N_2O_2$: 184.24).

Description Allylisopropylacetylurea occurs as white crystals or a crystalline powder. It is tasteless and odorless. It is freely soluble in acetic acid(100), sparingly soluble in methanol, ethanol(95) and chloroform, slightly soluble in ether and boiling water, and very slightly soluble in water.

Melting point—Between 192 and 196 °C.

Identification (1) Transfer 0.3 g of Allylisopropylacetylurea into an evaporating dish, add 1.0 g of anhydrous sodium carbonate, mix, and gently warm; the resulting vapor turns moistened red litmus paper to blue. Cover the evaporating dish with a beaker containing water, and continuously heat; a white sublimate forms at the bottom of the beaker, and the melting point of the sublimate is between 106 and 110 ℃.

(2) To 10 mL of a solution of Allylisopropylacetylurea in ethanol (1 in 100), add 0.5 mL of bromine TS; the yellowish brown color of bromine TS disappears.

(3) To 10 mL of a solution of Allylisopropylacetylurea in ethanol (1 in 100), add 0.1 mL of potassium permanganate TS; the resulting solution exhibits a yellow color.

Purity (1) ***Acid***—Add 1.5 g of Allylisopropylacetylurea to 75 mL of water, boil for 1 minute, cool, and filter. To 10 mL of the filtrate, add 5 drops of bromothymol blue TS; the resulting solution exhibits a yellow to green color and turns blue on adding 0.2 mL of 0.01 mol/L sodium hydroxide TS.

(2) ***Chloride***—Perform the test with 20 mL of the filtrate in (1) as the test solution. Prepare the control solution with 0.4 mL of 0.01 mol/L hydrochloric acid (NMT 0.036%).

(3) ***Sulfate***—Perform the test with 20 mL of the filtrate in (1) as the test solution. Prepare the control solution with 0.4 mL of 0.005 mol/L sulfuric acid (NMT 0.048%).

(4) ***Heavy metals***—Proceed with 2.0 g of Allylisopropylacetylurea according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Readily carbonizable substances***—Weigh 0.5 g of Allylisopropylacetylurea, and perform the test; the color of the solution is not more intense than that of the Matching Fluid C.

(6) ***Arsenic***—Proceed with 1.0 g of Allylisopropylacetylurea according to Method 3 under the Arsenic and perform the test (NMT 2 ppm).

Loss on drying NMT 0.5% (0.5 g, in vacuum, phosphorus pentoxide, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Allylisopropylacetylurea, previously dried, transfer into a stoppered Erlenmeyer flask, dissolve by adding 30 mL of acetic acid(100), and add 20 mL of potassium bromide (3 in 20) and 10 mL of hydrochloric acid. Again, add exactly 25 mL of 1/60 mol/L potassium bromate while shaking vig-

orously to mix, immediately stopper the flask, and shake vigorously to mix. Add 10 mL of potassium iodide TS and 50 mL of water, and titrate with 0.1 mol/L sodium thiosulfate VS (indicator: 1 mL of starch TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1/60 mol/L potassium bromate VS
= 9.212 mg of $C_9H_{16}N_2O_2$

Packaging and storage Preserve in tight containers.

Almagate
알마게이트

$Al_2Mg_6C_2H_{14}O_{20}\cdot 4H_2O$: 630.00
Aluminum trimagnesium carbonate heptahydroxide dihydrate [*66827-12-1*]

Almagate contains NLT 15.0% and NMT 17.0% of aluminum oxide (Al_2O_3: 101.96), NLT 36.0% and NMT 40.0% of magnesium oxide (MgO: 40.30), and NLT 12.5% and NMT 14.5% of carbon dioxide (CO_2 :44.01).

Description Almagate occurs as a white fine crystalline powder.
It is practically insoluble in water, ethanol(95) or dichloromethane.
It dissolves in dilute mineral acid, foaming with heat.

Identification (1) Determine the infrared spectra of Almagate and almagate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve 0.15 g of Almagate in dilute hydrochloric acid to make 20 mL. To 2 mL of this solution, add about 0.5 mL of dilute hydrochloric acid and about 0.5 mL of thioacetamide TS; no precipitate forms. To this solution, drop 2 mol/L sodium hydroxide TS; a white gelatinous precipitate is produced, and the precipitate dissolves on more addition of 2 mol/L sodium hydroxide TS. Gradually add ammonium chloride TS; a gelatinous precipitate reappears.

(3) Dissolve 0.15 g of Almagate in dilute hydrochloric acid to make 20 mL. To 2 mL of this solution, add 1 mL of ammonia TS; a white participate forms, and the precipitate dissolves on adding 1 mL of ammonium chloride TS. Add 1 mL of disodium hydrogen phosphate dodecahydrate solution (9 in 100); a white crystalline precipitate forms.

pH Disperse 4.0 g of Almagate in 100 mL of water without carbon dioxide, mix for 2 minutes, and filter; the pH of the filtrate is between 8.4 and 10.4.

Purity (1) ***Chloride***—Dissolve 0.33 g of Almagate in 5 mL of dilute nitric acid, add water to make 100 mL, and use this solution as the test solution. Prepare the control solution with 10 mL of chloride standard solution, 0.7 mL of dilute nitric acid and 5 mL of water. To 15 mL each of the test solution and the standard solution, add 1 mL of dilute nitric acid TS and 1 mL of silver nitrate TS, allow these solutions to stand for 5 minutes without exposure to daylight, and compare the turbidity of both solutions by observing them in Nessler tubes against a black background; the turbidity of the test solution is not more intense than that of the control solution (NMT 0.1%).

Chloride standard solution—Weigh accurately 0.824 g of sodium chloride, add water to make exactly 1000 mL, and to 1 mL of this solution, add water to make exactly 100-mL before use.

(2) ***Sulfate***—Dissolve 0.25 g of Almagate in 5 mL of dilute hydrochloric acid, add water to make 100 mL, and use this solution as the test solution. Prepare the control solution with 15 mL of sulfate standard solution and 0.8 mL of dilute hydrochloric acid. To 3 mL of barium chloride TS, add 4.5 mL of sulfate standard solution, mix, and allow it to stand for 1 minute. Add 2.5 mL of this solution to 15 mL each of the test solution and the control solution, and add 0.5 mL of acetic acid(31). Allow these solutions to stand for 5 minutes, and compare the turbidity; the turbidity produced in the test solution is not more intense than that produced in the control solution.

Sulfate standard solution—Dissolve 0.181 g of potassium sulfate in water to make exactly 100 mL. Pipet 1 mL of this solution and add water to make exactly 100 mL. Proceed this solution before use.

(3) ***Sodium***—Dissolve 0.25 g of Almagate in 50 mL of 3 mol/L hydrochloric acid TS, and use this solution as the test solution. Separately, weigh accurately 3.050 g of sodium chloride (standard reagent), previously dried at 130 ℃ for 2 hours, dissolve in water to make exactly 1000 mL, and prepare a solution containing 1.20 mg of sodium per mL, and use this solution as the standard solution. If necessary, dilute with 3 mol/L hydrochloric acid TS. With the test and standard solutions, perform the test as directed under the Atomic Absorption Spectroscopy according to the following conditions, and determine the potassium content in the test solution using the calibration curve obtained from the standard solution (NMT 1000 ppm).

Gas: Air–acetylene
Lamp: Potassium hollow cathode lamp
Wavelength: 589.0 nm

(4) ***Heavy metals***—Weigh 1.0 g of Almagate, and add dilute hydrochloric acid to make 20 mL. Take 12 mL of this solution, and use this solution as the test solution. Separately, to 10 mL of diluted lead standard solution, add 2mL of the test solution, and use this solution as the

control solution. Also, to 10 mL of water, add 2 mL of the test solution, and use this solution as the blank test solution. To 12 mL each of the test solution, the control solution and the blank test solution, add 2 mL of acetate buffer solution, pH 3.5, mix, add 1.2 mL of thioacetamide TS, and mix immediately. Allow this solution to stand for 2 minutes; the brown color produced from the test solution is not more intense than the brown color from the control solution (NMT 10 ppm).

Diluted lead standard solution—Before use, take exactly 5mL of the lead standard solution, and add water to make exactly 50 mL.

System suitability—The control solution exhibits a faint brown color compared to the blank test solution.

Loss on ignition Between 43.0% and 49.0% (1 g, 900 ± 50 ℃).

Microbiological examination of non-sterile products The total aerobic microbial count is NMT 1000 CFU, and the total combined yeasts/molds count is NMT 100 CFU per g of Almagate. Also, *Escherichia coli* and *Pseudomonas aeruginosa* are not detected.

Acid-neutralizing capacity Weigh accurately 0.5 g of Almagate, disperse in 100 mL of water, warm at 37 ± 2 ℃, add 100 mL of 0.1 mol/L hydrochloric acid, previously warmed at 37 ± 2 ℃, and continuously stir. This solution maintains pH between 3.0 and 4.5 for 5 to 20 minutes. Add 10 mL of 0.5 mol/L hydrochloric acid, previously warmed at 37 ± 2 ℃, and stir for 1 hour on a steam bath at 37 ± 2 ℃. Titrate until the pH of this solution becomes 3.5; NMT 20 mL of 0.1 mol/L of sodium hydroxide VS is consumed.

Assay (1) ***Aluminum***—Weigh accurately about 1.0 g of Almagate, and dissolve in 5 mL of hydrochloric acid. If necessary, heat. After cooling to room temperature, add water to make exactly 100 mL. Take 10 mL of this solution, transfer into a 250-mL Erlenmeyer flask, add 25 mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt solution, 20 mL of acetate buffer solution, pH 3.5, 40 mL of ethanol(95) and 2 mL of dithizone TS prepared immediately before use. Titrate excess ethylenediaminetetraacetic acid disodium salt with 0.05 mol/L zinc sulfate VS until the greenish purple color of the solution becomes pink.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.549 mg of Al_2O_3

(2) ***Magnesium***—Weigh accurately about 1.0 g of Almagate, and dissolve in 5 mL of hydrochloric acid. If necessary, heat. After cooling to room temperature, add water to make exactly 100 mL. Pipet 10 mL of this solution, transfer into a 500 mL of Erlenmeyer flask, add 200 mL of water and 20 mL of 2,2',2″-nitrilotriethanol (95) with mixing, and add 10 mL of ammonium chloride buffer solution, pH 10.0, and 50 mg of eryochrome black T-sodium chloride indicator. Titrate this solution with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS until the violet color of the solution becomes blue.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.015 mg of MgO

(3) ***Carbonate***—Weigh accurately about 200 mg of Almagate, transfer into the flask (B), and add 50 mL of water. To flask (B), add 2 to 3 drops of methyl orange TS. Add a boiling stone, connect the funnel (A) and the flask (B), and close the control valve (F). Separately, to the flask (J), add 25 mL of 0.1 mol/L sodium hydroxide TS, immediately add 300 mL of barium chloride solution (1 in 100), stir, and connect the flask (J) and the flask (H). Use a rubber tube to connect the control valve (F) and flask (H), and open the control valve (F). Rapidly proceed with this process. To the funnel (A), add 50 mL of 1 mol/L hydrochloric acid TS, open the rotary valve (L), heat the flask (B) until the solution begins to boil, and continue heating for 10 minutes. Immediately after heating is complete, close the control valve (F) and the rotary valve (L), and separate the rubber tube (D_2) and the glass column (E). Separate the flask (J) and the flask (H), vigorously shake them up and down for 2 minutes to mix, allow them to stand at room temperature for 10 minutes, and open the control valve (F) and the rotary valve (L). Filter the solution in flask (J) in vacuum, add 2 to 3 drops of methyl orange TS, and titrate with 0.1 mol/mL hydrochloric acid VS until the pale orange color of the solution becomes red. Perform a blank test in the same manner and make any necessary correction.

$$\text{Content (\%) of carbonate} = \frac{(a-b)\times f}{Amount\ (mg)\ of\ sample\ taken} \times 2.200 \times 100$$

Each mL of 0.1 mol/L hydrochloric acid VS
= 2.200 mg of CO_2

a: Volume (mL) of 0.1 mol/L hydrochloric acid VS consumed for titration in the blank test

b: Volume (mL) of 0.1 mol/L hydrochloric acid VS consumed for titration in the test

f: Titrimetric factor of 0.1 mol/L hydrochloric acid

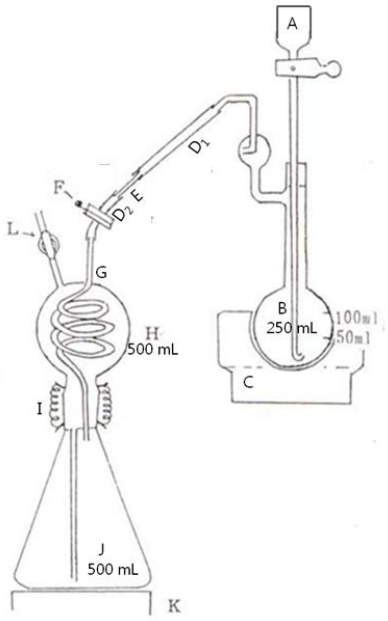


Figure. Carbon dioxide measurement apparatus

A: Funnel for adding acid to decompose the sample
B: Flask to decompose sample
C: Heating mantle
D_1, D_2: Rubber tube
E: Glass tube
F: Control valve
G: Cooling glass column
H: Safety flask
I: Spring container
J: CO_2 absorption flask
K: Stirring device
L: Rotary valve

Packaging and storage Preserve in tight containers.

Almagate Suspension
알마게이트 현탁액

Almagate Suspension contains NLT 15.0% and NMT 17.0% of aluminum oxide (Al_2O_3 : 101.96) and NLT 36.0% and NMT 40.0% of magnesium oxide (MgO : 40.30) of the labeled amount of almagate (on the dried basis).

Method of preparation Prepare as directed under Suspensions, with Almagate.

Identification (1) Shake Almagate Suspension to mix, take an amount equivalent to about 2.0 g of almagate, add 30 mL of 3 mol/L hydrochloric acid TS, and 5 drops of methyl red TS. Heat to boil. Add ammonia TS until it turns to an intense yellow color, boil for 2 more minutes, and filter. The filtrate responds to the Qualitative Analysis (1) for magnesium salt.

(2) Add ammonium chloride solution (1 in 50) to the precipitate obtained in (1) to wash, and dissolve the precipitate with hydrochloric acid. The solution responds to the Qualitative Analysis (1) and (2) for aluminum salt.

pH NLT 8.5.

Acid-neutralizing capacity Shake Almagate Suspension to mix, pipet an amount equivalent to about 0.2 g of almagate (on the dried basis), and perform the test as directed under the Acid-neutralizing Capacity. Each gram of almagate (calculated on the dried basis) consumes NLT 260 mL of 0.1 mol/L hydrochloric acid.

Assay (1) ***Aluminum oxide***—Shake Almagate Suspension to mix, take exactly an amount equivalent to about 2.0 g of almagate (on the dried basis), dissolve in 10 mL of hydrochloric acid and water to make 200 mL, and use this solution as the test solution. Take 20.0 mL of the test solution, add 20 mL of water, 25.0 mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS and 20 mL of acetic acid-ammonium acetate buffer solution (pH 4.8), and boil for 5 minutes. After cooling, add 50 mL of ethanol and 2 mL of dithizone TS and titrate with 0.05 mol/L zinc sulfate VS. However, the endpoint of titration is when the reddish purple color of the solution turns to a pale red color. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.5490 mg of Al_2O_3

(2) ***Magnesium oxide***—Pipet 10.0 mL of the test solution obtained in (1), add 20 mL of water, 20 mL of triethanolamine, 15 mL of ethanol and 20 mL of ammonia-ammonium chloride buffer solution (pH 10.7), and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 40 mg of eriochrome black T-sodium chloride indicator). However, the endpoint of titration is when the bluish purple color of the solution turns to a completely blue color. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.0152 mg of MgO

Packaging and storage Preserve in well-closed containers.

Almagate Tablets
알마게이트 정

Almagate Tablets contain aluminum oxide (Al_2O_3: 101.96) equivalent to NLT 15.0% and NMT 17.0% and NLT 36.0% and NMT 40.0% of magnesium oxide (MgO: 40.30) of the labeled amount of almagate, calculated on the dried basis.

Method of preparation Prepare Almagate Tablets as directed under Tablets, with Almagate.

Identification (1) Weigh 0.7 g of Almagate Tablets, previously powdered, add 10 mL of 3 mol/L hydrochloric acid TS, add 5 drops of methyl red TS, and heat to boil. Add ammonia TS until the solution turns dark yellow, boil for 2 minutes, and filter. The filtrate responds to the Qualitative Analysis (1) for magnesium salt.

(2) Wash the precipitate obtained from (1) with ammonium chloride solution (1 in 50), and dissolve the precipitate in hydrochloric acid. This solution responds to the Qualitative Analysis (1) and (2) for aluminum salt.

Acid-neutralizing capacity Weigh accurately the mass of NLT 20 tablets of Almagate Tablets, and powder. Weigh accurately an amount of Almagate Tablets, equivalent to about 0.2 g of almagate, calculated on the dried basis, according to the labeled amount, and perform the test as directed under the Acid-neutralizing Capacity. Each gram of almagate, calculated on the dried basis, consumes NLT 260 mL of 0.1 mol/L hydrochloric acid.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Aluminum oxide***—Weigh accurately the mass of NLT 20 tablets of Almagate Tablets, and powder. Weigh accurately an amount equivalent to about 2.0 g of almagate, calculated on the dried basis, dissolve in 10 mL of hydrochloric acid and water to make 200 mL, and use this solution as the test solution. Take 20.0 mL of the test solution, add 20 mL of water, 25 mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS and 20 mL of acetic acid-ammonium acetate buffer solution (pH 4.8), and boil for 5 minutes. After cooling, add 50 mL of ethanol and 2 mL of dithizone TS and titrate with 0.05 mol/L zinc sulfate VS. The endpoint of titration is when the reddish purple color of the solution changes to pale red. Perform a blank test in the same manner and make any necessary correction.

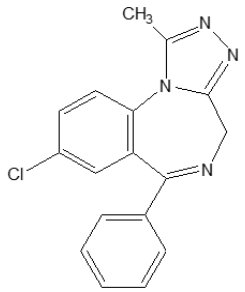
Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.5490 mg of Al_2O_3

(2) ***Magnesium oxide***—Take 10.0 mL of the test solution obtained from (1), add 20 mL of water, 20 mL of triethanolamine, 15 mL of ethanol and 20 mL of ammonia-ammonium chloride buffer solution (pH 10.7), and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS. (indicator: 40 mg of eriochrome black T-sodium chloride indicator). The endpoint of titration is when the bluish purple color of the solution changes to blue. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.0152 mg of MgO

Packaging and storage Preserve in well-closed containers.

Alprazolam
알프라졸람



$C_{17}H_{13}ClN_4$: 308.77
8-Chloro-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine [*28981-97-7*]

Alprazolam, when dried, contains NLT 98.5% and NMT 101.0% of alprazolam ($C_{17}H_{13}ClN_4$).

Description Alprazolam occurs as a white or almost white, crystalline powder.
It is freely soluble in chloroform, soluble in methanol or ethanol(95), sparingly soluble in acetic anhydride and practically insoluble in water.
It dissolves in dilute nitric acid.

Identification (1) Determine the absorption spectrum of a solution of Alprazolam in ethanol(95) (1 in 200000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum absorption at around 222 nm.

(2) Dissolve 50 mg of Alprazolam in 0.7 mL of deuterated chloroform for nuclear magnetic resonance spectroscopy and measure the ^1H spectrum using tetramethylsilane for nuclear magnetic resonance spectroscopy as the internal standard as directed under the Nuclear Magnetic Resonance Spectroscopy; it exhibits a singlet signal A at δ 2.6 ppm, doublet signals B and C at δ 4.0 ppm and δ 5.4 ppm, and a broad signal D spanning from δ 7.1 ppm to δ 7.96 ppm, and the area intensity ratio of each signal, A : B : C : D, is about 3 : 1 : 1 : 8.

(3) Perform the test with Alprazolam as directed under the Flame Coloration (2); a green color appears.

Melting point Between 228 and 232 ºC.

Purity (1) ***Chloride***—Dissolve 0.5 g of Alprazolam in 10 mL of dilute nitric acid, add water to make 50 mL, and use this solution as the test solution. Prepare the control solution with 0.20 mL of 0.01 mol/L hydrochloric acid (NMT 0.014%).

(2) ***Heavy metals***—Proceed with 2.0 g of Alprazolam according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 50 mg of Alprazolam in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution and add methanol to make exactly 100 mL. Pipet 1 mL of Alprazolam, add methanol to make exactly 10 mL, and use this solution as the standard solution. Spot 10 mL each of these solutions on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of acetone, hexane, ethyl acetate andethanol (95) (4: 2 : 2 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum not exceeding 0.67 kPa, 60 ℃, 4 hours).

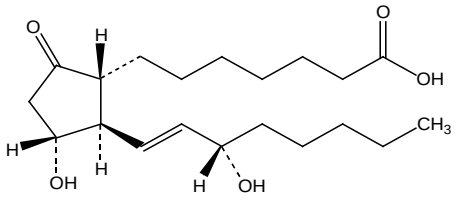
Residue on ignition NMT 0.1% (1.0 g).

Assay Weigh accurately about 0.25 g of Alprazolam, previously dried, dissolve in 100 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 15.438 mg of $C_{17}H_{13}ClN_4$

Packaging and storage Preserve in tight containers.

Alprostadil
알프로스타딜



Prostaglandin E_1 $C_{20}H_{34}O_5$: 354.48
7-{(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(1*E*,3*S*)-3-hydroxy-oct-1-enyl]-5-oxocyclopent-1-yl}heptanoic acid [*745-65-3*]

Alprostadil, when dried, contains NLT 97.0% and NMT 103.0% of Alprostadil ($C_{20}H_{34}O_5$).

Description Alprostadil occurs as white crystals or a crystalline powder.
It is freely soluble in ethanol(99.5) or tetrahydrofuran, slightly soluble in acetonitrile and practically insoluble in water.

Identification (1) To 10 mL each of solutions of Alprostadil and alprostadil RS in ethanol(99.5) (1 in 100000), add 1 mL of potassium hydroxide-ethanol TS, and allow to stand away for 15 minutes. Determine the absorption spectra of the solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Alprostadil and alprostadil RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy, respectively; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between 53° and -61° (25 mg after drying, tetrahydrofuran, 5 mL, 100 mm).

Melting point Between 114 and 232 ºC.

Purity ***Related substances***—Dissolve 4 mg of Alprostadil in 2 mL of a mixture of acetonitrile and water (9 : 1) and use this solution as the test solution. Pipet 0.5 mL of this solution, add a mixture of acetonitrile and water (9 : 1) to make exactly 10 mL. Pipet 2.0 mL of this solution, add a mixture of acetonitrile and water (9 : 1) to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area by the automatic integration method; the peak area with the relative retention time of 0.7 and 1.26 to the peak of alprostadil from the test solution is not larger than 0.5 times the peak area of alprostadil obtained from the standard solution, the peak area with the relative retention time of 0.88 and 1.18 to the peak of alprostadil from the test solution is not larger than the peak of alprostadil from the standard solution, and the peak area other than the alprostadil peak from the test solution and the above is not larger than 0.1 times the peak area of alprostadil from the standard solution. The total area of all peaks other than alprostadil of the solution is not larger than 2 times the peak area of alprostadil from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed under the operating conditions in the Assay.

System suitability

Test for required detectability: Take 2 mL of the standard solution and add a mixture of acetonitrile and water (9 : 1) to make 20 mL. Confirm that the peak area of alprostadil obtained from 5 μL of this solution is within the range of 7% to 13% of that of alprostadil from the standard solution.

System performance: Proceed as directed under the system suitability under the Assay.

System repeatability: Perform the test six times with 5 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of alfacalcidol is NMT 1.5%.

Time span of measurement: About 5 times the retention time of the alprostadil peak after the solvent peak

Loss on drying NMT 1.0% (0.1 g, in vacuum, phosphorus pentoxide, 4 hours).

Assay Weigh accurately about 5 mg each of Alprostadil and alprostadil RS, previously dried, dissolve in exactly 5 mL of the internal standard solution, add a mixture of acetonitrile and water (9 : 1) to make exactly 50 mL, and use the solutions as the test solution and the standard solution, respectively. Perform the test with 5 mL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios of the peak area, Q_T and Q_S, of Alprostadil to that of the internal standard.

$$\text{Amount (mg) of alprostadil } (C_{20}H_{34}O_5) = \text{Amount (mg) of alprostadil RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of dimethyl phthalate in a mixture of acetonitrile and water (9 : 1) (1 in 10000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 196 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 9.07 g of potassium dihydrogen phosphate in water to make 1000 mL. To this, add the solution prepared by dissolving 9.46 g of anhydrous sodium dihydrogen phosphate in water to make 1000 mL, and adjust the pH to 6.3. To this solution, add water to dilute to 10 times. To 360 mL of this solution, add 110 mL of acetonitrile and 30 mL of methanol and mix.

Flow rate: Adjust the flow rate so that the retention time of alprostadil peak is about 10 minutes.

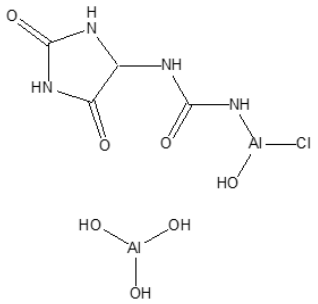
System suitability

System performance: Perform the test with 5 μL of the standard solution according to the above operating conditions; alprostadil and the internal standard are eluted in this order with the resolution being NLT 9.

System repeatability: Perform the test 6 times with 5 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area ratio of alprostadil to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers at below 5 °C.

Aluminum Chlorohydroxy Allantoinate
알란토인클로로히드록시 알루미늄



$C_4H_9Al_2ClN_4O_7$: 314.55

Chloro[*N*-(2,5-dioxo-4-imidazolidinyl)ureato]tetrahydroxydi-aluminum, [*1317-25-5*]

Aluminum Chlorohydroxy Allantoinate, when dried, contains NLT 36.0% and NMT 44.0% of allantoin ($C_4H_6N_4O_3$: 158.12) and NLT 25.0% and NMT 31.0% of aluminum oxide (Al_2O_3: 101.96).

Description Aluminum Chlorohydroxy Allantoinate occurs as a white powder. It is odorless and has an astringent taste.

Identification (1) Add 0.2 g of Aluminum Chlorohydroxy Allantoinate to 10 mL of dilute hydrochloric acid, boil for 5 minutes, add 1 mL of phenylhydrazine hydrochloride solution (1 in 100), and cool. Add 0.5 mL of potassium ferricyanide TS and 1 mL of hydrochloric acid; the resulting solution exhibits a red color.

(2) Dissolve 0.2 g of Aluminum Chlorohydroxy Allantoinate in 10 mL of water by heating, and cool; the resulting solution responds to the Qualitative Analysis for aluminum salt and chloride.

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g of Aluminum Chlorohydroxy Allantoinate in 10 mL of water by heating; the solution is colorless and almost clear.

(2) ***Heavy metals***—Add 2.0 g of Aluminum Chlorohydroxy Allantoinate to 5 mL of sulfuric acid and 5 mL of nitric acid, and gently heat. Occasionally add 2 to 3

mL of nitric acid, and continue heating until the solution becomes colorless to pale yellow. After cooling, add 10 mL of saturated ammonium oxalate, and concentrate the solution by heating until white smoke appears. After cooling, add water to make 50 mL, and use this solution as the test solution. Take 25 mL of the test solution, and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

Loss on drying NMT 7% (2 g, 105 ℃, 2 hours).

Assay (1) ***Allantoin***—Weigh accurately about 0.7 g of Aluminum Chlorohydroxy Allantoinate, previously dried, and perform the test according to the Nitrogen Determination (Method 2).

Each mL of 0.05 mol/L sulfuric acid VS
= 3.953 mg of $C_4H_6N_4O_3$

(2) ***Aluminum oxide***—Weigh accurately about 0.5 g of Aluminum Chlorohydroxy Allantoinate, previously dried, dissolve in 20 mL of dilute nitric acid by heating, and add water to make about 250 mL. To this solution, add 1 g of ammonium chloride and 3 drops of methyl red TS, heat to boiling, and slowly add ammonia TS until the solution becomes yellow. Filter the precipitate, collect the residue, and wash well with ammonium nitrate solution (1 in 400). After drying, ignite to a constant mass with the filter paper, and weigh.

Packaging and storage Preserve in tight containers.

Aluminum Hydroxide Gel
수산화알루미늄 겔

$Al(OH)_3$: 78.00

Aluminum Hydroxide Gel, as an aluminum hydroxide suspension, contains NLT 3.6% and NMT 4.4% of aluminum oxide (Al_2O_3 : 101.96). Mint oil, glycerin, sorbitol, sucrose, saccharin or other appropriate fragrances and appropriate antiseptics may be added to Aluminum Hydroxide Gel.

Description Aluminum Hydroxide Gel occurs as a white, viscous suspension. When it is allowed to stand, a small amount of water is separated from it.

Identification Dissolve 5 mL of Aluminum Hydroxide Gel in 10 mL of dilute hydrochloric acid and lightly warm to dissolve. The solution responds to the Qualitative Analysis for aluminum salt.

pH Between 5.5 and 8.0.

Purity (1) ***Chloride***—Place 10 g of Aluminum Hydroxide Gel in a porcelain dish, add 0.1 mL of potassium chromate TS and 25 mL of water, stir to mix, and add 0.1 mol/L of silver nitrate solution until the resulting solution exhibits a pale red color; the consumed amount is NMT 8.0 mL (NMT 0.28%).

(2) ***Sulfate***—To 5 g of Aluminum Hydroxide Gel, add 5.0 mL of 3 mol/L hydrochloric acid, and heat to dissolve. After cooling, add water to make 250 mL. Filter if necessary. To 20 mL of the filtrate, add 1 mL of dilute hydrochloric acid, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid (NMT 0.05%).

(3) ***Arsenic***—To 1.2 g of Aluminum Hydroxide Gel, add 10 mL of dilute sulfuric acid, shake well to mix, and heat until it boils. After cooling, add water to make 20 mL, and filter. Use 10 mL of the filtrate as the test solution and perform the test (NMT 0.6 ppm).

(4) ***Heavy metals***—To 5.0 g of Aluminum Hydroxide Gel, add 5 mL of dilute hydrochloric acid, shake to mix, and heat until it boils. Then, evaporate to dryness on a steam bath. To the residue, add 30 mL of water, warm with shaking to mix. After cooling, filter. To the filtrate, add 2 mL of dilute acetic acid, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by evaporating 5 mL of dilute hydrochloric acid to dryness on a steam bath, adding 2.5 mL of lead standard solution and 2 mL of dilute acetic acid, and adding water to make 50 mL (NMT 5 ppm).

Acid-neutralizing capacity Stir Aluminum Hydroxide Gel well to mix, transfer about 1.5 mL of it in a flask with a glass stopper, previously measured in the mass, weigh accurately the mass, and perform the test; the consumed amount of 0.1 mol/L hydrochloric acid VS per 1.0 g of Aluminum Hydroxide Gel is between 12.5 mL and 25.0 mL.

Microbiological examination of non-sterile products The total aerobic microbial count is NMT 100 CFU per mL of Aluminum Hydroxide Gel, and *Escherichia coli* is not detected.

Assay Weigh accurately about 25 g of Aluminum Hydroxide Gel, place in a beaker, add 15 mL of hydrochloric acid, and slowly heat to completely dissolve. After cooling, transfer to a 500-mL volumetric flask, add water to the gauge line, and shake to mix. Place exactly 20 mL of this solution in a 250-mL beaker. While continuously stirring to mix, add 25.0 mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt solution and 20 mL of pH 4.8 acetic acid-ammonium acetate buffer solution, and heat for 5 minutes until it nearly boils. After cooling, add 50 mL of ethanol and 2 mL of dithizone TS, and titrate with 0.05 moL/L zinc sulfate solution until the greenish purple color of the resulting solution turns to a red color. Perform a blank test in the same manner.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS

= 2.5490 mg of Al_2O_3

Packaging and storage Preserve in tight containers, avoiding it from being frozen.

Aluminum Hydroxide and Magnesium Carbonate Codried Gel
수산화알루미늄·탄산마그네슘혼합건조 겔

Aluminum Hydroxide and Magnesium Carbonate Codried Gel contains NLT 40.0% of aluminum oxide (Al_2O_3 : 101.96) and NLT 6.0% of magnesium oxide (MgO : 40.30).

Description Aluminum Hydroxide and Magnesium Carbonate Codried Gel occurs as a fine white powder.
It is odorless, tasteless, and free of foreign matter.

Identification (1) Weigh 1 g of Aluminum Hydroxide and Magnesium Carbonate Codried Gel and dissolve in 10 mL of 3 mol/L hydrochloric acid; the resulting solution responds to the Qualitative Analysis for aluminum salt and magnesium salt.

(2) Aluminum Hydroxide and Magnesium Carbonate Codried Gel responds to the Qualitative Analysis (1) for carbonate.

pH Between 8.8 and 9.8 [suspension (1 in 25)].

Purity (1) ***Chloride***—Weight 1.42 g of Aluminum Hydroxide and Magnesium Carbonate Codried Gel, dissolve in 30 mL of 2 mol/L nitric acid, and heat. Add water to make exactly 100 mL, filter, and perform the test using the filtrate as the test solution. Prepare the control solution with 0.2 mL of 0.02 mol/L hydrochloric acid (NMT 0.2%).

(2) ***Sulfate***—Weight 0.66 g of Aluminum Hydroxide and Magnesium Carbonate Codried Gel, dissolve in 15 mL of 3 mol/L hydrochloric acid, and heat. Add water to make 250 mL, filter, and perform the test using the filtrate as the test solution. Prepare the control solution with 0.40 mL of 0.04 mol/L sulfuric acid (NMT 0.3%).

(3) ***Heavy metal***—Proceed with 4.0 g of Aluminum Hydroxide and Magnesium Carbonate Codried Gel according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 5 ppm).

(4) ***Arsenic***—Weight 2.4 g of Aluminum Hydroxide and Magnesium Carbonate Codried Gel, dissolve in 80 mL of 3.5 mol/L sulfuric acid, and add water to make 220 mL. Perform the test using 36 mL of this solution (NMT 5 ppm).

Acid-neutralizing capacity Weight accurately about 0.25 g of Aluminum Hydroxide and Magnesium Carbonate Codried Gel, transfer into a stoppered Erlenmeyer flask, add 100.0 mL of 0.1 mol/L hydrochloric acid, close the stopper, and warm at 37 ± 2 °C for 1 hour while shaking to mix. Pipet 50 mL of this solution, and titrate the excess hydrochloric acid with 0.1 mol/L sodium hydroxide VS to pH 3.5 using the potentiometric titration. 1.0 g of Aluminum Hydroxide and Magnesium Carbonate Codried Gel consumes NLT 260 mL of 0.1 mol/L hydrochloric acid.

Assay (1) ***Aluminum oxide***—Weigh accurately about 1 g of Aluminum Hydroxide and Magnesium Carbonate Codried Gel, dissolve in 15 mL of dilute hydrochloric acid, add water to make 100.0 mL, and use this solution as the test solution. Pipet 10.0 mL of the test solution, add 25.0 mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt and 20 mL of acetic acid-sodium acetate buffer solution, pH 4.5, boil for 5 minutes, and then cool to room temperature. Add 50 mL of ethanol and 2 mL of dithizone TS, and titrate with 0.05 mol/L zinc sulfate VS. The endpoint of titration is when the greenish purple color turns bright red. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.5490 mg of Al_2O_3

(2) ***Magnesium oxide***—Take 25.0 mL of the test solution obtained in (1), add 20 mL of triethanolamine, and mix. Add 20 mL of Ammonia-ammonium chloride buffer solution, pH 10.7, and 40 mg of eryochrome black T-sodium chloride indicator, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS. The endpoint of titration is when the violet in the bluish purple color completely disappears and turns into blue. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.015 mg of MgO

Packaging and storage Preserve in well-closed containers.

Aluminum Hydroxide, Magnesium Carbonate and Calcium Carbonate Coprecipitate
수산화알루미늄·탄산마그네슘·탄산칼슘공침물

Aluminum Hydroxide, Magnesium Carbonate and Calcium Carbonate Coprecipitate is a coprecipitate dry product of aluminum hydroxide, magnesium carbonate and calcium carbonate, with a molar ratio of about 2 : 1 : 2. Aluminum Hydroxide, Magnesium Carbonate and Cal-

cium Carbonate Coprecipitate contains NMT 19.5% and NLT 24.5% of aluminum oxide (Al_2O_3 : 101.96), NMT 9.5% and NLT 14.5% of magnesium oxide (MgO : 40.30), and NMT 21.5% and NLT 26.5% of calcium oxide (CaO : 56.08), calculated on the dried basis.

Description Aluminum Hydroxide, Magnesium Carbonate and Calcium Carbonate Coprecipitate occurs as a white powder or granule, which is odorless and tasteless. It is practically insoluble in water or ethanol(95).
It dissolves in dilute hydrochloric acid with effervescence.

Identification (1) To 0.5 g of Aluminum Hydroxide, Magnesium Carbonate and Calcium Carbonate Coprecipitate, add 10 mL of dilute hydrochloric acid and warm to dissolve. Cool and add 20 mL of water and ammonia TS to make it neutral. Filter the precipitate formed. Use the filtrate in the Identification (2). Dissolve the residue in dilute hydrochloric acid; the solution responds to the Qualitative Analysis for aluminum salt.

(2) Add ammonium oxalate TS to the filtrate in (1), filter the resulting precipitate, and add dilute hydrochloric acid to the residue; the resulting solution responds to the Qualitative Analysis for calcium salt.

(3) Add sodium monohydrogen phosphate TS to a portion of the filtrate obtained from (2); a white crystalline precipitate is formed. In addition, add sodium hydroxide TS to a portion of the filtrate from (2); a white gel precipitate is formed. Even when an excess of sodium hydroxide TS is added, the precipitate does not dissolve, but when iodine TS is added, the precipitate turns dark brown (magnesium salt).

(4) Add dilute hydrochloric acid to Aluminum Hydroxide, Magnesium Carbonate and Calcium Carbonate Coprecipitate; gas is generated as it effervesces. When this gas is passed through calcium hydroxide TS, a white precipitate is immediately formed (carbonate).

Purity (1) ***Soluble salt*—**Dissolve 2.0 g of Aluminum Hydroxide, Magnesium Carbonate and Calcium Carbonate Coprecipitate in 100 mL of water, shake to mix, and heat to boiling. Cool it, add water to make 100.0 mL, and filter it. Take 50.0 mL of the filtrate, evaporate on a steam bath to dryness, and dry the residue at 120 °C for 3 hour. The mass of the residue is NMT 30 mg.

(2) ***Chloride*—**Add 30 mL of dilute nitric acid to 1.0 g of Aluminum Hydroxide, Magnesium Carbonate and Calcium Carbonate Coprecipitate and heat to boiling to dissolve. Cool, add water to make 100 mL and filter it. Take 5 mL of the filtrate, add water to make 50 mL, and use this solution as the test solution. Perform the test according to the Chloride. Prepare the control solution with 0.4 mL of 0.01 mol/L hydrochloric acid (NMT 0.284%).

(3) ***Sulfate*—**Add 15 mL of dilute hydrochloric acid to 1.0 g of Aluminum Hydroxide, Magnesium Carbonate and Calcium Carbonate Coprecipitate and heat to boiling to dissolve. Cool, add water to make 100 mL, and filter it. Pipet 10 mL of the filtrate, add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution, and perform the test according to the Sulfate. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.48%).

(4) ***Heavy metals*—**Add 12 mL of dilute hydrochloric acid to 1.0 g of Aluminum Hydroxide, Magnesium Carbonate and Calcium Carbonate Coprecipitate, dissolve by warming, and filter after cooling. Add 12 mL of sodium acetate TS, 2 mL of dilute acetic acid and water to the filtrate to make 50 mL and perform the test according to the Heavy Metals. Prepare the control solution by evaporating 12 mL of dilute hydrochloric acid to dryness and adding 2 mL of dilute acetic acid, 2.0 mL of lead standard solution and water to make 50 mL (NMT 20 ppm).

(5) ***Iron*—**Take 1.0 g of Aluminum Hydroxide, Magnesium Carbonate and Calcium Carbonate Coprecipitate, add 20 mL of dilute nitric acid, and dissolve by warming. Cool it, add water to make 250.0 mL, and filter it. Take 25.0 mL of the filtrate, add 20 mL of water, 50 mg of ammonium persulfate and 5 mL of ammonium thiocyanate TS, shake to mix, and allow to stand for 5 minutes; the color of the solution should be not more intense than the color of the following control solution. Prepare the control solution by adding 3.0 mL of iron standard solution, 5 drops of dilute nitric acid and water to make 50 mL, and proceed in the same manner as the test solution.

(6) ***Arsenic*—**Add 5 mL of dilute hydrochloric acid to 0.2 g of Aluminum Hydroxide, Magnesium Carbonate and Calcium Carbonate Coprecipitate, warm to dissolve, cool, and use this solution as the test solution. Perform the test according to the Arsenic (NMT 10 ppm).

Loss on drying NMT 17.0% (1 g, 105 °C, 3 hours).

Acid-neutralizing capacity Weigh accurately an amount, equivalent to about 0.25 g of Aluminum Hydroxide, Magnesium Carbonate and Calcium Carbonate Coprecipitate, transfer into a flask with a stopper, and add exactly 100 mL of 0.1 mol/L hydrochloric acid. With the stopper closed, shake to mix at 37 ± 2 ℃ for 1 hour and then filter. Pipet 50 mL of the filtrate, and titrate the excess hydrochloric acid with 0.1 mol/L sodium hydroxide VS while shaking well to mix until the pH becomes 3.5. The volume of 0.1 mol/L hydrochloric acid consumed for 1 g of Aluminum Hydroxide, Magnesium Carbonate and Calcium Carbonate Coprecipitate, calculated on the dried basis, is NLT 220 mL.

Assay (1) ***Aluminum oxide***—Weigh accurately about 0.4 g of Aluminum Hydroxide, Magnesium Carbonate and Calcium Carbonate Coprecipitate, and dissolve in 10 mL of dilute hydrochloric acid and 5 mL of dilute nitric acid by warming. Cool it, add water to make exactly 250 mL, and use it as the test solution. Pipet 25 mL of the test solution and adjust the pH to 3.0 by adding 75 mL of water, 30 mL of acetic acid-ammonium acetate buffer solution and pH 3.0 and ammonia TS. Add 0.4 mL of Cu-Pan TS and heat the solu-

tion until it is almost boiling. Titrate with 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS. The endpoint of the titration is when the color of the solution changes from red to yellow persisting for NLT 1 minute. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 0.5098 mg of Al_2O_3

(2) ***Calcium oxide*—**Pipet 25 mL of the test solution obtained from (1) and put 175 mL of water, 10 mL of triethanolamine (1 in 2) and 1.0 mL of 8 mol/L potassium hydroxide. After allowing to stand for 5 minutes, titrate slowly with 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 0.1 g of NN indicator). The endpoint of titration is when the reddish purple color of the solution turns into a blue color. Perform a blank test in the same way and make any necessary correction.

Each mL of 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 0.5608 mg of CaO

(3) ***Magnesium oxide*—**Pipet 50 mL of the test solution obtained in (1), add 60 mL of water and 10 mL of triethanolamine solution (1 in 2) and 10 mL of ammonium chloride buffer solution (pH 10.7), and titrate with 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 40 mg of eriochrome black T-sodium chloride indicator). The endpoint of titration is when the reddish purple color of the solution turns into a blue color. Perform a blank test in the same way and make any necessary correction. In addition, from the amount of 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS consumed, subtract the amount of 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS, equivalent to the amount of calcium oxide (CaO) consumed in the Assay (2), which is the consumption corresponding to magnesium oxide (MgO).

Each mL of 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 0.4030 mg of MgO

Packaging and storage Preserve in tight containers.

Dried Aluminum Hydroxide Gel
건조수산화알루미늄 겔

Dried Aluminum Hydroxide Gel contains NLT 50.0% of aluminum oxide (Al_2O_3 : 101.96).

Description Dried Aluminum Hydroxide Gel occurs as a white, amorphous powder.
It is odorless and tasteless.
It is practically insoluble in water, ethanol(95) or ether.
It mostly dissolves in dilute hydrochloric acid or sodium hydroxide TS.

Identification Add 20 mL of dilute hydrochloric acid to 0.2 g of Dried Aluminum Hydroxide Gel, dissolve by warming, centrifuge, and take the clear supernatant; this solution responds to the Qualitative Analysis for aluminum salt.

Purity (1) ***Alkali***—To 1.0 g of Dried Aluminum Hydroxide Gel, add 25 mL of water, shake well to mix, and centrifuge; the clear supernatant is neutral.

(2) ***Chloride***—To 1.0 g of Dried Aluminum Hydroxide Gel, add 30 mL of dilute nitric acid, and heat gently to boiling while shaking well to mix. After colling, add water to make 100 mL, and centrifuge. To 5 mL of the clear supernatant, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.4 mL of 0.01 mol/L hydrochloric acid (NMT 0.284%).

(3) ***Nitrate***—To 1.0 g of Dried Aluminum Hydroxide Gel, add 5 mL of water, carefully put 5 mL of sulfuric acid, and dissolve by shaking well to mix, cool, and superimpose 2 mL of iron(II) sulfate TS; a brown rim is not formed at the interface of the two solutions.

(4) ***Sulfate***—To 1.0 g of Dried Aluminum Hydroxide Gel, add 15 mL of dilute hydrochloric acid, heat gently to boiling while shaking well to mix, cool, add water to make 250 mL, and centrifuge. To 25 mL of the clear supernatant, add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.480%).

(5) ***Heavy metals***—Dissolve 2 g of Dried Aluminum Hydroxide Gel in 10 mL of dilute hydrochloric acid by warming, filter the solution if necessary, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by evaporating 10 mL of dilute hydrochloric acid to dryness, and adding 2.0 mL of lead standard solution, 2 mL of dilute acetic acid and water to make 50 mL (NMT 10 ppm).

(6) ***Arsenic***—To 0.8 g of Dried Aluminum Hydroxide Gel, add 10 mL of dilute sulfuric acid, heat gently to boiling while shaking well to mix, cool, and filter. Take 5 mL of the filtrate as the test solution and perform the test (NMT 5 ppm).

Acid-neutralizing capacity Weight accurately about 0.2 g of Dried Aluminum Hydroxide Gel, and perform the test; the volume of 0.1 mol/L hydrochloric acid consumed for about 1 g of Dried Aluminum Hydroxide Gel is NLT 250 mL.

Assay Weigh accurately about 2 g of Dried Aluminum Hydroxide Gel, add 15 mL of hydrochloric acid, heat on a steam bath for 30 minutes while shaking to mix, cool,

and add water to make exactly 500 mL. Pipet 20 mL of this solution, add exactly 30 mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt, add 20 mL of pH 4.8 acetic acid-ammonium acetate buffer solution, and then boil for 5 minutes. After cooling, add 55 mL of ethanol(95), and titrate with 0.02 mol/L zinc sulfate VS (indicator: 2 mL of dithizone TS). The endpoint of the titration is when the pale dark green color of this solution turns to pale red. Perform a blank test in the same manner.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.5490 mg of Al_2O_3

Packaging and storage Preserve in tight containers.

Dried Aluminum Hydroxide Gel Fine Granules
건조수산화알루미늄겔 세립

Dried Aluminum Hydroxide Gel Fine Granules contain NLT 47.0% of aluminum oxide (Al_2O_3: 101.96).

Method of preparation Prepare as directed under Powders, with Dried Aluminum Hydroxide Gel.

Identification Add 20 mL of dilute hydrochloric acid to 0.2 g of Dried Aluminum Hydroxide Gel Fine Granules, followed by warming, centrifuge, and take the clear supernatant; this solution responds to the Qualitative Analysis for aluminum salt.

Particle size distribution estimation by analytical sieving Meets requirements.

Acid-neutralizing capacity Perform the test as directed under the Acid-neutralizing Capacity of Dried Aluminum Hydroxide Gel. The volume of 0.1 mol/L of hydrochloric acid VS consumed is NLT 235 mL per g of Aluminum Hydroxide Gel.

Assay Proceed as directed under the Assay of Dried Aluminum Hydroxide Gel.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.5490 mg of Al_2O_3

Packaging and storage Preserve in tight containers.

Dried Aluminum Hydroxide Gel, Magnesium Carbonate and Oxethazaine Tablets
건조수산화알루미늄겔·탄산마그네슘·옥세타자인 정

Dried Aluminum Hydroxide Gel, Magnesium Carbonate and Oxethazaine Tablets contain aluminum oxide (Al_2O_3 : 101.96) NLT 50.0% of the labeled amount of dried aluminum hydroxide gel, magnesium oxide (MgO : 40.30) corresponding to NLT 38.0% and NMT 46.0% of the labeled amount of magnesium carbonate, and NLT 90.0% and NMT 110.0% of the labeled amount of oxethazaine ($C_{28}H_{41}N_3O_3$: 467.70).

Method of preparation Prepare as directed under Tablets, with Dried Aluminum Hydroxide Gel, Magnesium Carbonate and Oxethazaine.

Identification (1) ***Dried aluminum hydroxide gel***—Weigh about 1 g of Dried Aluminum Hydroxide Gel, Magnesium Carbonate and Oxethazaine Tablets and carbonize. After cooling, add 30 mL of dilute hydrochloric acid to the residue, warm on a steam bath for 10 minutes, add water to make 50 mL, and filter. Add 1 drop of methyl orange TS to the filtrate, and add ammonia TS until the solution turns yellow. Perform the test with a precipitate produced by warming on a steam bath under the Qualitative Analysis (1) and (4) for aluminum salt.

(2) ***Magnesium carbonate***—Warm the filtrate in (1) on a steam bath, add 5 mL of thermosaturated ammonium oxalate TS, and allow to stand for 1 hour on a steam bath to complete precipitation. Filter while hot and wash with hot water. With these solutions, perform the test as directed under the Qualitative Analysis for magnesium salt.

(3) ***Oxethazaine***—Determine the absorption spectra of Dried Aluminum Hydroxide Gel, Magnesium Carbonate and Oxethazaine Tablets as directed under the Ultraviolet-visible Spectroscopy under the Assay; the test solution and the standard solution exhibit a maximum at the same wavelength.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Acid-neutralizing capacity Weigh accurately the mass of NLT 20 tablets of Dried Aluminum Hydroxide Gel, Magnesium Carbonate and Oxethazaine Tablets, and powder. The amount of 0.1 mol/L hydrochloric acid consumed for daily dose (4 tablets) as directed under the Acid-neutralizing Capacity is NLT 110 mL.

Assay (1) ***Dried aluminum hydroxide gel***—Weigh accurately the mass of NLT 20 tablets of Dried Aluminum Hydroxide Gel, Magnesium Carbonate and Oxethazaine Tablets, and powder. Weigh accurately an amount,

equivalent to about 0.5 g of dried aluminum hydroxide gel, and carbonize. After cooling, add 30 mL of dilute hydrochloric acid to the residue, warm on a steam bath for 10 minutes, cool, then add water to make 100.0 mL. Filter and use the filtrate as the test solution. To 10.0 mL of the filtrate, add 30.0mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt, add 20 mL of acetic acid-ammonium acetate buffer solution, pH 4.8, and then boil for 5 minutes. After cooling, add 55 mL of ethanol, and titrate with 0.05 mol/L zinc acetate VS (indicator: 2 mL of dithizone TS). The endpoint of the titration is when the color of the solution changes from pale green to pale red. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.5490 mg of Al_2O_3

(2) ***Magnesium carbonate***—Take 50.0 mL of the test solution obtained in (1), add 2 drops of methyl orange TS, 2 g of ammonium chloride, and add ammonia TS until a yellow color is observed. Warm on a steam bath, filter, and wash. Warm the filtrate and the washings on a steam bath, add 5 mL of thermosaturated ammonium oxalate TS, and allow to stand for 1 hour on a steam bath to complete precipitation. Filter while it is hot, add barium chloride TS to the washings, and wash until no white precipitate is produced. To the filtrate and the washings, add 3 mL of triethanolamine, 2 mL of potassium cyanide TS (5 in 100) and 10 mL of ammonia-ammonium chloride buffer solution (pH 10.7), and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 1 drop of eryochrome black T-sodium chloride indicator). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.0152 mg of MgO

(3) ***Oxethazaine***—Weigh accurately the mass of NLT 20 tablets of Dried Aluminum Hydroxide Gel, Magnesium Carbonate and Oxethazaine Tablets, and powder. Weigh accurately an amount, equivalent to about 20 mg of oxethazaine ($C_{28}H_{41}N_3O_3$), put in a glass-stoppered Erlenmeyer flask, add 50.0 mL of anhydrous ethanol, stir with a stirrer for 30 minutes, and allow to stand for 10 minutes. Transfer the clear supernatant to a glass-stoppered centrifuge tube, centrifuge at about 3000 rpm for 30 minutes, take 10.0 mL of the clear supernatant, add 2.0 mL of dilute hydrochloric acid, and shake to mix. Use this solution as the test solution. Separately, weigh accurately about 20 mg of oxethazaine RS, put in a glass-stoppered Erlenmeyer flask, and dissolve in 50.0 mL of anhydrous ethanol. To 10.0 mL of this solution, add 2.0 mL of dilute hydrochloric acid, shake to mix, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, at the wavelength of 259 nm as directed under the Ultraviolet-visible Spectroscopy, using a mixture of 10 mL of anhydrous ethanol and 2.0 mL of dilute hydrochloric acid as a control solution.

Amount of oxethazaine ($C_{28}H_{41}N_3O_3$)
= Amount (mg) of oxethazaine RS $\times \frac{A_T}{A_S}$

Packaging and storage Preserve in tight containers.

Labeling description Describe the amounts of aluminum oxide and magnesium oxide.

Dried Aluminum Hydroxide Gel, Magnesium Hydroxide and Oxethazaine Oral Suspension

건조수산화알루미늄겔·수산화마그네슘·옥세타자인 현탁액

Dried Aluminum Hydroxide Gel, Magnesium Hydroxide and Oxethazaine Oral Suspension contains NLT 90.0% and NMT 110.0% of the labeled amount of aluminum oxide in dried aluminum hydroxide gel (Al_2O_3 : 101.96), magnesium oxide [$Mg(OH)_2$: 58.32] and oxethazaine ($C_{28}H_{41}N_3O_3$: 467.70).

Method of preparation Prepare as directed under Suspensions, with Dried Aluminum Hydroxide Gel, Magnesium Hydroxide and Oxethazaine.

Identification (1) ***Dried aluminum hydroxide gel—*** Take 1 g of dried aluminum hydroxide gel according to the labeled amount of Dried Aluminum Hydroxide Gel, Magnesium Hydroxide and Oxethazaine Oral Suspension and carbonize. After cooling, add 30 mL of dilute hydrochloric acid to the residue, warm on a steam bath for 10 minutes, add water to make 50 mL, and filter. To the filtrate, add 1 drop of methyl orange TS and add ammonia TS until it exhibits a yellow color. Warm on a steam bath, take the formed precipitate, and perform the test with it as directed under the Qualitative Analysis (1) and (4).

(2) ***Magnesium hydroxide—***Take 5 g of Dried Aluminum Hydroxide Gel, Magnesium Hydroxide and Oxethazaine Oral Suspension, add 25 mL of 1 mol/L sulfuric acid, mix, and allow to stand for 5 minutes. To this solution, add 25 mL of ethanol, mix, allow to stand in an ice bath for 30 minutes, and filter. To the filtrate, add 5 drops of methyl red TS and boil. Add 6 mol/L ammonium hydroxide solution until the resulting solution turns to a yellow color, and continue to boil for 2 more minutes, and filter. To the filtrate, add ammonium carbonate TS in the presence of ammonium chloride; no more precipitate is formed. To this, add sodium monohydrogen phosphate TS; a white crystalline precipitate is formed. To this, add

6 mol/L ammonium hydroxide solution; the precipitate is not dissolved.

(3) ***Oxethazaine*—**Determine the absorption spectrum of Dried Aluminum Hydroxide Gel, Magnesium Hydroxide and Oxethazaine Oral Suspension as directed under the Ultraviolet-visible Spectroscopy; the spectra of the test solution and the standard solution exhibit similar intensities of absorption at the same wavelengths.

pH Between 7.5 and 9.5.

Assay (1) ***Aluminum oxide in dried aluminum hydroxide gel***—Weigh accurately Dried Aluminum Hydroxide Gel, Magnesium Hydroxide and Oxethazaine Oral Suspension in the amount equivalent to about 0.20 g of aluminum oxide (Al_2O_3) and carbonize. After cooling, add 30 mL of dilute hydrochloric acid to the residue, and warm on a steam bath for 10 minutes. After cooling, add water to make 100.0 mL, filter, and use the filtrate as the test solution. Take 20.0 mL of the filtrate, add 30.0 mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt solution and 20 mL of acetic acid-ammonium acetate buffer solution (pH 4.8), and boil for 5 minutes. After cooling, add 55 mL of ethanol and titrate with 0.05 mol/L zinc acetate VS (indicator: 2 mL of dithizone TS). However, the endpoint of titration is when the pale dark green color of the solution turns to a pale red color. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.5490 mg of Al_2O_3

(2) ***Magnesium hydroxide*—**Weigh accurately an amount of Dried Aluminum Hydroxide Gel, Magnesium Hydroxide and Oxethazaine Oral Suspension, equivalent to about 0.8 g as magnesium hydroxide, add 20 mL of water, and mix. Slowly add 40 mL of 3 mol/L hydrochloric acid, melt with slow heating, if necessary, cool, and add water to make 200.0 mL. Take 10.0 mL of this solution, add 200 mL of water and 20 mL of triethanolamine, and mix well. Add 50 mL of ammonia-ammonium chloride buffer solution (pH 10.7) and 2 drops of eryochrome black T indicator (prepared by dissolving 200 mg of eryochrome black T in 15 mL of triethanolamine and 5 mL of dehydrated alcohol). Allow to stand in an ice bath to cool to 3 to 4 ℃ and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS until the resulting solution turns to a blue color. Perform a blank test using 10 mL of water instead of the test solution and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.9160 mg of $Mg(OH)_2$

(3) ***Oxethazaine*—**Weigh accurately an amount of Dried Aluminum Hydroxide Gel, Magnesium Hydroxide and Oxethazaine Oral Suspension, equivalent to about 20 mg of oxethazaine ($C_{28}H_{41}N_3O_3$), put in an Erlenmeyer flask with a glass stopper, and add 50.0 mL of anhydrous ethanol. Stir with a stirrer for 30 minutes and allow to stand for 10 minutes. Take the clear supernatant, put in a centrifuge column with a glass stopper, and centrifuge at 3000 rpm for 30 minutes. Take 10.0 mL of the clear supernatant, add 2.0 mL of dilute hydrochloric acid, shake to mix, and use this solution as the test solution. Separately, weigh accurately about 20 mg of oxethazaine RS, put in an Erlenmeyer with a glass stopper, and dissolve in 50.0 mL of anhydrous ethanol. Take 10.0 mL of this solution, add 2.0 mL of dilute hydrochloric acid, shake to mix, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using a mixture of 10 mL of anhydrous ethanol and 2.0 mL of dilute hydrochloric acid as the control solution, and determine the absorbances, A_T and A_S, respectively, at the wavelength of 259 nm.

Amount (mg) of oxethazaine ($C_{28}H_{41}N_3O_3$)
= Amount (mg) of oxethazaine RS $\times \frac{A_T}{A_S}$

Packaging and storage Preserve in tight containers.

Labeling The amount of aluminum oxide is indicated.

Colloidal Aluminum Phosphate
콜로이드성알루미늄인산염

$AlPO_4$: 121.95
Phosphoric acid, aluminum salt, [*98499-64-0*]

Colloidal Aluminum Phosphate contains NLT 20.0% and NMT 25.0% of aluminum phosphate ($AlPO_4$).

Description Colloidal Aluminum Phosphate occurs as a white to milky white, viscous suspension. It is insoluble in water, and soluble in dilute hydrochloric acid.

pH Between 5.0 and 7.2 (1 in 2 aqueous solution).

Identification Weigh 2 g of Colloidal Aluminum Phosphate, add 20 mL of dilute hydrochloric acid, heat to boiling to dissolve, and filter; the filtrate responds to the Qualitative Analysis for aluminum salt and phosphate.

Purity (1) ***Chloride***—Weigh 1.0 g of Colloidal Aluminum Phosphate, add 15 mL of dilute nitric acid, dissolve by boiling, cool, and add water to make 200 mL. Filter and take 25 mL of the filtrate, if needed, and perform the test. Prepare the control solution with 1.0 mL of 0.01 mol/L hydrochloric acid (NMT 0.28%).

(2) ***Sulfate***—Weigh 5.0 g of Colloidal Aluminum Phosphate, add 30 mL of dilute hydrochloric acid, dissolve by boiling, cool, and add water to make 100 mL.

Take 10 mL of this solution and perform the test. Prepare the control solution with 1.25 mL of 0.01 mol/L sulfuric acid (NMT 0.12%).

(3) ***Soluble phosphate***—Filter 8 g of Colloidal Aluminum Phosphate. Wash the residue with 30 mL of water, combine the filtrate and washings, add 2 mL of nitric acid, and heat to 60 ℃. Add 20 mL of ammonium molybdate TS, heat for 30 minutes at 50 ℃, and filter. Wash the precipitate with diluted nitric acid (1 in 36), then wash with potassium nitrate solution (1 in 100) until the filtrate becomes neutral. Dissolve the precipitate in 50.0 mL of 0.1 mol/L sodium hydroxide VS, add phenolphthalein TS, and titrate with 0.1 mol/L hydrochloric acid VS. Perform a blank test in the same manner and make any necessary correction (NMT 0.2%).

Each mL of 0.1 mol/L sodium hydroxide VS
= 0.413 mg of PO_4

(4) ***Heavy metal***—Weigh 1.0 g of Colloidal Aluminum Phosphate, dissolve in 10 mL of water and 0.5 mL of hydrochloric acid, filter if needed, neutralize with 2 mol/L sodium hydroxide TS, add water to make 50 mL, and perform the test. Prepare the control solution with 4.0 mL of lead standard solution (NMT 40 ppm).

(5) ***Arsenic***—Dissolve 1.0 g of Colloidal Aluminum Phosphate in 5 mL of water and 5 mL of hydrochloric acid. Take 5 mL of this solution and perform the test (NMT 4 ppm).

Acid-neutralizing capacity Weigh accurately about 0.5 g of Colloidal Aluminum Phosphate, add 50.0 mL of 0.1 mol/L hydrochloric acid, heat for 30 minutes at 37 ℃, shake occasionally, cool, and titrate to pH 3.5 using 0.1 mol/L sodium hydroxide VS. The volume of 0.1 mol/L hydrochloric acid consumed per 1.0 g of aluminum phosphate ($AlPO_4$) in Colloidal Aluminum Phosphate is NLT 50 mL.

Assay Weigh accurately about 0.5 g of Colloidal Aluminum Phosphate, add 15 mL of dilute nitric acid, and heat to dissolve. After cooling, add 25.0 mL of disodium ethylenediaminetetraacetate VS, boil on a steam bath for 5 minutes, and cool. To this solution, add 20 mL of acetic acid-sodium acetate buffer solution, pH 4.5, and 50 mL of ethanol, add 1 mL of dithizone TS and back-titrate with 0.05 mol/L zinc sulfate VS until the color changes from bluish green to bright violet. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L disodium ethylenediaminetetraacetate VS
= 6.098 mg of $AlPO_4$

Packaging and storage Preserve in tight containers.

Natural Aluminum Silicate
천연규산알루미늄

Description Natural Aluminum Silicate occurs as a white or slightly colored powder, and is odorless and tasteless.
It is practically insoluble in water, ethanol(95) or ether.
To 1 g of Natural Aluminum Silicate, add 20 mL of sodium hydroxide solution (1 in 5) and heat; it is partially decomposed to dissolve, but it mostly remains undissolved.

Identification (1) To 0.5 g of Natural Aluminum Silicate, add 3 mL of diluted sulfuric acid (1 in 3), heat until white fumes are produced, cool, add 20 mL of water and filter. Render the filtrate slightly acidic with ammonia TS; the solution responds to the Qualitative Analysis for aluminum salt.

(2) Prepare a bead by fusing sodium ammonium phosphate tetrahydrate on a platinum loop. Place the bead in contact with Natural Aluminum Silicate and fuse again; an infusible mass appears in the bead, and the bead becomes opaque upon cooling, and a web-like shape appears.

Purity (1) ***Acidity or alkalinity***—Add 5.0 g of Natural Aluminum Silicate in 100 mL of water, shake to mix and centrifuge; the clear supernatant obtained is neutral.

(2) ***Chloride***—To 5.0 g of Natural Aluminum Silicate, add 100 mL of water, boil gently for 15 minutes while shaking well to mix, then cool, add water to make 100 mL and centrifuge. To 10 mL of the clear supernatant, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.021%).

(3) ***Sulfate***—To the residue obtained from (6), add 3 mL of dilute hydrochloric acid, heat on a steam bath for 10 minutes, dilute with 50 mL of water and filter. To 2.0 mL of the filtrate, add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.480%).

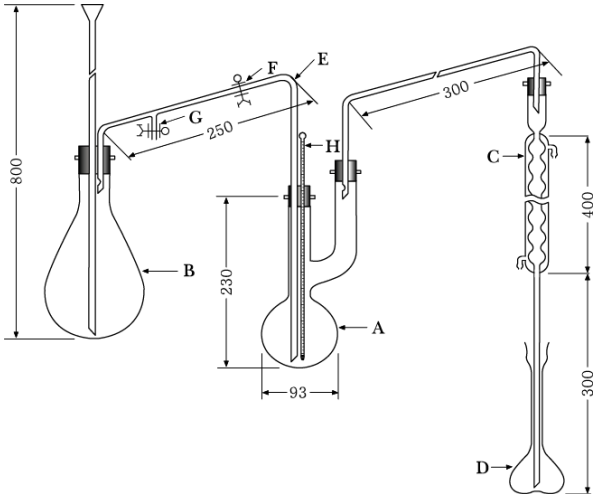
(4) ***Heavy metals***—To 1.5 g of Natural Aluminum Silicate, add 50 mL of water and 5 mL of hydrochloric acid, boil gently for 20 minutes while shaking well to mix, then cool, centrifuge, take the clear supernatant, wash the residue twice with 10 mL each of water and centrifuge each time. Combine the washings with the clear supernatant, and add ammonia water(28) dropwise until precipitate is formed slightly. Add dilute hydrochloric acid dropwise with vigorous shaking and redissolve the precipitate. Heat this solution with 0.45 g of hydroxylamine hydrochloride, cool and add 0.45 g of sodium acetate trihydrate, 6 mL of dilute acetic acid and water to make 150 mL. Perform the test with 50 mL of this solution as the test solution. Prepare the control solution with 2.0 mL of lead standard solution, 0.15 g of hydrox-

ylamine hydrochloride, 0.15 g of sodium acetate trihydrate, 2 mL of dilute acetic acid and water to make 50 mL (NMT 40 ppm).

(5) ***Arsenic***—To 1.0 g of Natural Aluminum Silicate, add 5 mL of dilute hydrochloric acid, heat gently to boil while shaking well to mix, cool rapidly and centrifuge. Add 5 mL of dilute hydrochloric acid to the residue, shake well to mix, and centrifuge. Add 10 mL of water again to perform the same procedure, add all the extracts, and heat to concentrate on a steam bath to make 5 mL. Use this solution as the test solution (NMT 2 ppm).

(6) ***Soluble Salts***—Evaporate 50 mL of the clear liquid obtained from (1) on a steam bath to dryness and ignite the residue at 700 ºC for 2 hours; the amount (mg) of the ignited residue is NMT 40 mg.

(7) ***Fluoride***—(i) Apparatus: Use an apparatus as illustrated in the figure. The apparatus is made of hard glass and ground-glass joints may be used.



*Numbers are indicated in mm.

A: Distilling flask of about 300-mL capacity
B: Steam generator of about 1000-mL capacity
Add a boiling stone to prevent bumping.
C: Condenser
D: Receiver, 200-mL volumetric flask
E: Steam-introducing tube about 8 mm in internal diameter
F, G: Rubber tube with a pinch-coke
H: Thermometer

(ii) Procedure: Transfer 5.0 g of Natural Aluminum Silicate to the distilling flask A using 20 mL of water, and add about 1 g of glass wool and 50 mL of diluted purified sulfuric acid (1 in 2). Connect A to the distillation apparatus, previously washed with steam through the steam-introducing tube E. Add 10 mL of 0.01 mol/L sodium hydroxide solution and 10 mL of water into the receiver D, and immerse the lower end of condenser C in this solution. Heat A gradually until the temperature of the solution reaches 130 ºC, then open the rubber tube F, close the rubber tube G, and pass the steam in the steam generator B by boiling water vigorously. At the same time, heat A to maintain the temperature of the solution in A between 135 and 145 ºC. Adjust the distilling rate to about 10 mL per minute. Collect about 170 mL of the distillate, then stop the distillation, wash C with a small quantity of water, combine the washings with the distillate, and add water to make exactly 200 mL. Use this solution as the test solution, and perform the test with the test solution as directed under the fluoride assay under the Oxygen Flask Combustion. Calculate the amount of fluoride (F) in the test solution according to the following formula; the amount is NMT 0.01%. However, no corrective solution is prepared.

$$\text{Amount (mg) of fluoride (F: 19.00) in the test solution} = \text{Amount (mg) of fluoride in 5 mL of the standard solution} \times \frac{A_T}{A_S} \times \frac{200}{V}$$

Loss on drying NMT 20.0% (1 g, 105 ºC, 3 hours).

Adsorptive power To 0.10 g of Natural Aluminum Silicate, add 20 mL of methylene blue solution (3 in 2000), shake for 15 minutes to mix, allow to stand for 5 hours at 37 ± 2 ºC and centrifuge. Take 1.0 mL of the clear supernatant, and add water to make 200 mL. Place 50 mL of the solution in a Nessler tube and observe horizontally or vertically against a white background; the color of the solution is not more intense than that of the following control solution.

Control solution—Dilute 1.0 mL of a solution of methylene blue (3 in 2000) with water to make 400 mL, and use 50 mL of this solution.

Packaging and storage Preserve in well-closed containers.

Synthetic Aluminum Silicate
합성규산알루미늄

Description Synthetic Aluminum Silicate occurs as a white powder.
It is odorless and tasteless.
It is practically insoluble in water, ethanol(95), or ether.
To 1 g of Synthetic Aluminum Silicate, add 20 mL of sodium hydroxide solution (1 in 5), and heat; it dissolves, leaving behind slight insoluble substances.

Identification Perform the test as directed under the Identification of Natural Aluminum Silicate.

Purity (1) ***Acidity or alkalinity***—To 1.0 g of Synthetic Aluminum Silicate, add 20 mL of water, shake to mix, and centrifuge; the clear supernatant is neutral.

(2) ***Chloride—***Perform the test as directed in Purity (2) under Natural Aluminum Silicate.

(3) ***Sulfate***—Take 2.0 mL of the clear liquid from

(2), and add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.480%).

(4) ***Heavy metals***—Proceed with 3.0 g of Synthetic Aluminum Silicate according to Purity (4) of Natural Aluminum Silicate and perform the test. However, prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

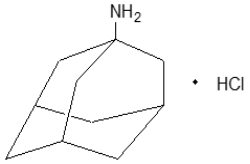
(5) ***Arsenic***—To 1.0 g of Synthetic Aluminum Silicate, add 10 mL of dilute hydrochloric acid, perform the test according to Purity (5) of Natural Aluminum Silicate (NMT 2 ppm).

Loss on drying NMT 20.0% (1 g, 105 ℃, 3 hours)

Acid-neutralizing capacity Weigh accurately about 1 g of Synthetic Aluminum Silicate, transfer into a stoppered flask, add exactly 200 mL of 0.1 mol/L hydrochloric acid, close the stopper, shake to mix for 1 hour at 37 ± 2 ℃, and filter. Pipet 50 mL of the filtrate, and titrate the excess hydrochloric acid while stirring well, with 0.1 mol/L sodium hydroxide VS until the pH becomes 3.5. The volume of 0.1 mol/L hydrochloric acid consumed for 1 g of Synthetic Aluminum Silicate is NLT 50.0 mL.

Packaging and storage Preserve in well-closed containers.

Amantadine Hydrochloride
아만타딘염산염



$C_{10}H_{17}N \cdot HCl$: 187.71

Adamantan-1-amine hydrochloride [*665-66-7*]

Amantadine Hydrochloride, when dried, contains NLT 99.0% and NMT 101.0% of amantadine hydrochloride ($C_{10}H_{17}N \cdot HCl$).

Description Amantadine Hydrochloride occurs as a white crystalline powder, which is odorless and has a bitter taste.

It is very soluble in formic acid, freely soluble in water, methanol or ethanol(95), and practically insoluble in ether.

Identification (1) Add 1 mL of pyridine and 0.1 mL of acetic anhydride to 0.1 g of Amantadine Hydrochloride, boil for 1 minute to dissolve, add 10 mL of dilute hydrochloric acid, and cool in iced water. Take the precipitated crystals by filtering, wash with water, and dry at 105 °C for 1 hour; the melting point is between 147 and 151 °C.

(2) Determine the infrared spectra of Amantadine Hydrochloride and amantadine hydrochloride RS, previously dried, as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Amantadine Hydrochloride (1 in 50) responds to the Qualitative Analysis for chloride.

pH Dissolve 1.0 g of Amantadine Hydrochloride in 5 mL of water; the pH of this solution is between 4.0 and 6.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Amantadine Hydrochloride in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 2.0 g of Amantadine Hydrochloride according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Amantadine Hydrochloride according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.50 g of Amantadine Hydrochloride in 10 mL of water, add 10 mL of sodium hydroxide TS and 10 mL of chloroform, and shake to mix well. Filter the chloroform layer through a funnel where 3 g of anhydrous sodium sulfate is placed on absorbent cotton ball and use the filtrate as the test solution. Pipet 1 mL of this solution, add chloroform to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 2 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution according to the automatic integration method; each peak area other than the major peak from the test solution is not greater than 1/3 of the major peak area from the standard solution. Also, the sum of each peak area is not greater than the major peak area from the standard solution.

Operating conditions

Detector: A flame ionization detector

Column: A glass column, about 3 mm in inside diameter and about 2 m in length, filled with diatomaceous earth for gas chromatography (150 to 180 μm in particle diameter) coated with petroleum-based hexamethyltetracosane branched hydrocarbon mixture for gas chromatography (L) and potassium hydroxide at the ratio of 2% and 1%, respectively.

Column temperature: Inject at a constant temperature of about 125 °C, keep this temperature for 5 minutes, then raise to 150 °C at a rate of 5 °C per minute, and keep at a constant temperature of about 150 °C for 15 minutes.

Carrier gas: Nitrogen

Flow rate: Adjust the flow rate so that the retention time of amantadine is about 11 minutes.

System suitability

Detection sensitivity: Adjust the sensitivity so that the peak height of amantadine from 2 μL of the standard solution is about 10% of the full scale.

System performance: Dissolve 0.15 g of naphthalene in 5 mL of the test solution and add chloroform to make 100 mL. Proceed with 2 μL of this solution under the above operating conditions; naphthalene and amantadine are eluted in this order with the resolution being NLT 2.5.

Time span of measurement: About 2 times the retention time of amantadine beginning after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.2 g of Amantadine Hydrochloride, previously dried, dissolve in 2 mL of formic acid, add exactly 15 mL of 0.1 mol/L perchloric acid and heat on a steam bath for 30 minutes. After cooling, add acetic acid(100) to make 70 mL and titrate the exceeding amount of perchloric acid with 0.1 mol/L sodium acetate VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner.

Each mL of 0.1 mol/L perchloric acid VS
= 18.771 mg of $C_{10}H_{17}N \cdot HCl$

Packaging and storage Preserve in well-closed containers.

Ambroxol Hydrochloride Injection
암브록솔염산염 주사액

Ambroxol Hydrochloride Injection contains NLT 93.0% and NMT 107.0% of the labeled amount of ambroxol hydrochloride ($C_{13}H_{18}Br_2N_2O \cdot HCl$: 414.56).

Method of preparation Prepare Ambroxol Hydrochloride Injection as directed under Injections, with Ambroxol Hydrochloride.

Identification Take an amount of Ambroxol Hydrochloride Injection equivalent to 30 mg of ambroxol hydrochloride according to the labeled amount, add water to make 10 mL, and use this solution as the test solution. Separately, weigh accurately about 30 mg of ambroxol hydrochloride RS, dissolve in 10 mL of water, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of toluene, isopropanol and strong ammonia water (80 : 20 : 0.2) as the developing solvent and air-dry the plate. Examine the plate under ultraviolet light (main wavelength 254 nm); the R_f values and colors of the spots obtained from the test solution and the standard solution are the same.

pH Between 4.0 and 6.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 1 EU per mg of ambroxol hydrochloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Ambroxol Hydrochloride Injection equivalent to 30 mg of ambroxol hydrochloride ($C_{13}H_{18}Br_2N_2O \cdot HCl$) according to the labeled amount. Place in a 100-mL separatory funnel, add 10 mL of 2 mol/L sodium hydroxide TS, and extract 2 times with 45 mL of ether. Combine the ether layers and place in a 250-mL separatory funnel, and wash 2 times with 10 mL of water. Place anhydrous sodium sulfate on the filter paper, filter the ether layer, and evaporate the filtrate to dryness. Add 0.1 mol/L methanolic hydrochloric acid TS to the residue to make 100 mL, and filter. Take 10.0 mL of the filtrate, add 0.1 mol/L methanolic hydrochloric acid TS to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 30 mg of ambroxol hydrochloride RS, transfer to a 100-mL separatory funnel, proceed in the same manner as the test solution, and use this solution as the standard solution. With the test solution and the standard solution, perform the test as directed under the Ultraviolet-visible Spectroscopy using 0.1 mol/L methanolic hydrochloric acid TS as the control solution, and determine the absorbances, A_T and A_S, at 313 nm.

Amount (mg) of ambroxol hydrochloride ($C_{13}H_{18}Br_2N_2O \cdot HCl$)
$= \text{Amount (mg) of ambroxol hydrochloride RS} \times \frac{A_T}{A_S}$

Packaging and storage Preserve in hermetic containers.

Ambroxol Hydrochloride Syrup
암브록솔염산염 시럽

Ambroxol Hydrochloride Syrup contains NLT 93.0% and NMT 107.0% of the labeled amount of am-

broxol hydrochloride ($C_{13}H_{18}Br_2N_2O \cdot HCl$: 414.56).

Method of preparation Prepare as directed under Syrups, with Ambroxol Hydrochloride.

Identification Weigh accurately an amount of Ambroxol Hydrochloride Syrup, equivalent to 30 mg of ambroxol hydrochloride according to the labeled amount, and transfer to a separatory funnel. Add 10 mL of 1 mol/L sodium hydroxide TS and extract 2 times with each 45 mL of ether. Combine the ether layers, transfer to a 250-mL separatory funnel, and wash 2 times with each 10 mL of water. Filter the ether extracts through a layer of anhydrous sodium sulfate and evaporate the filtrate to dryness. Dissolve the residue in 10 mL of water and use the solution as the test solution. Separately, weigh accurately 45 mg of ambroxol hydrochloride RS and dissolve in 15 mL of water. Take 10 mL of the solution, transfer to a separatory funnel, proceed in the same manner as for the preparation of the test solution, and use the resulting solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each 5 μL of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate using a mixture of toluene, isopropanol and ammonia water(28) (40 : 10 : 0.1) as a developing solvent, and air-dry the plate. Examine the plate under ultraviolet light (principal wavelength 254 nm); the spots of the test solution exhibit an R_f values and color corresponding to that of the standard solution.

pH Between 2.0 and 4.0.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Shake Ambroxol Hydrochloride Syrup to mix, pipet an amount equivalent to 30 mg of ambroxol hydrochloride ($C_{13}H_{18}Br_2N_2O \cdot HCl$: 414.56). Place in a 100-mL separatory funnel, add 10 mL of 2 mol/L sodium hydroxide TS, and extract 2 times with 45 mL of ether. Combine the ether layers, transfer to a 250-mL separatory funnel, and wash 2 times with each 10 mL of water. Place anhydrous sodium sulfate on the filter paper, filter the ether layer, and evaporate the filtrate to dryness. To the residue, add 0.1 mol/L methanolic hydrochloric acid TS to make exactly 100 mL, and filter. Pipet 10 mL of this solution, add 0.1 mol/L methanolic hydrochloric acid TS to make exactly 50 mL, and use the solution as the test solution. Separately, weigh accurately about 0.15 g of ambroxol hydrochloride RS and add water to make exactly 50 mL. Pipet 10 mL of the solution, transfer to a 100-mL separatory funnel, proceed in the same manner as for the preparation of the test solution, and use the resulting solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution at the wavelength of 313 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of ambroxol hydrochloride ($C_{13}H_{18}Br_2N_2O \cdot HCl$)
= Amount (mg) of ambroxol hydrochloride RS
$\times (A_T / A_S) \times (1 / 5)$

Packaging and storage Preserve in tight containers.

Ambroxol Hydrochloride Tablets
암브록솔염산염 정

Ambroxol Hydrochloride Tablets contain NLT 93.0% and NMT 107.0% of ambroxol hydrochloride ($C_{13}H_{18}Br_2N_2O$ HCl : 414.56) of the labeled amount.

Method of preparation Prepare Ambroxol Hydrochloride Tablets as directed under Tablets, with Ambroxol Hydrochloride.

Identification Weigh an amount of Ambroxol Hydrochloride Tablets, equivalent to about 40 mg of ambroxol hydrochloride, according to the labeled amount, and transfer to a 100-mL separatory funnel. Add 5 mL of water and 0.5 mL of 0.5 mol/L sodium hydroxide TS, and extract with 10 mL of ether. Filter the ether extract, and use the filtrate as the test solution. Separately, weigh accurately 40 mg of ambroxol hydrochloride RS, transfer to a 100-mL separatory funnel, proceed in the same manner as for the test solution, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of toluene, isopropanol and strong ammonia water (80 : 20 : 0.2) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f value and color of the spots obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 tablet of Ambroxol Hydrochloride Tablets at 50 revolutions per minute according to Method 2, using 900 mL of water as the dissolution medium. Take the dissolved solution 30 minutes after starting the dissolution test, filter and use the filtrate as the test solution. Separately, weigh accurately about 30 mg of ambroxol hydrochloride RS, and add water to make 100 mL. Take 5.0 mL of this solution, add water to make 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 313 nm as directed under the Ultraviolet-visible Spectroscopy. The acceptable dissolution criterion is NLT 80% of Ambroxol Hydrochloride Tablets dissolved in 30 minutes.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Ambroxol Hydrochloride Tablets, and powder. Weigh accurately an amount, equivalent to about 15 mg of ambroxol hydrochloride ($C_{13}H_{18}Br_2N_2O$·HCl), transfer to a 100-mL volumetric flask, add 60 mL of methanol and extract for 15 minutes. Add methanol to make 100 mL, and filter. Transfer 50.0 mL of the filtrate to a 100-mL volumetric flask, add 10 mL of 0.1 mol/L methanolic hydrochloric acid TS, add methanol to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 75 mg of ambroxol hydrochloride RS, transfer to a 100-mL volumetric flask, and add 0.1 mol/L methanolic hydrochloric acid TS to make 100 mL. Take 10.0 mL of this solution, add 0.1 mol/L methanolic hydrochloric acid TS to make 100 mL, and use this solution as the standard solution. With the test solution and the standard solution, perform the test as directed under the Ultraviolet-visible Spectroscopy using 0.1 mol/L methanolic hydrochloric acid TS as a control solution; determine the absorbances, A_T and A_S, at the wavelength of 313 nm.

$$\text{Amount (mg) of ambroxol hydrochloride } (C_{13}H_{18}Br_2N_2O\cdot HCl) = \text{Amount (mg) of ambroxol hydrochloride} \times \frac{A_T}{A_S} \times \frac{1}{5}$$

Packaging and storage Preserve in well-closed containers.

Ambroxol Hydrochloride and Clenbuterol Hydrochloride Syrup
암브록솔염산염·클렌부테롤염산염 시럽

Ambroxol Hydrochloride and Clenbuterol Hydrochloride Syrup contains NLT 90.0% and NMT 110.0% of ambroxol hydrochloride ($C_{13}H_{18}Br_2N_2O$ ·HCl : 414.56) and clenbuterol hydrochloride ($C_{12}H_{18}Cl_2N_2O$ ·HCl : 313.65), according to the labeled amount.

Method of preparation Prepare as directed under Syrups, with Ambroxol Hydrochloride and Clenbuterol Hydrochloride.

Identification (1) ***Ambroxol hydrochloride***—Weigh accurately an amount of Ambroxol Hydrochloride and Clenbuterol Hydrochloride Syrup, equivalent to 30 mg of ambroxol hydrochloride according to the labeled amount, and transfer to a separatory funnel. Add 10 mL of 1 mol/L sodium hydroxide TS and extract 2 times with each 45 mL of ether. Combine the ether layers, transfer to a 250-mL separatory funnel, and wash 2 times with each 10 mL of water. Filter the ether extracts through anhydrous sodium sulfate placed on a filter paper and evaporate the filtrate to dryness. Dissolve the residue in 10 mL of water and use this solution as the test solution. Separately, weigh 45 mg of ambroxol hydrochloride RS and dissolve in 15 mL of water. Take 10 mL of the solution, transfer to a separatory funnel, proceed in the same manner as for the preparation of the test solution, and use the resulting solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each 5 μL of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate using a mixture of toluene, isopropanol and ammonia water(28) (40 : 10 : 0.1) and air-dry the plate. Expose the plate to ultraviolet rays (main wavelength: 254 nm); the R_f values and the colors of the spots obtained from the test solution and the standard solution are the same.

(2) ***Clenbuterol hydrochloride***—Weigh an amount of Ambroxol Hydrochloride and Clenbuterol Hydrochloride Syrup, equivalent to 0.1 mg of clenbuterol hydrochloride, transfer to a 250-mL separatory funnel, and add 50 mL of water to mix. Next, add 5 mL of 2 mol/L sodium hydroxide to make the solution alkaline and extract 3 times with each 50 mL of ether. Combine the extracts, wash with 50 mL of water, remove water by filtering through anhydrous sodium sulfate placed on a filter paper, and evaporate to dryness on a steam bath. Dissolve the residue in 0.5 mL of methanol and use this solution as the test solution. Separately, dissolve 10 mg of clenbuterol hydrochloride RS in 50 mL of methanol and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with fluorescent indicator). Next, develop the plate with a mixture of toluene, isopropanol, and ammonia (80 : 20 : 1) and air-dry the plate. Expose the plate to ultraviolet rays (main wavelength: 254 nm); the R_f values and the colors of the spots obtained from the test solution and the standard solution are the same.

(3) The retention times of the major peaks obtained from the test solution and the standard solution under the Assay are the same.

pH Between 4.0 and 6.0.

Uniformity of dosage units (distribution) Meets the requirements.

Assay (1) ***Ambroxol hydrochloride***—Weigh accurately an amount of Ambroxol Hydrochloride and Clenbuterol Hydrochloride Syrup, equivalent to 10 mg of ambroxol hydrochloride ($C_{13}H_{18}Br_2N_2O$ ·HCl), transfer to a 250-mL separatory funnel, and add 50 mL of water to mix. Add 10 mL of 2 mol/L sodium hydroxide solution to make it alkaline, shake well to mix 5 times with 30 mL each of ether using a shaker, collect the ether layer, and wash with 30 mL of water. Put anhydrous sodium sulfate on a filter paper, filter the collected ether layer, and evap-

orate the filtrate to dryness. To the residue, add 0.1 mol/L methanolic hydrochloric acid TS to make exactly 100 mL. Filter the solution, take exactly 10 mL of the filtrate, add 0.1 mol/L methanolic hydrochloric acid TS to make exactly 50 mL, and use the solution as the test solution. Separately, weigh accurately about 50 mg of ambroxol hydrochloride RS and add water to make exactly 50 mL. Take exactly 10 mL of the solution, transfer to a separatory funnel, proceed in the same manner as for the preparation of the test solution, and use the resulting solution as the standard solution. Perform the test with each 20 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak areas, A_T and A_S, of ambroxol hydrochloride from the test solution and the standard solution.

Amount (mg) of ambroxol hydrochloride ($C_{13}H_{18}Br_2N_2O$·HCl)
= Amount (mg) of ambroxol hydrochloride RS × (A_T / A_S) × 1/5

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with cyanosilyl silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Adjust the pH of a mixture of 0.15% sodium 1-heptanesulfonate, methanol and isopropanol (40 : 9 : 1) to 3.0 with acetic acid(100).

Flow rate: 1.2 mL/min

(2) ***Clenbuterol hydrochloride***—Weigh accurately an amount of Ambroxol Hydrochloride and Clenbuterol Hydrochloride Syrup, equivalent to 0.1 mg of clenbuterol hydrochloride ($C_{12}H_{18}Cl_2N_2O$·HCl), transfer to a 500-mL separatory funnel, and add 50 mL of water to mix. Add 5 mL of 2 mol/L sodium hydroxide to make the solution basic, extract 5 times with each 40 mL of ether while mixing well with a shaker, collect the ether layers, and wash with 30 mL of water. Extract the washed ether layer 2 times with each 10 mL of 1 mol/L, collect the water layers into a 25-mL volumetric flask, add 1 mol/L hydrochloric acid TS to make exactly 25 mL, and use the solution as the test solution. Separately, weigh accurately about 25 mg of clenbuterol hydrochloride RS and add 1 mol/L hydrochloric acid TS to make exactly 250 mL. Pipet 1 mL of the solution, add 1 mol/L hydrochloric acid TS to make exactly 25 mL and use this solution as the standard solution. Pipet each 25 μL of the test solution and the standard solution and perform the test according to the operating conditions in (1) Ambroxol hydrochloride under the Assay.

Amount (mg) of clenbuterol hydrochloride ($C_{12}H_{18}Cl_2N_2O$·HCl)
= Amount (mg) of clenbuterol hydrochloride RS × (A_T / A_S) × 1/250

Packaging and storage Preserve in tight containers.

Ambroxol Hydrochloride and Clenbuterol Hydrochloride Tablets
암브록솔염산염·클렌부테롤염산염 정

Ambroxol Hydrochloride and Clenbuterol Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of ambroxol hydrochloride ($C_{13}H_{18}Br_2N_2O$·HCl : 414.56) and clenbuterol hydrochloride ($C_{12}H_{18}Cl_2N_2O$ HCl : 313.65).

Method of preparation Prepare Ambroxol Hydrochloride and Clenbuterol Hydrochloride Tablets as directed under Tablets, with Ambroxol Hydrochloride and Clenbuterol Hydrochloride.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Ambroxol hydrochloride***—Weigh accurately the mass of NLT 20 tablets of Ambroxol Hydrochloride and Clenbuterol Hydrochloride Tablets, and powder. Weigh accurately an amount equivalent to about 10 mg of ambroxol hydrochloride ($C_{13}H_{18}Br_2N_2O$ HCl) and transfer to a 250-mL separatory funnel, add 50 mL of water, and mix. Add 10 mL of 2 mol/L sodium hydroxide solution to make it alkaline, shake well to mix 5 times each with 30 mL of ether using a shaker, collect the ether layer, and wash with 30 mL of water. Place anhydrous sodium sulfate on the filter paper, filter the ether layer, and evaporate the filtrate to dryness. Add 0.1 mol/L methanolic hydrochloric acid TS to the residue to make exactly 100 mL. Filter this solution, take exactly 10 mL of the filtrate, add 0.1 mol/L methanolic hydrochloric acid TS to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of ambroxol hydrochloride RS, and add water to make exactly 50 mL. Take exactly 10 mL of this solution, transfer to a separatory funnel, proceed in the same manner as the test solution, and use this solution as the standard solution. Pipet 20 μL each of the test solution and the standard solution, and perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S of ambroxol hydrochloride of each solution.

Amount (mg) of ambroxol hydrochloride ($C_{13}H_{18}Br_2N_2O$·HCl)
= Amount (mg) of ambroxol hydrochloride RS

$$\times (A_T / A_S) \times 1/5$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with cyanosilyl silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of 0.15% sodium 1-heptanesulfonate solution, methanol, and isopropanol (40 : 9 : 1) adjusted to pH 3.0 with acetic acid(100).

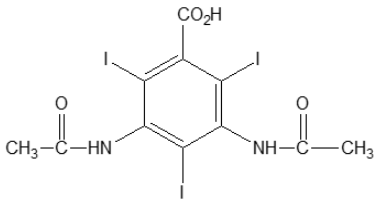
Flow rate: 1.2 mL/min

(2) ***Clenbuterol hydrochloride*—**Weigh accurately the mass of NLT 20 tablets of Ambroxol Hydrochloride and Clenbuterol Hydrochloride Tablets, and powder. Weigh accurately an amount equivalent to about 0.1 mg of clenbuterol hydrochloride ($C_{12}H_{18}Cl_2N_2O \cdot HCl$), transfer to a 500-mL separatory funnel, add 50 mL of water, and mix. Next, add 5 mL of 2 mol/L sodium hydroxide TS to make it alkaline, shake to mix 5 times each with 40 mL of ether using a shaker, collect the ether layer, and wash with 30 mL of water. Extract the washed ether layer twice each with 10 mL of 1 mol/L hydrochloric acid TS, add 1 mol/L hydrochloric acid TS to the water layer to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg of clenbuterol hydrochloride RS, and add 1 mol/L hydrochloric acid TS to make exactly 250 mL. Pipet 1 mL of this solution, add 1 mol/L hydrochloric acid TS to make exactly 25 mL, and use this solution as the standard solution. Pipet 25 μL each of the test solution and the standard solution, and perform the test according to the operating conditions as directed in (1) Ambroxol hydrochloride under Assay.

Amount (mg) of clenbuterol hydrochloride ($C_{12}H_{18}Cl_2N_2O \cdot HCl$)
= Amount (mg) of clenbuterol hydrochloride RS
$\times (A_T / A_S) \times 1/250$

Packaging and storage Preserve in well-closed containers.

Amidotrizoic Acid
아미도트리조산



$C_{11}H_9I_3N_2O_4$: 613.91

3,5-Diacetamido-2,4,6-triiodobenzoic acid [*117-96-4*]

Amidotrizoic Acid contains NLT 98.0% and NMT 101.0% of amidotrizoic acid ($C_{11}H_9I_3N_2O_4$), calculated on the dried basis.

Description Amidotrizoic Acid occurs as a white crystalline powder and is odorless.
It is slightly soluble in ethanol(95), very slightly soluble in water and practically insoluble in ether.
It dissolves in sodium hydroxide TS.

Identification (1) Heat 0.1 g of Amidotrizoic Acid directly over flame; a violet gas is produced.

(2) Determine the infrared spectra of Amidotrizoic Acid and amidotrizoic acid RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Amidotrizoic Acid in 10 mL of 0.2 mol/L sodium hydroxide TS; the resulting solution is colorless and clear.

(2) ***Primary aromatic amines*—**Dissolve 0.20 g of Amidotrizoic Acid in 5 mL of water and 1 mL of sodium hydroxides TS, add 4 mL of a sodium nitrite solution (1 in 100) and 10 mL of 1 mol/L hydrochloric acid TS, shake to mix, and allow to stand for 2 minutes. Next, add 5 mL of ammonium sulfamate TS, shake well to mix, allow to stand for 1 minute, and add 0.4 mL of a solution of 1-naphthol in ethanol (1 in 10), 15 mL of sodium hydroxide TS and water to make exactly 50 mL. Perform the test as directed under the Ultraviolet-visible Spectroscopy using the blank test solution prepared in the same manner as the control solution; the absorbance at 485 nm is NMT 0.15.

(3) ***Soluble halides*—**Dissolve 2.5 g of Amidotrizoic Acid in 20 mL of water and 2.5 mL of ammonia TS, add 20 mL of dilute nitric acid and water to make 100 mL, allow to stand for 15 minutes with occasional shaking, and filter. Discard the first 10 mL of the filtrate, transfer the subsequent 25 mL of the filtrate to a Nessler tube, and add ethanol(95) to make 50 mL. Proceed as directed under the Chloride using this solution as the test solution. Prepare the control solution as follows: to 0.10 mL of 0.01 mol/L hydrochloric acid TS, add 6 mL of dilute nitric acid and water to make 25 mL, and add ethanol(95) to make 50 mL.

(4) ***Iodine*—**Dissolve 0.20 g of Amidotrizoic Acid in 2.0 mL of sodium hydroxide TS, add 2.5 mL of 0.5 mol/L sulfuric acid TS, allow to stand for 10 minutes with occasional shaking, add 5 mL of chloroform, shake well to mix, and allow to stand; the chloroform layer is colorless.

(5) ***Heavy metals***—Proceed with 2.0 g of Amidotrizoic Acid according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(6) **Arsenic**—Prepare the test solution with 0.6 g of Amidotrizoic Acid according to Method 3 and perform

the test (NMT 3.3 ppm).

Loss on drying NMT 7.0% (1 g, 105 ℃, 4 hours).

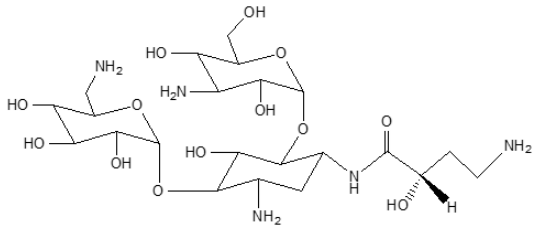
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Amidotrizoic Acid, transfer it into a flask, dissolve in 40 mL of sodium hydroxide TS, and add 1 g of zinc powder. After connecting the flask to a reflux condenser, boil for 30 minutes, cool, and filter. Wash the flask and the filter paper with 50 mL of water and combine the solution used for washings with the filtrate. Add 5 mL of acetic acid(100) to this solution and titrate with 0.1 mol/L silver nitrate VS (indicator: 1 mL of Tetrabromophenolphthalein ethyl ester TS). However, the endpoint of the titration is when the color of the precipitate is changed from yellow to green.

Each mL of 0.1 mol/L silver nitrate VS
= 20.464 mg of $C_{11}H_9I_3N_2O_4$

Packaging and storage Preserve in light-resistant, tight containers.

Amikacin
아미카신



$C_{22}H_{43}N_5O_{13}$: 585.60

(2*S*)-4-Amino-*N*-[(1*R*,2*S*,3*S*,4*R*,5*S*)-5-amino-2-{[(2*S*,3*R*,4*S*,5*S*,6*R*)-4-amino-3,5-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy}-4-{[(2*R*,3*R*,4*S*,5*S*,6*R*)-6-(aminomethyl)-3,4,5-trihydro-xy-oxan-2-yl]oxy}-3-hydroxycyclohexyl]-2-hydroxybutanamide [*37517-28-5*]

Amikacin contains NLT 900 μg (potency) of amikacin ($C_{22}H_{43}N_5O_{13}$) per mg, calculated on the anhydrous basis.

Description Amikacin occurs as a white to pale grayish white, wool-like powder.

Identification (1) Weigh about 60 mg each of Amikacin and amikacin RS, dissolve each in water to obtain solutions having known concentrations of 6 mg per mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 3 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of methanol, ammonia water(28) and chloroform (60:35:25) as the developing solvent for 5 hours and 30 minutes in a 230 x 230 x 90 mm developing chamber. Before the start of the development, fold a 200 x 30 mm Whatman filter paper No. 3 or a filter paper strip made of the same material in the length-wise direction, hang it over the front end of the developing chamber, and place the plate in such a way that it protrudes about 10 mm from the end of the developing chamber to make the silica gel layer slanted forward. Cover all the open areas, except for the filter paper area, for which the developing chamber is closed with a lid for the developing chamber having a hole of 200 × 6 mm, with adhesive tape. After the development is completed, air-dry the plate. Spray evenly the mixture of 100 mL of 1% ninhydrin-butanol solution and 1 mL of pyridine on the plate and heat the plate at 110 °C for 15 minutes to develop a color; the R_f values of the spots obtained from the test solution and the standard solution are the same.

(2) The retention times of the major peaks obtained from the test solution and the standard solution under the Assay are the same.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{25}$: Between +97° and +105° (0.5 g, calculated on the anhydrous basis, water, 25 mL, 100 mm).

pH Dissolve 0.1 g of Amikacin in 10 mL of water; the pH of this solution is between 9.5 and 11.5.

Water NMT 8.5% (0.1 g, volumetric titration, direct titration).

Residue on ignition NMT 1.0% (1 g). However, moisten the carbonized residue with 2 mL of nitric acid and 5 drops of sulfuric acid.

Assay ***The cylinder-plate method***—(1) Medium Agar medium for seed and base layer Use the medium in (A) (2) (a) ① ⓑ under the Microbial Assays for Antibiotics.

(2) Test organism Use *Bacillus subtilis* ATCC 6633 as the test organism.

(3) Weigh accurately about 15 mg (potency) of Amikacin and dissolve it in sterile distilled water to obtain a solution having a known concentration of 400 μg (potency) per mL. Pipet a suitable amount of this solution, add 0.1 mol/L phosphate buffer (pH 8.0) to obtain solutions having a known concentrations of 20.0 μg (potency) and 5.0 μg (potency) per mL., and use these solutions as the high-concentration test solution and the low-concentration test solution, respectively. Separately, weigh accurately about 15 mg (potency) of amikacin sulfate RS, dissolve in 0.05 mol/L phosphate buffer (pH 6.0) to obtain a solution having a known concentration of 400 μg (potency) per mL, and use the solution as the standard

stock solution. Keep this standard stock solution at between 5 and 15 °C, and use it within 30 days. For the assay, pipet a suitable amount of the standard stock solution, add 0.1 mol/L phosphate buffer (pH 8.0) to obtain solutions having a known concentrations of 20.0 μg (potency) and 5.0 μg (potency) per mL, and use these solutions as the high-concentration standard solution and the low-concentration standard solution, respectively. With these solutions, perform the test according to (A)(8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in tight containers.

Amikacin Injection
아미카신 주사액

Amikacin Injection contains NLT 90.0% and NMT 120.0% of the labeled amount of amikacin ($C_{22}H_{43}N_5O_{13}$: 585.61).

Method of preparation Prepare as a liquid injection by adding sulfuric acid to Amikacin as directed under Injections.

Description Amikacin Injection occurs as a colorless to pale yellow liquid.

Identification Proceed as directed under the Identification under Amikacin.

pH Between 3.5 and 5.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.33 EU per mg (potency) of amikacin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

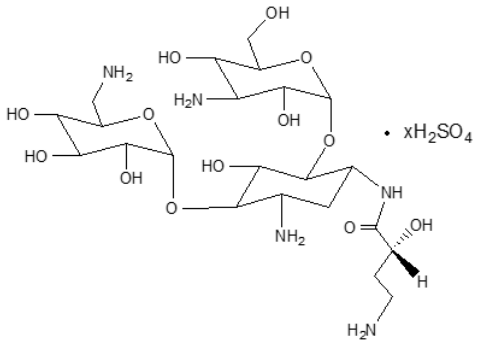
Assay ***Nephelometry***—(1) Medium: Use the liquid medium for suspending a test organism described in (B) (2) under the Microbial Assays for Antibiotics.

(2) Test organism and test organism suspension: Use *Staphylococcus aureus* ATCC 6538P as the test organism. Add 0.1 mL of the cell suspension to 100 mL of the liquid medium for suspending the test organism and use it as the test organism suspension.

(3) Weigh accurately an amount of Amikacin Injection, dilute with sterile purified water to a suitable concentration, pipet an appropriate amount of the solution, and dilute with sterile purified water to obtain a solution having a known concentration of 10.0 μg (potency) per mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of amikacin sulfate RS, and dissolve in a sufficient amount of sterile purified water to obtain a solution having known concentration of 1 mg (potency) per mL. Use this solution as the standard stock solution. Store the standard stock solution at a temperature NLT 5 °C and use it within 14 days. Pipet an appropriate volume of the standard stock solution, dilute with sterile purified water to obtain a solution having known concentrations of 8.0, 8.9, 10.0, 11.2, and 12.5 μg (potency) per mL and use these solutions as the standard solutions. Perform the test with these solutions as directed in (B) (6) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in hermetic containers.

Amikacin Sulfate
아미카신황산염



$C_{22}H_{43}N_5O_{13}·xH_2SO_4$

4-Amino-*N*-[5-amino-2-[4-amino-3,5-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-4-[6-(amino-methyl)-3,4,5-trihydroxyoxan-2-yl]oxy-3-hydroxy-cyclohexyl]-2-hydroxybutanamide; sulfuric acid [*39831-55-5*]

Amikacin Sulfate is a sulfate of amikacin derivatives.

Amikacin Sulfate contains NLT 691 μg and NMT 791 μg (potency) of amikacin ($C_{22}H_{43}N_5O_{13}$: 585.60) per mg, calculated on the dried basis.

Description Amikacin Sulfate occurs as a white to yellowish white powder.

It is very soluble in water and practically insoluble in ethanol(95).

Identification (1) Determine the infrared spectra of Amikacin Sulfate and amikacin sulfate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Weigh 0.1 g each of Amikacin Sulfate and ami-

kacin sulfate RS, dissolve in 4 mL of water, and use these solutions as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of water, ammonia water(28), methanol, and tetrahydrofuran (1:1:1:1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly ninhydrin-citric acid-acetic acid TS on the plate, and heat at 100 ℃ for 10 minutes; the spots obtained from the test solution and the standard solution show a purple color, and the R_f values are the same.

(3) The aqueous solution of Amikacin Sulfate (1 in 100) responds to the Qualitative Analysis (1) for sulfate.

Optical rotation $[\alpha]_D^{20}$: Between +76° and +84° (1 g, calculated on the dried basis, water, 100 mL, 100 mm).

pH Dissolve 1.0 g of Amikacin Sulfate in 100 mL of water; the pH is between 6.0 and 7.5.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Amikacin Sulfate according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 0.1 g of Amikacin Sulfate in 4 mL of water, and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the test solutions and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of water, ammonia water(28), methanol, and tetrahydrofuran (1:1:1:1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly ninhydrin-citric acid-acetic acid TS on the plate, and heat at 100 ℃ for 10 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Sterility It meets the requirements when used in a sterile preparation. However, it is excluded in cases where there is a final sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins Less than 0.50 EU per mg (potency) of amikacin when used for the manufacturing of sterile preparations.

Loss on drying NMT 4.0% (1 g, in vacuum, 60 ℃, 3 hours).

Assay Weigh accurately about 20 mg (potency) of Amikacin Sulfate, and add water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make 100 mL, and use this solution as the test solution. Separately, weigh accurately 20 mg (potency) of amikacin sulfate RS, and add water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas, A_T and A_S, of the test solution and the standard solution, according to the automatic integration method.

$$\text{Potency (mg) of amikacin } (C_{22}H_{43}N_5O_{13}) = \text{Potency (mg) of amikacin sulfate RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: Electrochemical detector

Current		Time (ms)
No.	Voltage	
E1	0.04	200
E2	0.8	190
E3	-0.8	190

Column: A plastic column about 4 mm in internal diameter and about 25 cm in length, packed with 10 μm porous trimethylamine-substituted anion-exchange resin for liquid chromatography (pore size: 8 μm). Use a guard column packed with porous trimethylamine-substituted anion-exchange resin for liquid chromatography.

Mobile phase: 0.115 mol/L sodium hydroxide.

Flow rate: 0.5 mL/min

System suitability

System performance: Weigh accurately about 20 mg (potency) of amikacin sulfate RS and 8 mg (potency) of kanamycin sulfate, and add water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and proceed with the resulting solution according to the above conditions; the relative retention time of kanamycin and amikacin is 0.8 and 1.0, respectively, with the resolution being NLT 3.

System repeatability: Repeat the test 6 times with 20 mL each of the standard solutions; the relative standard deviation of the peak area of amikacin is NMT 3.0%.

Packaging and storage Preserve in hermetic containers.

Amikacin Sulfate Injection
아미카신황산염 주사액

Amikacin Sulfate Injection is an aqueous injection and contains NLT 90.0% and NMT 115.0% of the labeled amount of amikacin ($C_{22}H_{43}N_5O_{13}$: 585.60).

Method of preparation Prepare as directed under Injections, with Amikacin Sulfate.

Description Amikacin Sulfate Injection occurs as a colorless to a pale yellow, clear liquid.

Identification Weigh an amount of Amikacin Sulfate Injection, equivalent to 0.1 g (potency) of amikacin sulfate according to the labeled amount, add water to make 4 mL, and use this solution as the test solution. Separately, dissolve an amount of amikacin sulfate RS, equivalent to 25 mg (potency), in 1 mL of water and use this solution as the standard solution. Perform the test as directed under the Identification (2) of Amikacin Sulfate.

pH Between 6.0 and 7.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.50 EU per mg (potency) of amikacin

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Amikacin Sulfate Injection, equivalent to about 20 mg (potency) of amikacin sulfate according to the labeled amount and add water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg (potency) of amikacin sulfate RS, and add water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make 100 mL, and use this solution as the standard solution. Perform the test with each 20 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions. Determine the peak areas, A_T and A_S, in the chromatograms of the test solution and standard solution by the automatic integration method.

$$\text{Potency (mg) of amikacin } (C_{22}H_{43}N_5O_{13}) = \text{Potency (mg) of amikacin sulfate RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: Electrochemical detector

Current		Time (ms)
No.	Voltage	
E1	0.04	200
E2	0.8	190
E3	-0.8	190

Column: A plastic column about 4 mm in internal diameter and about 25 cm in length, packed with 10 μm porous trimethylamine-substituted anion-exchange resin for liquid chromatography (pore size: 8 μm). Use a guard column packed with porous trimethylamine-substituted anion-exchange resin for liquid chromatography.

Mobile phase: 0.115 mol/L sodium hydroxide.

Flow rate: 0.5 mL/min

System suitability

System performance: Weigh accurately about 20 mg (potency) of amikacin sulfate RS and 8 mg (potency) of kanamycin sulfate and add water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and proceed with the resulting solution according to the above operating conditions; the relative retention time of kanamycin and amikacin is 0.8 and 1.0, respectively, with the resolution being NLT 3.

System repeatability: Repeat the test 6 times with each 20 mL of the standard solution; the relative standard deviation of the peak area of amikacin is NMT 3.0%.

Packaging and storage Preserve in hermetic containers.

Aminocaproic Acid
아미노카프로산

$H_2NCH_2CH_2CH_2CH_2CO_2H$

$C_6H_{13}NO_2$: 131.17

6-Aminohexanoic acid [*60-32-2*]

Aminocaproic Acid contains NLT 98.5% and NMT 101.5% of aminocaproic acid ($C_6H_{13}NO_2$), calculated on the anhydrous basis.

Description Aminocaproic Acid occurs as a white crystalline, fine powder and is almost odorless.

It is freely soluble in water, in acid or in alkali, slightly soluble in methanol or in ethanol(95) and practically insoluble in chloroform or in ether.

An aqueous solution of Aminocaproic Acid is neutral.

Melting point—About 205 °C.

Identification Determine the infrared spectra of Aminocaproic Acid and Aminocaproic acid RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity ***Heavy metals***—Proceed with 1.0 g of Aminocaproic Acid according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Water NMT 0.5% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.12 g of Aminocaproic Acid and add water to make exactly 10 mL. To 5.0 mL of this solution, add 2.0 mL of the internal standard solution and water to make exactly 100 mL and use this solution as the test solution. Separately, weigh accurately about 0.12 g of aminocaproic acid RS, previously dried at 105 ºC for 30 minutes and dissolve in water to make exactly 10 mL. To 5.0 mL of this solution, add 2.0 mL of the internal standard solution and water to make exactly 100 mL and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of aminocaproic acid to the internal standard, respectively.

Potency (μg) of aminocaproic acid ($C_6H_{13}NO_2$)
= Potency (μg) of aminocaproic acid RS × $\frac{Q_T}{Q_S}$

Internal standard solution—Weigh accurately 25.0 mg of methionine and dissolve in 20 mL of water.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Dissolve 0.55 g of sodium 1-heptanesulphonate in water to make 1000 mL and use this solution as solution A. Dissolve 10 g of potassium dihydrogen phosphate in 300 mL of solution A, add 250 mL of methanol, then add another 300 mL of solution A, and shake to mix. Adjust the pH of this mixture to 2.2 with phosphoric acid and add solution A to make 1000 mL.

Flow rate: 0.7 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; aminocaproic acid and methionine are eluted in this order with the resolution between these peaks being NLT 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Aminocaproic Acid Tablets
아미노카프로산 정

Aminocaproic Acid Tablets contain NLT 95.0% and NMT 105.0% of aminocaproic acid ($C_6H_{13}NO_2$: 131.17).

Method of preparation Prepare as directed under Tablets, with Aminocaproic Acid.

Identification Powder 2 tablets of Aminocaproic Acid Tablets, add 10 mL of water, shake well to mix, and filter to 100 mL of acetone and filter. Shake well the mixture and allow to stand for 15 minutes until crystals are formed. Filter the crystals through a glass filter (G4), wash with 25 mL of acetone, and remove the solvent under reduced pressure. Dry at 105 ℃ for 30 minutes and cool. Proceed with the residue as directed under the Identification under Aminocaproic Acid and perform the test.

Dissolution Perform the test with 1 tablet of Aminocaproic Acid Tablets at 100 revolutions per minute according to Method 1 under the Dissolution, using 900 mL of water as dissolution medium. Take the dissolved solution after 45 minutes after starting the test and use this solution as the test solution. Separately, weigh accurately an appropriate amount of aminocaproic acid RS, previously dried at 105 ºC for 30 minutes, dissolve in water to obtain a solution having known concentration of about 500 μg of aminocaproic acid per mL, and use this solution as the standard solution. To each 1 mL of the test solution and the standard solution, add 20.0 mL of borate buffer solution, pH 9.5, and 3.0 mL of freshly prepared sodium β-naphthoquinone-4-sulfonate (1 in 500), shake to mix, and allow to stand on a steam bath at 65 ± 5 ºC for 45 minutes. After cooling, add water to each to make exactly 50 mL and mix. Determine the absorbances of these solutions at the absorbance maximum wavelength (λmax), about 460 nm, as directed under the Ultraviolet-visible Spectroscopy, using the blank test solution as the control solution.

It meets the requirements if the dissolution of Aminocaproic Acid Tablets in 45 minutes is NLT 75%.

Borate buffer solution, pH 9.5—Dissolve 6.185 g of boric acid and 7.930 g of potassium chloride in water, add 60 mL of 0.1 mol/L of sodium hydroxide, and add water to make 2000 mL. Adjust the pH to 9.5 ± 0.1 with 0.1 mol/L sodium hydroxide, if necessary.

Uniformity of dosage units Meets the requirements.

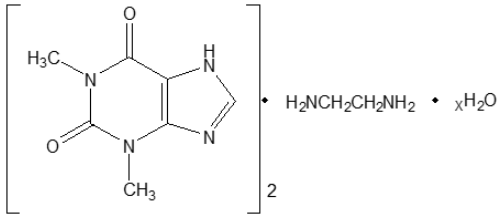
Assay Weigh accurately and powder NLT 20 tablets of Aminocaproic Acid Tablets. Weigh accurately an amount of the powder, equivalent to about 0.5 g of aminocaproic acid ($C_6H_{13}NO_2$), add 100 mL of acetic acid(100), dissolve by heating, and cool. Titrate with 0.1 mol/L perchloric acid-1,4-dioxane VS until a blue color develops [indicator: 10 drops of methylrozaniline chloride in chlo-

robenzene (1 in 500)]. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid-1,4-dioxane VS
= 13.12 mg of $C_6H_{13}NO_2$

Packaging and storage Preserve in tight containers.

Aminophylline Hydrate
아미노필린수화물



Aminophylline $C_{14}H_{16}N_8O_4 \cdot C_2H_8N_2 \cdot xH_2O$
bis(1,3-Dimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione) ethane-1,2-diamine hydrate [*76970-41-7*]

Aminophylline Hydrate contains NLT 84.0% and NMT 86.0% of theophylline ($C_7H_8N_4O_2$: 180.16) and NLT 14.0% and NMT 15.0% of ethylenediamine ($C_2H_8N_2$: 60.10), calculated on the anhydrous basis.

Description Aminophylline Hydrate occurs as a white to pale yellow granule or a powder. It is odorless or has a slight ammonia-like odor and has a bitter taste.
It is soluble in water, slightly soluble in methanol and practically insoluble in ethanol(95) or in ether.
To 1 g of Aminophylline Hydrate, add 5 mL of water and shake; it dissolves almost completely and crystallization begins in 2 to 3 minutes. These crystals are dissolved again with the addition of a small amount of ethylenediamine.
It is gradually colored by light and gradually loses ethylenediamine, if left in the air.

Identification (1) Weigh 0.75 g of Aminophylline Hydrate, dissolve in 30 mL of water, and use this solution as the test solution. To 20 mL of the test solution, add 1 mL of dilute hydrochloric acid; a precipitate is gradually formed. Filter and collect the precipitate, recrystallize from water, and dry at 105 ºC for 1 hour; the melting point of the crystals so obtained is between 271 and 275 ºC.

(2) Dissolve 0.1 g of the crystals obtained in (1) in 50 mL of water. To 2 mL of this solution, add tannic acid TS dropwise; a white precipitate is formed, which is dissolved upon more dropwise addition of tannic acid TS.

(3) To 10 mg of the crystals obtained in (1), add 10 drops of hydrogen peroxide TS and 1 drop of hydrochloric acid and evaporate on a steam bath to dryness; the resulting residue exhibits a yellowish red color. Transfer this residue into a vessel containing 2 to 3 drops of ammonia TS; the color of the residue changes to purple, which disappears upon the addition of 2 to 3 drops of sodium hydroxide TS.

(4) Dissolve 10 mg of the crystals obtained in (1) in 5 mL of water, add 3 mL of ammonia-ammonium chloride buffer (pH 8.0) and 1 mL of cupric sulfate-pyridine TS, and mix. Add 5 mL of chloroform to the mixture and shake; the chloroform layer exhibits a green color.

(5) To 5 mL of the test solution obtained in (1), add 2 drops of copper(II) sulfate TS; the resulting solution exhibits a violet color. Thereto, add 1 mL of copper(II) sulfate TS; the color of the solution changes to blue, and if is allowed to stand, a green precipitate is formed.

pH Dissolve 1.0 g of Aminophylline Hydrate in 25 mL of water; the pH of this solution is between 8.0 and 9.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Aminophylline Hydrate in 10 mL of hot water; the resulting solution is colorless to pale yellow and clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Aminophylline Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Water NMT 7.9% (0.3 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay (1) ***Theophylline***—Weigh accurately about 0.25 g of Aminophylline Hydrate and dissolve in 50 mL of water and 8 mL of ammonia TS by gentle warming on a steam bath. Add exactly 20 mL of 0.1 mol/L silver nitrate VS, warm on a steam bath for 15 minutes, allow to stand between 5 and 10 ºC for 20 minutes, collect the precipitate by filtration with suction, and wash the precipitate three time each time with 10 mL of water. Combine the filtrate and the solution used for washing, add dilute nitric acid to neutralize, add another 3 mL of dilute nitric acid, and titrate the excess silver nitrate with 0.1 mol/L ammonium thiocyanate VS (indicator: 2 mL of ammonium iron(III) sulfate TS). Perform a blank test in the same manner.

Each mL of 0.1 mol/L silver nitrate VS
= 18.016 mg of $C_7H_8N_4O_2$

(2) ***Ethylenediamine***—Weigh accurately about 0.5 g of Aminophylline Hydrate, dissolve in 30 mL of water, and titrate with 0.1 mol/L hydrochloric acid VS (indicator: 3 drops of bromophenol blue TS).

Each mL of 0.1 mol/L hydrochloric acid VS
= 3.0049 mg of $C_2H_8N_2$

Packaging and storage Preserve in light-resistant, tight containers.

Aminophylline Injection
아미노필린 주사액

Aminophylline Injection is an aqueous injection and contains NLT 75.0% and NMT 86% of theophylline ($C_7H_8N_4O_2$: 180.16) and NLT 13.0% and NMT 20.0% of ethylenediamine ($C_2H_8N_2$: 60.10) according to the labeled amount of Aminophylline.

The concentration of Aminophylline Injection is expressed as the quantity of aminophylline hydrate ($C_{16}H_{24}N_{10}O_4 \cdot 2H_2O$: 456.46).

Method of preparation Prepare as directed under Injections, with Aminophylline. Aminophylline Injection, may be prepared with theophylline and an equivalent amount of Ethylenediamine, instead of Aminophylline.
NMT 60 mg of Ethylenediamine, as a stabilizer, per g of Aminophylline may be added to Aminophylline Injection.

Description Aminophylline Injection occurs as a colorless and clear liquid with a slightly bitter taste.
It gradually changes in color by light.
pH—Between 8.0 and 10.0.

Identification Weigh an amount of Aminophylline Injection, equivalent to 0.75 g of Aminophylline according to the labeled amount, and add water to make 30 mL. Proceed with this solution as directed under the Identification under Aminophylline and perform the test.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.6 EU per mg of aminophylline.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay (1) ***Theophylline***—Weigh accurately an amount of Aminophylline Injection, equivalent to about 39.4 mg of theophylline ($C_7H_8N_4O_2$) (about 50 mg of aminophylline hydrate), add water to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 40 mg of theophylline RS, previously dried at 105 °C for 4 hours, dissolve in water to make exactly 50 mL, and use this solution as the standard solution. Perform the test with each 5 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak areas, A_T and A_S, of theophylline in the test solution and the standard solution.

$$\text{Amount (mg) of theophylline } (C_7H_8N_4O_2) = \text{Amount (mg) of theophylline RS} \times \frac{A_T}{A_S}$$

Operating conditions
Detector: An ultraviolet absorption photometer (wavelength: 270 nm).
Column: A stainless steel column 6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).
Column temperature: A constant temperature of about 40 °C.
Mobile phase: A mixture of diluted acetic acid(100) (1 in 100) and methanol (4 : 1).
Flow rate: Adjust the flow rate so that the retention time of theophylline is about 5 minutes.
System performance
Proceed with 5 μL of the standard solution according to the above operating conditions; the number of theoretical plates and symmetry factor of the theophylline peak are NLT 8000 and NMT 1.5, respectively.
System repeatability: Repeat the test 6 times with 5 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of theophylline is NMT 1.0%.

(2) ***Ethylenediamine***—Weigh accurately an amount of Aminophylline Injection, equivalent to about 30 mg of ethylenediamine ($C_2H_8N_2$) (about 0.2 g of aminophylline), add water to make 30 mL, and titrate with 0.1 mol/L hydrochloric acid VS (indicator: 2 to 3 drops of bromphenol blue TS).

$$\text{Each mL of 0.1 mol/L hydrochloric acid VS} = 3.0049 \text{ mg of } C_2H_8N_2$$

Packaging and storage Preserve in light-resistant, well-closed containers.

Aminophylline Tablets
아미노필린 정

Aminophylline Tablets contain NLT 75.0% and NMT 86.0% of the labeled amount of theophylline ($C_7H_8N_4O_2$: 180.16) and NLT 12.0% and NMT 14.0% of the labeled amount of ethylenediamine ($C_2H_8N_2$: 60.10).
The amount of Aminophylline Tablets is expressed as the quantity of aminophylline hydrate ($C_{16}H_{24}N_{10}O_4 \cdot 2H_2O$: 456.46).

Method of preparation Prepare as directed under Tablets, with Aminophylline Hydrate.

Identification (1) Weigh an amount of Aminophylline Tablets, previously powdered, according to the labeled amount, equivalent to about 0.5 g of aminophylline, add 25 mL of water, shake well to mix, and filter. This filtrate changes the color of a wet litmus paper from red to blue. Mix the filtrate with 1 mL of 3 mol/L of hydrochloric acid and shake to mix; a theophylline precipitate is formed. Cool, if necessary, and precipitate. Filter and collect the precipitate (The filtrate is used for the Identification (2).), wash with a small amount of cold water, and dry at 105 ºC for 1 hour. Proceed with these crystals as directed under the Identification (3) under Aminophylline Hydrate. Recrystallize these crystals with water and dry at 105 ºC for 1 hour; the melting point of the resulting crystals is between 270 and 274 ℃.

(2) To the filtrate from (1), add 0.5 mL of benzenesulfonyl chloride and 5 mL of 1 mol/L sodium hydroxide to obtain an alkaline solution and shake for 10 minutes. Acidify by adding 5 mL of 3 mol/L hydrochloric acid and collect ethylenediamine disulfonamide precipitates. Wash the precipitates with water, recrystallize, and dry at 105 ℃ for 1 hour; the melting point is between 164 and 171 ℃.

Dissolution This test applies to uncoated tablets. Perform the test with 1 tablet of Aminophylline Tablets at 50 revolutions per minute according to Method 2 under the Dissolution Test, using 900 mL of water as the dissolution medium. Take the dissolved solution 45 minutes after starting the test, filter, dilute if necessary, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of theophylline RS, previously dried at 105 ℃ for 4 hours, dissolve in the dissolution medium to the same concentration as the test solution, and use this solution as the standard solution. Determine the absorbances of the test solution and the standard solution at 269 nm, the absorbance maximum wavelength (λmax), as directed under the Ultraviolet-visible Spectroscopy.
It meets the requirements when the dissolution rate of theophylline in 45 minutes.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Theophylline***—Weigh accurately and powder NLT 20 tablets of Aminophylline Tablets. Weigh accurately an amount of the powder, equivalent to about 2 g of aminophylline hydrate ($C_{16}H_{24}N_{10}O_4 \cdot 2H_2O$), add 50 mL of water and 15 mL of ammonia TS, shake occasionally, and if necessary, warm to 50 ℃. Allow to stand for 30 minutes. Cool to room temperature if warmed and add water to make exactly 200 mL. Take 50 mL of this solution, centrifuge, transfer an amount of the clear supernatant, exactly equivalent to about 0.2 g of theophylline, into a Erlenmeyer flask, and add water to make about 40 mL. Then, add 8 mL of ammonia TS and 20 mL of 0.1 mol/L silver nitrate VS, warm on a steam bath for 15 minutes, cool at 5 to 10 ℃ for 20 minutes, and filter the precipitate using a glass filter (G4). Wash 3 times with each 10 mL of water. Combine the filtrate and the washings, acidify by adding nitric acid, and add 3 mL of nitric acid. After cooling, titrate the excess silver nitrate with 0.1 mol/L ammonium thiocyanate VS (indicator: 2 mL of ammonium iron(III) sulfate TS).

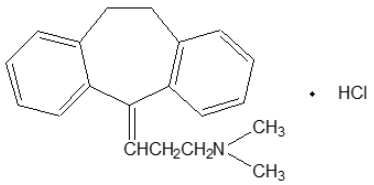
Each mL of 0.1 mol/L silver nitrate VS
= 18.016 mg of $C_7H_8N_4O_2$

(2) ***Ethylenediamine***—Weigh accurately and powder NLT 20 tablets of Aminophylline Tablets. Weigh accurately an amount of the powder, equivalent to about 0.35 g of aminophylline hydrate ($C_{16}H_{24}N_{10}O_4 \cdot 2H_2O$), transfer into an Erlenmeyer flask, add 200 mL of water, and decompose at 50 ℃ for 30 minutes by occasionally shaking. After cooling, filter this solution to another Erlenmeyer flask, wash with water repeatedly to ensure that the last washing is neutral with a litmus paper, and titrate with 0.1 mol/L hydrochloric acid VS (indicator: 2 to 3 drops of methyl orange TS).

Each mL of 0.1 mol/L hydrochloric acid VS
= 3.0049 mg of $C_2H_8N_2$

Packaging and storage Preserve in tight containers.

Amitriptyline Hydrochloride
아미트리프틸린염산염



$C_{20}H_{23}N \cdot HCl$: 313.86

N,*N*-Dimethyl-3-[tricyclo[9.4.0.03,8]pentadeca-1(11),3(8),4,6,12,14-hexaen-2-ylidene]propanamine hydrochloride [*549-18-8*]

Amitriptyline Hydrochloride, when dried, contains NLT 99.0% and NMT 101.0% of amitriptyline hydrochloride ($C_{20}H_{23}N \cdot HCl$).

Description Amitriptyline Hydrochloride occurs as colorless crystals or a white to pale yellow crystalline powder. It has a bitter taste, and numbs the tongue.
It is freely soluble in water, ethanol(95) or acetic acid(100), soluble in acetic anhydride, and practically insoluble in ether.

pH—Dissolve 1.0 g of Amitriptyline Hydrochloride in 20 mL of water; the pH is between 4.0 and 5.0.

Identification (1) Dissolve 5 mg of Amitriptyline Hydrochloride in 3 mL of sulfuric acid; the resulting solution exhibits a red color. Add 5 drops of potassium dichromate TS to this solution; the resulting solution turns

dark brown.

(2) Add 0.5 mL of dilute nitric acid to 1 mL of the aqueous solution of Amitriptyline Hydrochloride (1 in 500) to make it acidic, and add 1 drop of silver nitrate TS; a white precipitate is produced.

(3) Determine the absorption spectra of the aqueous solutions of Amitriptyline Hydrochloride and amitriptyline hydrochloride RS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Melting point Between 195 and 222 ºC.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Amitriptyline Hydrochloride in 20 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 2.0 g of Amitriptyline Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Weigh accurately an appropriate amount of Amitriptyline Hydrochloride, dissolve in the mobile phase to prepare a solution containing 1 mg in 1 mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of dibenzosuberone RS, dissolve in methanol to prepare a solution containing 1 mg per mL, and use this solution as the standard stock solution (1). Separately, weigh accurately an appropriate amount of amitriptyline hydrochloride RS, amitriptyline RS, cyclobenzaprine hydrochloride RS, and nortriptyline hydrochloride RS, respectively, dissolve in the mobile phase to prepare solutions containing 0.4 mg, 0.6 mg, 0.6 mg, and 0.6 mg in 1 mL, respectively. Use these solutions as the standard stock solution (2). Pipet an appropriate amount of the standard stock solutions (1) and (2), add the mobile phase to make a solution containing 1 μg of per amitriptyline hydrochloride, 0.5 μg of dibenzosuberone, 1.5 μg of amitriptyline, 1.5 μg of cyclobenzaprine hydrochloride, and 1.5 μg of nortriptyline hydrochloride per mL, respectively, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the amount of each related substance according to the following equation; dibenzosuberone is NMT 0.05%, amitriptyline, nortriptyline, and cyclobenzaprine are NMT 0.15%, respectively, other individual related substances are NMT 0.10%, and the total amount of the related substances is NMT 1.0%. However, peaks with a relative retention time for amitriptyline of less than 0.22 are excluded.

$$\text{Content (\%) of related substances} = 100 \times \frac{C_S}{C_T} \times \frac{A_T}{A_S}$$

C_S: Concentration (mg/mL) of each specified related substance in the standard solution

C_T: Concentration (mg/mL) of amitriptyline hydrochloride in the test solution

A_T: Peak area of each specified related substance in the test solution

A_S: Peak area of each specified related substance in the standard solution

$$\text{Content (\%) of each related substance} = 100 \times \frac{C_S}{C_T} \times \frac{A_i}{A_S}$$

C_S: Concentration (mg/mL) of amitriptyline hydrochloride in the standard solution

C_T: Concentration (mg/mL) of amitriptyline hydrochloride in the test solution

A_T: Peak area of each related substance in the test solution

A_S: Peak area of amitriptyline hydrochloride in the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octylsilane silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 45 °C.

Mobile phase: Dissolve 1.42 g of sodium hydrogen phosphate docahydrate in 1000 mL of water, and add dilute phosphoric acid (1 in 10) to adjust pH to 7.7. Take 300 mL of this solution and add 700 mL of methanol.

Flow rate: About 1.5 mL/min.

System suitability

System performance: Proceed with 20 μL of the standard solution under the above conditions; the resolution between amitriptyline and nortriptyline is NLT 1.5, and the relative retention time of dibenzosuberone, amitriptyline, nortriptyline hydrochloride, and cyclobenzaprine hydrochloride with respect to amitriptyline hydrochloride is approximately 0.35, 0.52, 0.60, and 0.76, respectively.

System repeatability: Weigh accurately an appropriate amount of amitriptyline hydrochloride RS, dissolve in the mobile phase to prepare a solution containing 0.2 mg in 1 mL, and repeat the test 6 times according to the above conditions; the relative standard deviation of the peak area of amitriptyline is NMT 2.0%.

Loss on drying NMT 0.5% (1 g, 105 °C, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Amitriptyline Hydrochloride, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7:3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 31.386 mg of $C_{20}H_{23}N \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Amitriptyline Hydrochloride Tablets
아미트리프틸린염산염 정

Amitriptyline Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of amitriptyline hydrochloride ($C_{20}H_{23}N \cdot HCl$: 313.86).

Method of preparation Prepare as directed under Tablets, with Amitriptyline Hydrochloride.

Identification (1) Weigh an amount of Amitriptyline Hydrochloride Tablets, previously powdered, equivalent to 0.1 g of amitriptyline hydrochloride according to the labeled amount, shake well to mix, and filter. Concentrate the filter to about 2 mL in the water bath, add ether until the solution becomes turbid, and allow to stand. Filter and collect the crystals using a glass filter (G4) and proceed as directed in the identification (1) and (2) under Amitriptyline Hydrochloride.

(2) Dissolve the crystals obtained in (1) in water (1 in 100000) and determine the absorption spectrum of the solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 238 nm and 240 nm and a minimum between 228 nm and 230 nm.

Dissolution Perform the test with 1 tablet of Amitriptyline Hydrochloride Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of diluted phosphate buffer solution, pH 6.8 (1 in 2) with the dissolution solution. Take NLT 20 mL of the dissolved solution 60 minutes after starting the test and filter through a membrane filter with a pore size not exceeding 0.8 μm. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, and add diluted phosphate buffer solution, pH 6.8 (1 in 2) to make exactly *V'* mL of a solution having known concentration of about 11 μg of amitriptyline hydrochloride ($C_{20}H_{23}N \cdot HCl$) per mL according to the labeled amount. Use this solution as the test solution. Separately, weigh accurately about 55 mg of amitriptyline hydrochloride RS, previously dried at 105 ℃ for 2 hours, and dissolve in diluted phosphate buffer solution, pH 6.8, (1 in 2) to make exactly 250 mL. Pipet 5 mL of the solution, add diluted phosphate buffer solution, pH 6.8, (1 in 2) to make exactly 100 mL and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 239 nm as directed under the Ultraviolet-visible Spectroscopy.
Meets the requirements if the dissolution rate of Amitriptyline Hydrochloride Tablets in 60 minutes is NLT 70%.

Dissolution rate (%) with respect to the labeled amount of amitriptyline hydrochloride ($C_{20}H_{23}N \cdot HCl$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 18$$

W_S: Amount (mg) of amitriptyline hydrochloride RS
C: Labeled amount (mg) of amitriptyline hydrochloride ($C_{20}H_{23}N \cdot HCl$) per tablet

Uniformity of dosage units Meets the requirements.

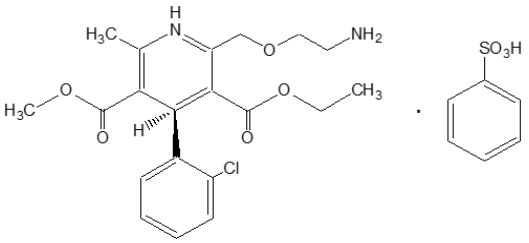
Assay Weigh accurately and powder NLT 20 tablets of Amitriptyline Hydrochloride Tablets. Weigh accurately an amount of the powder, equivalent to about 50 mg of amitriptyline hydrochloride ($C_{20}H_{23}N \cdot HCl$), add the mobile phase to make exactly 250, and filter. Discard the first 20 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 50 mg of amitriptyline hydrochloride RS, previously dried at 60 ℃ and 0.67 kPa to a constant weight, dissolve in the mobile phase to make exactly 250 mL, and use this solution as the standard solution. Perform the test with each 20 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak areas, A_T and A_S, of amitriptyline hydrochloride from each solution.

Amount (mg) of amitriptyline hydrochloride ($C_{20}H_{23}N \cdot HCl$)
= Amount (mg) of amitriptyline hydrochloride RS $\times \frac{A_T}{A_S}$

Operating conditions
Detector: An ultraviolet absorption photometer (wavelength: 254 nm).
Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).
Mobile phase: To 11.04 g of sodium dihydrogen phosphate dihydrate, dissolve in 900 mL of water, adjust the pH to 2.5 ± 0.5 by adding phosphoric acid, and add water to make 100 mL. Mix this solution with acetonitrile (58 : 42).
Flow rate: 2 mL/min
System suitability
System performance: Proceed with 20 μL of the standard solution according to the above operating conditions; the symmetry factor is NMT 2.0.
System repeatability: Repeat the test 6 times with each 20 μL the standard solution according to the above conditions; the relative standard deviation of the peak area is NMT 2.0%

Packaging and storage Preserve in tight containers.

Amlodipine Besylate
암로디핀베실산염



and enantiomer

$C_{20}H_{25}N_2O_5Cl \cdot C_6H_6O_3S$: 567.05

3-Ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate [*111470-99-6*]

Amlodipine Besylate contains NLT 97.0% and NMT 102.0% of amlodipine besylate ($C_{20}H_{25}N_2O_5Cl \cdot C_6H_6O_3S$), calculated on the anhydrous basis.

Method of preparation If there is a possibility that alkyl (methyl, ethyl, isopropyl, etc.) benzenesulfonate esters may be introduced as potential impurities in the manufacturing process of Amlodipine Besylate, pay attention to the control of starting materials, manufacturing processes, and intermediates to minimize residuals of impurities by considering the results of the risk assessment. If necessary, the manufacturing process may be verified by the test data proving that no quality risk exists in the final drug substance.

Description Amlodipine Besylate occurs as a white or almost white powder.
It is freely soluble in methanol, sparingly soluble in ethanol(95), and slightly soluble in water or 2-propanol.

Identification (1) To 30 mg of Amlodipine Besylate, add 0.1 g of sodium nitrate and 0.1 g of anhydrous sodium carbonate, mix, and gradually incinerate. After cooling, dissolve the residue in 2 mL of dilute hydrochloric acid and 10 mL of water, and filter if necessary. To the filtrate, add barium chloride TS; a white precipitate is formed.

(2) Dissolve 5.0 mg each of Amlodipine Besylate and amlodipine besylate RS in an 1 vol% methanol solution of 0.1 mol/L hydrochloric acid TS to make 100 mL. Determine the absorption spectra of both solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Amlodipine Besylate and amlodipine besylate RS, as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) The color and R_f value of the principal spots obtained from the test solution (2) of Related substances (A) and the standard solution (2) are the same.

Optical rotation $[\alpha]_D^{20}$: Between -0.10° and +0.10° (0.25 g, methanol, 25 mL, 100 mm).

Purity (1) ***Heavy metals*—**Proceed with 1.0 g of Amlodipine Besylate according to Method 4, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances*—**(i) Dissolve 0.140 g of Amlodipine Besylate in methanol to make exactly 2 mL and use this solution as the test solution (1). To 1.0 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the test solution (2). Separately, dissolve 70.0 mg of amlodipine besylate RS in 1.0 mL of methanol, and use this solution as the standard solution (1). To 0.5 mL of the standard solution (1), add methanol to make 5 mL, and use this solution as the standard solution (2). To 3.0 mL of the standard solution (2), add methanol to make 100 mL, and use this solution as the standard solution (3). To 1.0 mL of the standard solution (2), add methanol to make 100 mL, and use this solution as the standard solution (4). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of these solutions on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with the upper layer of a mixture of 4-methyl-2-pentanone, water and acetic acid(100) (2 : 1 : 1) to a distance of about 15 cm, and dry the plate at 80 °C for 15 minutes. Examine under ultraviolet light (dominant wavelengths: 254 nm and 366 nm); the spots other than the principal spot obtained from the test solution (1) is not more intense than the principal spot from the standard solution (3) (NMT 0.3%) and the number of spots more intense than the spots obtained from the standard solution (4) is NMT 2 (NMT 0.1%). This test is valid when two minor spots obtained by proceeding with the standard solution (1) in the same manner are clearly separated with R_f values of about 0.18 and 0.22, respectively.

(ii) Dissolve 50.0 mg of Amlodipine Besylate in the mobile phase to make exactly 50 mL, and use this solution as the test solution (1). To 5.0 mL of the test solution (1), add the mobile phase to make exactly 100 mL, and use this solution as the test solution (2). Separately, dissolve 50.0 mg of amlodipine besylate RS in the mobile phase to make exactly 50 mL. To 5.0 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution (1). To 3.0 mL of the test solution (1), add the mobile phase to make exactly 100 mL. To 5.0 mL of this solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution (2). Dissolve 5 mg of Amlodipine Besylate in 5 mL of hydrogen peroxide(30), heat at 70 °C for 45 minutes, and use this solution as the standard solution (3). Perform the test with 10 μL each of the test solutions and the standard solutions as directed under the

Liquid Chromatography according to the following conditions; the content (%) of amlodipine besylate related substance I {3-Ethyl-5-methyl-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methylpyridine-3,5-dicarboxylate} obtained from the test solution is NMT the area of the major peak from the standard solution (2) (0.3%), and the total area of all the other related substances is not lager than the area of the major peak from the standard solution (2) (0.3%). However, disregard any peak due to benzene sulfonate with the relative retention time being about 0.2 and any peak NMT 0.1 times the area of the major peak obtained from the standard solution (2).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 237 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 7.0 mL of triethylamine in 1000 mL of water and adjust to pH 3.0 ± 0.1 with phosphoric acid. Mix 50 volumes of this solution, 35 volumes of methanol and 15 volumes of acetonitrile.

Flow rate: 1.0 mL/min

System suitability

Proceed with 10 μL of the standard solution (3) according to the above operating conditions; the resolution between the peaks of amlodipine and related substance I is NLT 4.5. The relative retention time of related substance I to amlodipine (retention time of about 7 minutes) is about 0.5. Calculate the content of the related substance I by multiplying its peak area by 2.

Time span of measurement: About 3 times the retention time of amlodipine

Water NMT 0.5% (3.0 g, volumetric titration, direct titration).

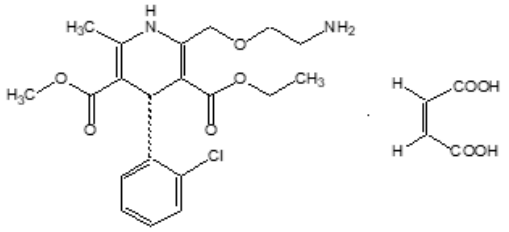
Residue on ignition NMT 0.2% (1 g).

Assay Perform the test with the test solution (2) and the standard solution (1) in Related substances (ii) according to the above operating conditions in Related substances (ii) and determine the peak areas, A_T and A_S, of amlodipine besylate.

Amount (mg) of amlodipine besylate ($C_{20}H_{25}N_2O_5Cl \cdot C_6H_6O_3S$)
= Amount (mg) of amlodipine besylate RS $\times \frac{A_T}{A_S}$

Packaging and storage Preserve in light-resistant, tight containers.

Amlodipine Maleate
암로디핀말레산염



$C_{20}H_{25}ClN_2O_5 \cdot C_4H_4O_4$: 524.95

3-Ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid ester (2*Z*)-2-butenedioate (1:1), [*88150-47-4*]

Amlodipine Maleate, when dried, contains NLT 99.0% and NMT 101.0% of amlodipine maleate ($C_{20}H_{25}ClN_2O_5 \cdot C_4H_4O_4$).

Description Amlodipine Maleate occurs as a white or off-white crystalline powder.

It is freely soluble in acetic acid(100), soluble in methanol, sparingly soluble in ethanol(95), and practically insoluble in water, chloroform or ether.

Melting point—Between 163 and 170 °C.

Identification (1) The retention times of the major peak of the test solution correspond to those of the standard solution, as obtained in the Assay.

(2) Determine the infrared spectra of Amlodipine Maleate and amlodipine maleate RS, previously dried at 105 °C for 3 hours, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -10.0° and + 10.0° (0.25 g, methanol, 25 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Amlodipine Maleate according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—(i) Dissolve 0.14 g of Amlodipine Maleate in methanol to make exactly 2 mL, and use this solution as the test solution. Pipet 1 mL of the test solution, add methanol to make exactly 10 mL, and use this solution as the standard solution (1). Pipet 3 mL of the standard solution (1), add methanol to make exactly 100 mL, and use this solution as the standard solution (2). Pipet 1 mL of the standard solution (1), add methanol to make exactly 100 mL, and use this solution as the standard solution (3). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solutions (1), (2) and (3) on the thin-layer chromatographic

plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with the supernatant of a mixture of methyl isobutyl ketone, water and acetic acid(100) (2 : 1 : 1) to a distance of about 15 cm, and dry the plate at 80 °C for 15 minutes. Examine under ultraviolet light (main wavelengths: 254 nm and 366 nm); the spots other than the principal spot obtained from the test solution is not more intense than the spots obtained from the standard solution (2) (0.3%) and the number of spots which are more intense than the spot obtained from the standard solution (3) is NMT 2 (0.1%).

(ii) Dissolve 50 mg of Amlodipine Maleate in the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, dissolve about 50 mg of amlodipine maleate RS in the mobile phase to make exactly 50 mL, and use this solution as the standard solution (a). Pipet 3 mL of the test solution, add the mobile phase to make exactly 100 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution (b). Perform the test with 10 μL each of the test solution and the standard solutions (a) and (b) as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas of each solution by the automatic integration method; the value obtained by multiplying the correction factor 3.03 to the peak area of related substance D obtained from the test solution is not larger than the area of the major peak obtained from the standard solution (b) (0.3%). The individual related substances other than the related substance D are not larger than one third of the area of the major peak obtained from the standard solution (b) (0.1%). Also, the total area of the peaks of individual related substances other than the related substance D is not larger than the area of the major peak obtained from the standard solution (b) (0.3%). However, disregard any peak due to maleic acid (relative retention time of about 0.2 to amlodipine) and any peak NMT 0.1 times the peak area of amlodipine from the standard solution (b).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 237 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of pH 3.0 buffer solution, acetonitrile and methanol (10 : 3 : 7).

Time span of measurement: About 3 times the retention time of amlodipine.

System suitability

System performance: Weigh accurately 5 mg of Amlodipine Maleate, add 10 mL of hydrogen peroxide solution, and heat the solution at 70 °C for 45 minutes. Proceed with 20 μL of this solution according to the above operating conditions; the retention time of the amlodipine peak is about 10 minutes, and the resolution between this peak and related substance D (relative retention time: about 0.45) is NLT 4.5.

Related substance D—3-ethyl-5-methyl-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl pyridine-3,5-dicarboxylate

pH 3.0 buffer solution—Take 7.0 mL of triethylamine, dilute to 1000 mL with purified water, and adjust to pH 3.0 with phosphoric acid.

Loss on drying NMT 0.5% (1 g, 105 °C, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately 50 mg of Amlodipine Maleate, add the mobile phase to make exactly 50 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of amlodipine maleate RS, add the mobile phase to make exactly 50 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the conditions directed in the related substances test, and determine the peak areas, A_T and A_S, of amlodipine maleate from each solution.

Amount (mg) of amlodipine maleate ($C_{24}H_{29}ClO_9$)
= Amount (mg) of amlodipine maleate RS × (A_T / A_S)

Packaging and storage Preserve in light-resistant, tight containers.

Ammonia Water
암모니아수

Azanium hydroxide

Ammonia Water contains NLT 9.5 w/v% and NMT 10.5 w/v% of ammonia (NH_3 : 17.03).

Description Ammonia Water occurs as a clear, colorless liquid and has a strong pungent, characteristic odor.
Ammonia Water, alkaline.
Specific gravity d_{20}^{20}: Between 0.95 and 0.96,

Identification (1) Hold a glass rod moistened with hydrochloric acid near the surface of Ammonia Water; dense white fumes are produced.

(2) Hold moistened red litmus paper near the surface of Ammonia Water; the paper turns blue.

Purity (1) ***Residue on evaporation***—Evaporate 10.0 mL of Ammonia Water evaporate to dryness the residue at

105 ºC for 1 hour; the weight of the residue is NMT 2.0 mg.

(2) ***Heavy metals***—Evaporate 5.0 mL of Ammonia Water to dryness on a steam bath, add 1 mL of dilute hydrochloric acid to the residue, and evaporate to dryness. Dissolve the residue in 2 mL of dilute acetic acid, add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by mixing 2.5 mL of lead standard solution, 2 mL of dilute acetic acid and water to make 50 mL (NMT 5 ppm).

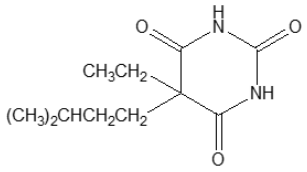
(3) ***Potassium permanganate reducing substances***—To 10.0 mL of Ammonia Water, add 40 mL of dilute sulfuric acid while cooling, and add 0.10 mL of 0.02 mol/L potassium permanganate; the red color of the resulting solution does not disappear within 10 minutes.

Assay Take exactly 5 mL of Ammonia Water, add 25 mL of water, and titrate with 0.5 mol/L sulfuric acid VS (indicator: 2 drops of methyl red TS).

Each mL of 0.5 mol/L sulfuric acid VS
= 17.031 mg of NH_3

Packaging and storage Preserve in tight containers at below 30 ℃.

Amobarbital
아모바르비탈



$C_{11}H_{18}N_2O_3$: 226.27

5-Ethyl-5-(3-methylbutyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione [*57-43-2*]

Amobarbital, when dried, contains NLT 99.0% and NMT 101.0% of amobarbital ($C_{11}H_{18}N_2O_3$).

Description Amobarbital occurs as white crystals or a crystalline powder, which is odorless and has a slightly bitter taste.
It is freely soluble in ethanol(95), acetone and ether, sparingly soluble in chloroform and practically insoluble in water.
It is soluble in sodium hydroxide TS or sodium carbonate TS.
The pH of a saturated solution of Amobarbital is between 5.0 and 5.6.

Identification (1) Add 10 mL of sodium hydroxide TS to 0.2 g of Amobarbital and boil; the gas produced changes the moistened red litmus paper to blue.

(2) Add 2 or 3 drops of ammonia·ammonium chloride buffer solution, pH 10.7 and 5 mL of diluted pyridine solution (1 in 10) to 50 mg of Amobarbital to dissolve, and put 5 mL of chloroform and 0.3 mL of cooper sulfate TS; purple precipitates are formed in the water layer. Shake to mix; the chloroform layer develops a purple color.

(3) To 0.4 g of Amobarbital, add 0.1 g of anhydrous sodium carbonate and 4 mL of water, and shake well to mix, and add a solution prepared by dissolving 0.3 g of 4-nitrobenzyl chloride in 7 mL of ethanol(95). Connect the reflux condenser, heat on a steam bath for 30 minutes, and allow to stand for 1 hour. Filter the precipitated crystals, wash with 7 mL of sodium hydroxide TS and a small amount of water, recrystalize with ethanol(95), and dry at 105 ℃ for 30 minutes; the melting point is between 168and 173℃, or between 150and 154℃.

Melting point Between 157 and 160 ºC.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Amobarbital in 5 mL of water; the resulting solution is clear and colorless.

(2) ***Chloride***—Dissolve 0.30 g of Amobarbital in 20 mL of acetone and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Add 20 mL of acetone, 6 mL of dilute nitric acid and water to 0.30 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.035%), and use this solution as the control solution.

(3) ***Sulfate***—Dissolve 0.40 g of Amobarbital in 20 mL of acetone and add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Add 20 mL of acetone, 1 mL of dilute hydrochloricacid and water to 0.40 mL of 0.005 mol/L sulfuric acid to make 50 mL (NMT 0.048%), and use this solution as the control solution.

(4) ***Heavy metals***—Proceed with 1.0 g of Amobarbital according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(5) ***Readily carbonizable substances***—Proceed with 0.5 g of Amobarbital and perform the test. This color of this solution is not more intense than that of the Matching Fluid for Color A.

Loss on drying NMT 1.0% (1 g, 105 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

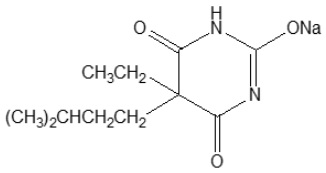
Assay Weigh accurately about 0.5 g of Amobarbital, previously dried, dissolve in 5 mL of ethanol(95) and 50 mL of chloroform, and titrate with 0.1 mol/L potassium hydroxide-ethanol VS (indicator: 1 mL of Alizarin Yellow GG-thymolphthalein TS). The endpoint of the titration is when the yellow color of this solution turns to pale blue and then finally to purple. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L potassium hydroxide-ethanol VS

= 22.627 mg of $C_{11}H_{18}N_2O_3$

Packaging and storage Preserve in well-closed containers.

Amobarbital Sodium for Injection
주사용 아모바르비탈나트륨



$C_{11}H_{17}N_2NaO_3$: 248.25

Amobarbital Sodium for Injection is a preparation for injection, which is dissolved before use. Amobarbital Sodium for Injection, when dried, contains NLT 98.5% and NMT 101.0% of amobarbital sodium ($C_{11}H_{17}N_2NaO_3$) and NLT 92.5% and NMT 107.5% of the labeled amount of amobarbital sodium ($C_{11}H_{17}N_2NaO_3$).

Method of preparation Prepare as directed under Injections.

Description Amobarbital Sodium for Injection occurs as odorless white crystals or a crystalline powder and has a bitter taste.
It is freely soluble in water or ethanol(95) and practically insoluble in ether or chloroform.
Dissolve 1 g of Amobarbital Sodium for Injection in 10 mL of water; the pH of the solution is between 10.0 and 11.0.
It is hygroscopic.

Identification (1) Dissolve 1.5 g of Amobarbital Sodium for Injection in 20 mL of water and add 10 mL of dilute hydrochloric acid, stirring to mix; a white precipitate is formed. Collect the precipitate, wash 4 times with each 10mL of water, and dry at 105 ºC for 3 hours; the melting point is 157 ºC to 160 ºC. With this precipitate, proceed again as directed under the Identification under Amobarbital.

(2) Ignite 0.5 g of Amobarbital Sodium for Injection, cool, and dissolve the residue in 10 mL of water; the solution responds to the Qualitative Analysis (1) for sodium salt.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Amobarbital Sodium for Injection in 10 mL of freshly boiled and cooled water; the solution is clear and colorless.

(2) ***Chloride***—Dissolve 1.0 g of Amobarbital Sodium for Injection in 49 mL of water, add 1 mL of acetic acid(100), shake, and filter. Discard the first 10 mL of the filtrate, add 6 mL of dilute nitric acid to the subsequent 30 mL of the filtrate, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by mixing 0.30 mL of 0.01 mol/L hydrochloric acid, 0.5 mL of ethanol(100), 6 mL of dilute nitric acid and water to make 50 mL (NMT 0.018%).

(3) ***Sulfate***—Dissolve 2.0 g of Amobarbital Sodium for Injection in 49 mL of water, add 1 mL of acetic acid(100), shake and filter. Discard the first 10 mL of the filtrate, add 2.5 mL of dilute hydrochloric acid to the subsequent 25 mL of the filtrate, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by mixing 0.40 mL of 0.005 mol/L sulfuric acid, 0.5 mL of acetic acid(100), 1 mL of dilute hydrochloric acid and water to make 50 mL (NMT 0.019%).

(4) ***Heavy metals***—Dissolve 2.0 g of Amobarbital Sodium for Injection in 45 mL of water, add 5 mL of dilute hydrochloric acid, shake vigorously and warm on a steam bath for 2 minutes with occasional shaking. Cool, add 30 mL of water, shake and filter. Discard the first 10 mL of the filtrate, add 1 drop of phenolphthalein TS to the subsequent 40 mL of the filtrate, and add ammonia TS until the solution exhibits a slight red color. Add 2.5 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. To 2.5 mL of dilute hydrochloric acid, Add 1 drop of phenolphthalein TS, add ammonia TS until the solution exhibits a slight red color, add 2.5 mL of dilute acetic acid and 2.0 mL of lead standard solution, and add water to make 50 mL (NMT 20 ppm). Use this solution as the control solution.

(5) ***Neutral or basic substances***—Dissolve about 1 g of Amobarbital Sodium for Injection, accurately weighed, in 10 mL of water and 5 mL of sodium hydroxide TS, then add 40 mL of chloroform and shake well. Separate the chloroform layer, wash with two 5mL volumes of water and filter. Evaporate the filtrate on a steam bath to dryness and dry the residue at 105 ºC for 1 hour: the weight of the residue is NMT 0.30%.

(6) ***Readily carbonizable substances***—Proceed with 0.5 g of Amobarbital Sodium for Injection and perform the test. The color of this solution is not more intense than that of the control solution for Color A.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.4 EU per mg of amobarbital sodium.

Loss on drying NMT 1.0% (1 g, 105 ℃, 4 hours).

Uniformity of dosage units Meets the requirements.

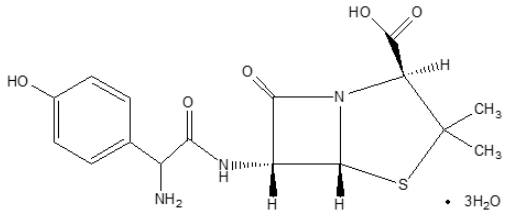
Assay Weigh accurately NLT 10 units of Amobarbital Sodium for Injection. Weigh accurately about 0.5 g of the contents, previously dried, transfer to a separatory funnel, dissolve in 20 mL of water, add 5 mL of ethanol(95) and

10 mL of dilute hydrochloric acid, and extract with 50 mL of chloroform, Then extract with three 25-mL volumes of chloroform. Combine the chloroform extracts, wash with two 5-mL volumes of water and extract the washings with two 10-mL volumes of chloroform. Filter the combined chloroform extracts into a Erlenmeyer flask. Wash the filter paper 3 times with each 5 mL of chloroform, combine the filtrate and the washings, add 10 mL of ethanol(95), and titrate with 0.1 mol/L potassium hydroxide-ethanol VS (indicator: 2 mL of Alizarin Yellow GG-thymolphthalein TS). The endpoint of the titration is when the color of the solution changes from yellow through pale blue to purple. Perform a blank test in the same manner with a solution of 30 mL of ethanol(95) in 160 mL of chloroform and make any necessary correction.

Each mL of 0.1 mol/L potassium hydroxide-ethanol VS
= 24.825 mg of $C_{11}H_{17}N_2NaO_3$

Packaging and storage Preserve in hermetic containers.

Amoxicillin Hydrate
아목시실린수화물



Amoxicillin $C_{16}H_{19}N_3O_5S \cdot 3H_2O$: 419.45
(3*S*)-6*b*-[(2*R*)-2-amino-2-(4-hydroxyphenyl) acetamido]-2,2-dimethylpenam-3-carboxylic acid trihydrate [*61336-70-7*]

Amoxicillin Hydrate contains NLT 950 μg (potency) and NMT 1010 μg (potency) of amoxicillin ($C_{16}H_{19}N_3O_5S$: 365.40) per mg, calculated on the anhydrous basis.

Description Amoxicillin Hydrate occurs as white to pale yellowish white crystals or a crystalline powder.
It is slightly soluble in water or methanol and very slightly soluble in ethanol(95).

Identification Determine the infrared spectra of Amoxicillin Hydrate and amoxicillin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between +290° and +315° (0.1 g, calculated on the anhydrous basis, water, 100 mL, 100 mm).

pH Dissolve 20 mg of Amoxicillin Hydrate in 10 mL of water; the pH of this solution is between 3.5 and 6.0.

Purity (1) ***Heavy metals***—Weigh 0.1 g of Amoxicillin Hydrate, add 2 mL of a solution of magnesium sulfate heptahydrate (1 in 4), mix, heat on a steam bath, and evaporate to dryness. Carbonize the residue by gently heating. After cooling, add 1 mL of sulfuric acid, heat carefully, and then heat at 500 to 600 °C to incinerate. After cooling, add 1 mL of hydrochloric acid to the residue and warm it on a steam bath to evaporate it to dryness. To the residue, add 10 mL of water and warm on a steam bath to dissolve. After cooling, adjust the pH to 3 to 4 with ammonia TS, add 2 mL of dilute acetic acid, filtrate, if necessary, and wash with 10 mL of water. Transfer the filtrate and the solution used for washing into a Nessler tube, and add water to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution as follows: to 2.0 mL of lead standard solution, add 2 mL of a solution of magnesium sulfate heptahydrate (1 in 4), and proceed in the same manner as in the preparation of the test solution (NMT 20 ppm).

(2) ***Arsenic***—Prepare the test solution with 1.0 g of Amoxicillin Hydrate according to Method 4 and perform the test (NMT 2 ppm).

(3) ***Related substances***—Dissolve 0.10 g of Amoxicillin Hydrate in 50 mL of a solution of sodium tetraborate decahydrate (1 in 200) and use this solution as the test solution. Pipet 1 mL of the test solution, add a solution of sodium tetraborate decahydrate (1 in 200) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas from each solution by calculating each peak area from each solution with the automatic integration method; the area of each peak other than the peak of amoxicillin obtained from the test solution is not larger than the peak area of amoxicillin from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with 10 μL of octadecylsilanized silica gel for liquid chromatography.

Column temperature: A constant temperature of about 25 °C.

Mobile phase A: Dissolve 1.36 g of sodium acetate trihydrate in 750 mL of water, adjust the pH to 4.5 with acetic acid(31), and add water to make 1000 mL. To 950 mL of this solution, add 50 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of amoxicillin is about 8 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution and add a solution of sodium tetraborate decahydrate (1 in 200) to make exactly 10 mL. Confirm that the peak area of amoxicillin obtained from 10 μL of this solution is equivalent to 7 to 13% of that from 10 μL of the standard solution.

System performance: Proceed with 10 mL of the standard solution according to the above conditions; the number of theoretical plates and the symmetry factor of the peak of amoxicillin are NLT 2500 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 10 mL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of amoxicillin is NMT 1.0%.

Time span of measurement: About 4 times the retention time of amoxicillin

(4) ***Dimethylaniline***—Weigh accurately about 1.0 g of Amoxicillin Hydrate, add 5 mL of 1 mol/L sodium hydroxide TS, shake to dissolve, add 1 mL of the internal standard solution, shake vigorously for 1 minute to mix, centrifuge, and use the clear supernatant as the test solution. Separately, weigh accurately about 50 mg of dimethylaniline, dissolve in 25 mL of 1 mol/L hydrochloric acid, and add water to make 50 mL. Pipet 5.0 mL of this solution and add water to make exactly 250 mL. Pipet 1.0 mL of this solution, add 5.0 mL of 1 mol/L sodium hydroxide TS and 1.0 mL of the internal standard solution, shake vigorously for 1 minute to mix, centrifuge, and use the clear supernatant as the standard solution. Perform the test with 1 μL each of the test solution, the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the peak area ratio, Q_T and Q_S, of dimethylaniline to the internal standard from the test solution and the standard solution, respectively (NMT 20 ppm).

$$\text{Content (ppm) of dimethylaniline} = \text{Amount (mg) of dimethylaniline taken} \times \frac{Q_T}{Q_S} \times \frac{Purity\ (\%)\ of\ dimethylaniline}{Amount\ (mg)\ of\ Amoxicillin\ Hydrate\ taken} \times 4$$

Internal standard solution—Dissolve about 50 mg of naphthalene in cyclohexane to make 50 mL. Take 5.0 mL of this solution, add cyclohexane to make 100 mL, and use this solution as the internal standard solution.

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A column about 0.53 mm in internal diameter and about 30 m in length, of which the inner surface is coated with 35% phenyl-65% dimethylpolysiloxane for gas chromatography (1.0 μm in thickness).

Column temperature: Inject the sample at a constant temperature of about 110 °C, hold the temperature for 4 minutes, then raise the temperature at a rate of 8 °C per minute until it reaches 200 °C, and hold the temperature at a constant temperature of about 200 °C for 5 minutes.

Temperatures of the sample injection port and the detector : 250 °C

Carrier gas: Helium

Flow rate: 30 cm/sec

Split ratio: About 1:10.

System suitability

System performance: Proceed with 1 μL of the standard solution according to the above conditions; the relative retention time of naphthalene with respect to dimethylaniline is about 1.3 with the signal to noise ratio of dimethylaniline being NLT 10.

Water Between 11.5% and 15.0% (0.1 g, volumetric titration, direct titration).

Assay Weigh accurately 30 mg (potency) each of Amoxicillin Hydrate and amoxicillin RS, dissolve each in a solution of boric acid (1 in 200) to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak areas, A_T and A_S, of amoxicillin from each solution.

$$\text{Potency (μg) of amoxicillin } (C_{16}H_{19}N_3O_5S) = \text{Potency (μg) of amoxicillin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Flow rate: Adjust the flow rate so that the retention time of amoxicillin is about 8 minutes.

Mobile phase A: Dissolve 1.361 g of sodium acetate trihydrate in 750 mL of water, adjust the pH to 4.5 with acetic acid(31), and add more water to make 1000 mL. To 950 mL of this solution, add 50 mL of methanol.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the number of theoretical plates of amoxicillin is NLT 2500.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of amoxicillin is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Amoxicillin Capsules
아목시실린 캡슐

Amoxicillin Capsules contain NLT 92.0% and NMT 105.0% of the labeled amount of amoxicillin ($C_{16}H_{19}N_3O_5S$: 365.40).

Method of preparation Prepare as directed under Capsules, with Amoxicillin Hydrate.

Identification Take the content of Amoxicillin Capsules, weigh the amount equivalent to 8 mg (potency) of amoxicillin hydrate according to the labeled amount, add 2 mL of 0.01 mol/L hydrochloric acid TS, and shake to mix for 30 minutes. Filter, and use the filtrate as the test solution. Separately, dissolve an amount equivalent to 8 mg (potency) of amoxicillin RS in 2 mL of 0.01 mol/L hydrochloric acid TS, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of tetrahydrofuran, water and formic acid (50 : 5 : 2) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly a solution of ninhydrin in ethanol(95) (1 in 20) on the plate, and heat at 110 ℃ for 15 minutes; the principal spots obtained from the test solution and the standard solution exhibit a purple color, and have the same R_f values.

Purity ***Related substances*—**Take the content of Amoxicillin Capsules, weigh an amount equivalent to 0.1 g (potency) of amoxicillin according to the labeled amount, add 30 mL of boric acid solution (1 in 200), and shake to mix for 15 minutes. Add boric acid solution (1 in 200) to make 50 mL. Centrifuge this solution and use the supernatant as the test solution. Pipet 1 mL of this solution, add boric acid solution (1 in 200) to make exactly 100 mL, and use this solution as the standard solution. Pipet 10 μL each of the test solution and the standard solution, and perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the peak areas other than amoxicillin in the test solution are not greater than the peak area of amoxicillin in the standard solution.

Operating conditions

Proceed according to the operating conditions as directed in Purity (3) of Amoxicillin Hydrate.

System suitability

For confirmation of detection and system repeatability, perform the test as directed under the System suitability under Purity (3) of Amoxicillin Hydrate.

System performance: Proceed with 10 μL of the standard solution under the above conditions; the number of theoretical plates and the symmetry factor of the peak of amoxicillin are NLT 2500 and NMT 1.5, respectively.

Water NMT 15.0% (0.1 g, volumetric titration, direct titration).

Dissolution Perform the test with 1 Amoxicillin Capsule at 100 revolutions per minute according to Method 2 under the Dissolution, with a sinker using 900 mL of water as the dissolution medium. Take NLT 20 mL of the dissolved solution 60 minutes after starting the test and filter through a membrane filter with a pore size of NMT 0.45 μm. Discard the first 10 mL of the filtrate, pipet the subsequent filtrate of V mL, add the water to make exactly V' mL, containing about 56 μg (potency) of amoxicillin ($C_{16}H_{19}N_3O_5S$) per mL, according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately an amount equivalent to about 28 mg (potency) of amoxicillin RS, and dissolve in the water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of amoxicillin. Meets the requirements if the dissolution rate of Amoxicillin Capsules in 60 minutes is NLT 75%.

Dissolution rate (%) of the labeled amount of amoxicillin ($C_{16}H_{19}N_3O_5S_2$)

$$= \text{Potency (mg) of amoxicillin RS} \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 180$$

C: Labeled amount [mg (potency)] of amoxicillin ($C_{16}H_{19}N_3O_5S$) per capsule

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 1.361 g of sodium acetate trihydrate in 750 mL of water, adjust the pH to 4.5 with acetic acid(31), and add water to make 1000 mL. Add 50 mL of methanol to 950 mL of this solution and mix.

Flow rate: Adjust the flow rate so that the retention time of the amoxicillin peak is about 8 minutes.

Column temperature: A constant temperature of about 25 ℃.

System suitability

System performance: Proceed with 50 μL of the standard solution under the above conditions; the number of theoretical plates and the symmetry factor are NLT 2500 plates and NMT 2.0, respectively.

System repeatability: Repeat the test 6 times with 50 μL each of the standard solutions according to the above conditions; the relative standard deviation of

the peak areas of amoxicillin is NMT 1.5%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the content NLT 20 Amoxicillin Capsules. Weigh accurately an amount equivalent to about 0.1 g (potency) of amoxicillin hydrate according to the labeled potency, add 70 mL of water, shake to mix for 15 minutes, and add water to make exactly 100 mL. Centrifuge, and use the supernatant as the test solution. Separately, weigh accurately an amount equivalent to about 20 mg (potency) of amoxicillin RS, dissolve in water to make exactly 20 mL, and use this solution as the standard solution. Perform the test with each 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of amoxicillin in the test solution and the standard solution.

$$\text{Potency (μg) of amoxicillin } (C_{16}H_{19}N_3O_5S) = \text{Potency (μg) of amoxicillin RS} \times \frac{A_T}{A_S} \times 5$$

Operating conditions

For the column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay of Amoxicillin Hydrate.

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the number of theoretical plates and the symmetry factor of the peak of amoxicillin are NLT 2500 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of amoxicillin is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Amoxicillin for Syrup
시럽용 아목시실린

Amoxicillin for Syrup is a preparation for syrup, which is dissolved before use, and contains NLT 90.0% and NMT 120.0% of the labeled amount of amoxicillin ($C_{16}H_{19}N_3O_5S$: 365.40).

Method of preparation Prepare as directed under Syrups, with Amoxicillin Hydrate.

Identification (1) Dissolve an amount of Amoxicillin for Syrup, equivalent to about 0.2 g of amoxicillin, and about 0.2 g of amoxicillin RS in 0.1 mol/L hydrochloric acid TS to make 50 mL and use the solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each 10 μL of the test solution and the standard solution on a thin-layer chromatographic plate of silica gel for thin-layer chromatography. Develop the plate using a mixture of methanol, chloroform, water and pyridine (9 : 8 : 3 : 1) as the developing solvent and air-dry the plate. Spray evenly a solution prepared by dissolving 0.3 g of ninhydrin in 100 mL of methanol on the plate and heat at 110 ℃ for 15 minutes; the R_f values of the spots from the test solution and the standard solution are the same.

pH Dissolve Amoxicillin for Syrup according to the label; the pH of the resulting solution is between 5.0 and 7.5.

Water NMT 3.0% (0.2 g, volumetric titration, direct titration).

Uniformity of dosage units (distribution) Meets the requirements.

Assay Weigh accurately an amount of Amoxicillin for Syrup, equivalent to about 0.1 g (potency) according to the labeled potency, dissolve in water, add 15.0 mL of the internal standard solution and water to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g (potency) of amoxicillin RS, dissolve in water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with each 20 mL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the ratios, Q_T and Q_S, of the peak area of amoxicillin to that of the internal standard for the test solution and standard solution.

$$\text{Potency (μg) of amoxicillin } (C_{16}H_{19}N_3O_5S_2) = \text{Potency (μg) of amoxicillin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh accurately about 0.7 g of sodium benzoate and dissolve it in water to make exactly 1000 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column, about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography.

Flow rate: Adjust the flow rate so that the retention time of the internal standard is about 1.5 minutes.

Mobile phase: Dissolve 6.3 g of ammonium formate in 750 mL of water, adjust the pH to 6.0 with formic acid or ammonia TS, add 30 mL of methanol, and add water to make exactly 1000 mL.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions and perform the test; the internal standard and amoxicillin are eluted in this order, with the resolution being NLT 2.0.

Packaging and storage Preserve in tight containers.

Amoxicillin Tablets
아목시실린 정

Amoxicillin Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of amoxicillin ($C_{16}H_{19}N_3O_5S$: 365.40).

Method of preparation Prepare as directed under Tablets, with Amoxicillin Hydrate.

Identification Proceed with Amoxicillin Tablets, previously powdered, as directed under the Identification under Amoxicillin for Syrup.

Water NMT 9.0% for 50 mg (potency) of tablets (0.1 g, volumetric titration, direct titration); NMT 13.0% for 0.125 g (potency) and 0.25 g (potency) of tablets (0.1 g, volumetric titration, direct titration).

Dissolution Perform the test with 1 tablet of Amoxicillin Tablets at 75 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take NLT 20 mL of the dissolved solution 30 minutes after starting the test and filter through a membrane filter with a pore size not exceeding 0.5 μm. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add water to make *V'* mL according to the labeled amount to obtain a solution having a known concentration of about 45 μg (potency) of amoxicillin ($C_{16}H_{19}N_3O_5S$) per mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of amoxicillin RS, dissolve in pH 5.0 buffer solution to the same concentration as the test solution, and use this solution as the standard solution. Use the test solution and the standard solution within 6 hours. Perform the test with each 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the amoxicillin peak areas, A_T and A_S. It meets the requirements if the dissolution rate of Amoxicillin Tablets in 30 minutes is NLT 75% (Q).

Dissolution rate (%) with respect to the labeled amount of amoxicillin ($C_{16}H_{19}N_3O_5S_2$)

$$= C_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 90000$$

Cs: Concentration [mg (potency)/mL] of the standard solution

C: Labeled amount [mg (potency)] of amoxicillin ($C_{16}H_{19}N_3O_5S$) in 1 tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 300 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Filter a mixture of pH 5.0 phosphate buffer solution and acetonitrile (3900 : 100) through a membrane filter with a pore size not exceeding 0.5 μm and use the filtrate as the mobile phase.

Flow rate: 0.7 mL/min

Column temperature: A constant temperature of about 40 °C.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions and perform the test; the mass distribution ratio is between 1.1 and 2.8; the number of theoretical plates and symmetry factor are NLT 1700 and NMT 2.5, respectively.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of amoxicillin is NMT 1.5%.

Phosphate buffer solution, pH 5.0—Dissolve 27.2 g of potassium dihydrogen phosphate in about 3000 mL of water. Adjust the pH to 5.0 ± 0.1 with 45% (w/w) potassium hydroxide solution and add water to make 4000 mL.

Uniformity of dosage units Meets the requirements

Assay Weigh accurately NLT 20 tablets of Amoxicillin Tablets and powder it. Weigh an amount, equivalent to about 0.1 g (potency) according to the labeled potency, add a solution of sodium borate (1 in 200), and shake to mix for about 10 minutes. Add a solution of sodium borate (1 in 200) to make exactly 50 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 0.1 g (potency) of amoxicillin RS, proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with each 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of amoxicillin in the test solution and the standard solution.

Potency (μg) of amoxicillin ($C_{16}H_{19}N_3O_5S_2$)

$$= \text{Potency } (\mu g) \text{ of amoxicillin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

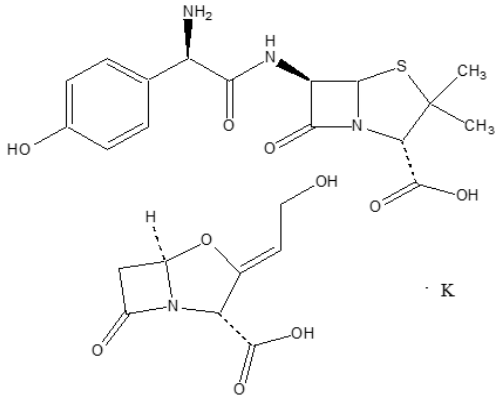
Mobile phase: Dissolve 1.361 g of sodium acetate trihydrate in 750 mL of water, adjust the pH to 4.5 with acetic acid(100), and add water to make 1000 mL. To 950 mL of this solution, add 50 mL of ethanol(95) and mix.

Flow rate: Adjust the flow rate so that the retention time of amoxicillin is about 8 minutes.

Selection of column: Proceed with 10 μL of the standard solution under the above operating conditions and perform the test; the number of theoretical plates of the amoxicillin peak is NLT 2500.

Packaging and storage Preserve in tight containers.

Amoxicillin·Clavulanate Potassium
아목시실린·클라불란산칼륨



$C_{16}H_{19}N_3O_5S \cdot C_8H_9NO_5 \cdot K$: 603.66

(2*R*,3*Z*,5*R*)-3-(2-Hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid potassium salt with (2*S*,5*R*,6*R*)-6-[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (1:1) mixture, [*74469-00-4*]

Amoxicillin·Clavulanate Potassium occurs as a white powder obtained by mixing amoxicillin and clavulanate potassium at a ratio of 2 : 1, 4 : 1 or 7 :1 (potency). Amoxicillin·Clavulanate Potassium contains NLT 530 μg and NMT 590 μg (potency) of amoxicillin ($C_{16}H_{19}N_3O_5S$: 365.41) and NLT 265 μg and NMT 295 μg (potency) of clavulanic acid ($C_8H_9NO_5$: 199.16) per mg (1) when amoxicillin and clavulanate potassium are mixed at a ratio of 2 : 1 (potency); NLT 640 μg and NMT 700 μg (potency) of amoxicillin ($C_{16}H_{19}N_3O_5S$: 365.41) and NLT 160 μg and NMT 175 μg (potency) of clavulanic acid ($C_8H_9NO_5$: 199.16) per mg (2) when amoxicillin and clavulanate potassium are mixed at a ratio of 4 : 1 (potency); NLT 697 μg and NMT 770 μg (potency) of amoxicillin ($C_{16}H_{19}N_3O_5S$: 365.41) and NLT 99.5 μg and NMT 110 μg (potency) of clavulanic acid ($C_8H_9NO_5$: 199.16) per mg (3) when amoxicillin and clavulanate potassium are mixed at a ratio of 7 : 1 (potency).

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

pH The pH of 0.2% aqueous solution of Amoxicillin·Clavulanate Potassium is between 3.7 and 5.7.

Ratio of amoxicillin and clavulanate potassium (1) The ratio of amoxicillin and clavulanate potassium is between 1.9 : 1 and 2.1 : 1 when tested as directed under the Assay if they are mixed at a ratio of 2 : 1 (potency).

(2) The ratio of amoxicillin and clavulanate potassium is between 3.8 : 1 and 4.2 : 1 when tested as directed under the Assay if they are mixed at a ratio of 4 : 1 (potency).

(3) The ratio of amoxicillin and clavulanate potassium is between 6.65 : 1 and 7.35 : 1 when tested as directed under the Assay if they are mixed at a ratio of 7 : 1 (potency).

Water (1) Between 7.5% and 9.5% when amoxicillin and clavulanate potassium are mixed at a ratio of 2 : 1 (potency).

(2) Between 9.0% and 11.5% when amoxicillin and clavulanate potassium are mixed at a ratio of 4 : 1 (potency).

(3) NMT 14.5% when amoxicillin and clavulanate potassium are mixed at a ratio of 7 : 1 (potency) (0.1 g, volumetric titration, direct titration).

Assay ***Amoxicillin and clavulanate potassium***

(1) When amoxicillin and clavulanate potassium are mixed at a ratio of 2 : 1 (potency)

Weigh accurately an amount of Amoxicillin·Clavulanate Potassium, equivalent to about 0.1 g (potency) of amoxicillin ($C_{16}H_{19}N_3O_5S$) {an amount equivalent to about 50 mg of clavulanic acid ($C_8H_9NO_5$)}, dissolve in water, and add 15 mL of the internal standard solution and water to make exactly 100 mL. Use this solution as the test solution. Separately, weigh accurately about 0.1 g (potency) of amoxicillin RS and about 50 mg (potency) of clavulanic acid RS, dissolve them in water, and add 15 mL of the internal standard solution and water to make exactly 100 mL. Use this solution as the test solution.

(2) When amoxicillin and clavulanate potassium are mixed at a ratio of 4 : 1 (potency)

Weigh accurately Amoxicillin·Clavulanate Potassium in an amount equivalent to about 0.1 g (potency) as amoxicillin ($C_{16}H_{19}N_3O_5S$)) {an amount to about 25 mg

as clavulanic acid ($C_8H_9NO_5$)}, dissolve it in water, then add 15 mL of the internal standard solution and water to make exactly 100 mL. Use this solution as the test solution. Separately, weigh accurately about 0.1 g (potency) of amoxicillin RS and about 25 mg (potency) of clavulanic acid RS, dissolve them in water, then add 15 mL of the internal standard solution and water to make exactly 100 mL. Use this solution as the test solution.

(3) When amoxicillin and clavulanate potassium are mixed at a ratio of 7 : 1 (potency)

Weigh accurately an amount of Amoxicillin·Clavulanate Potassium, equivalent to about 0.1 g (potency) of amoxicillin ($C_{16}H_{19}N_3O_5S$)) {an amount, equivalent to about 14 mg as clavulanic acid ($C_8H_9NO_5$)}, dissolve in water, and add 15 mL of the internal standard solution and water to make exactly 100 mL. Use this solution as the test solution. Separately, weigh accurately about 0.1 g (potency) of amoxicillin RS and about 14 mg (potency) of clavulanic acid RS, dissolve them in water, and add 15 mL of the internal standard solution and water to make exactly 100 mL. Use this solution as the test solution.

Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of peak areas of amoxicillin and clavulanic acid, Q_{T1}, Q_{S1}, Q_{T2} and Q_{S2}, to that of the internal standard in each solution.

Amount [potency (μg)] of amoxicillin ($C_{16}H_{19}N_3O_5S$)
= Amount [potency (mg)] of amoxicillin RS
× (Q_{T1} / Q_{S1})× 1000

Amount [potency (μg)] of clavulanic acid ($C_8H_9NO_5$)
= Amount [potency (mg)] of clavulanic acid RS
× (Q_{T2} / Q_{S2}) × 1000

Internal standard solution—Weigh accurately about 0.7 g of sodium benzoate, dissolve in water, and make exactly 1000 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography.

Flow rate: Adjust the flow rate so that the retention time of the internal standard is about 1.5 minutes.

Mobile phase: Dissolve 6.3 g of ammonium formate in 750 mL of water, adjust the pH to 6.0 with formic acid or ammonia TS, add 30 mL of methanol and add water to make exactly 1000 mL.

System suitability

Selection of column: Repeat the test with 10 μL of the standard solution according to the above operating conditions; clavulanic acid, the internal standard and amoxicillin are eluted in this order with the resolution between the peaks of internal standard and clavulanic acid being 3.9 and the resolution between the peaks of internal standard and amoxicillin being NLT 2.0.

Packaging and storage Preserve in tight containers.

Amoxicillin·Clavulanate Potassium for Syrup
시럽용 아목시실린·클라불란산칼륨

Amoxicillin·Clavulanate Potassium for Syrup is a preparation for syrup, which is dissolved before use, and contains NLT 90.0% and NMT 120.0% of the labeled amount of amoxicillin ($C_{16}H_{19}N_3O_5S$: 365.40) and clavulanic acid ($C_8H_9NO_5$: 199.16).

Method of preparation Prepare as directed under Syrups to contain Amoxicillin and Clavulanate Potassium in the ratio of 4 : 1 (potency), 7 : 1 (potency) or 14 : 1 (potency).

Identification (1) The retention times of the major peaks obtained from the test solution and the standard solution prepared as directed under the Assay are the same.

pH Dissolve Amoxicillin·Clavulanate Potassium for Syrup according to the label; the pH of the resulting solution is between 4.0 and 6.0.

Water NMT 8.0% if the ratio of amoxicillin to potassium clavulanate is 4 : 1 (potency), NMT 9.0% if the ratio of amoxicillin to potassium clavulanate is 7 : 1 (potency), and NMT 11.0% if the ratio of amoxicillin to potassium clavulanate is 14 : 1 (potency) (0.1 g, volumetric titration, direct titration).

Uniformity of dosage units (distribution) Meets the requirements.

Assay Proceed as directed under the Assay under Amoxicillin Clavulanate Potassium Tablets. Weigh accurately an amount of Amoxicillin ·Clavulanate Potassium for Syrup, equivalent to about 50 mg (potency) of amoxicillin according to the labeled potency, add about 70 mL of water, shake well to dissolve for 60 minutes, and add water to make exactly 100 mL. Filter if necessary and use the solution as the test solution. Separately, weigh accurately about 50 mg (potency) of amoxicillin RS and 12.5 mg (4 : 1), 7.1 mg (7 : 1) or 3.6 mg (14 : 1) of clavulanic acid RS, add about 70 mL of water, shake well to dissolve for 60 minutes, add water to make 100 mL, and use this solution as the standard solution.

Packaging and storage Preserve in tight containers.

Amoxicillin·Clavulanate Potassium Tablets
아목시실린·클라불란산칼륨 정

Amoxicillin·Clavulanate Potassium Tablets contain NLT 90.0% and NMT 120.0% of the labeled amounts of amoxicillin ($C_{16}H_{19}N_3O_5S$: 365.40) and clavulanic acid ($C_8H_9NO_5$: 199.16).

Method of preparation Prepare as directed under Tablets to contain Amoxicillin and Clavulanate Potassium in the ratio of 2 : 1 (potency), 4 : 1 (potency) or 7 : 1 (potency).

Identification (1) The retention times of the major peaks obtained from the test solution and the standard solution prepared as directed under the Assay are the same.

Water (1) NMT 7.0% if the ratio of amoxicillin to clavulanate potassium is 2 : 1 (potency),

(2) NMT 9.0% if the ratio of amoxicillin to clavulanate potassium is 4 : 1 (potency),

(3) NMT 11.0% if the ratio of amoxicillin to potassium clavulanate is 7 : 1 (potency) (0.1 g, volumetric titration, direct titration).

Dissolution Perform the test with 1 tablet of Amoxicillin·Clavulanate Potassium Tablets at 75 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take the dissolved solution after 30 minutes after starting the test and filter. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately an appropriate amount of amoxicillin RS and clavulanic acid RS, dissolve each in water to the same concentration as the test solution, and use these solutions as the standard solutions. Perform the test with each 20 μL of the test solution and the standard solutions as directed under the Assay, and determine the peak areas, A_T and A_S, of amoxicillin and clavulanic acid. It meets the requirements when the dissolution rates of amoxicillin and clavulanic acid in 30 minutes are NLT 85% (Q) and 80% (Q), respectively.

Dissolution rate (%) with respect to the labeled amount of amoxicillin ($C_{16}H_{19}N_3O_5S$) or clavulanic acid ($C_8H_9NO_5$).

$$= C_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 90000$$

C_S: Concentration [mg (potency)/mL] of amoxicillin or clavulanic acid in the standard solution

C: Labeled amount [mg (potency)] of amoxicillin ($C_{16}H_{19}N_3O_5S$) or clavulanic acid ($C_8H_9NO_5$) per tablet

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately NLT 10 tablets of Amoxicillin·Clavulanate Potassium Tablets, dissolve in a sufficient amount of water by shaking to mix to obtain a solution having a known concentration of 1.25 mg (potency) of amoxicillin per mL according to the labeled potency, filter, if necessary, and use as the test stock solution. Pipet 40 mL of the test stock solution, add water to make 100 mL, and use this solution as the test solution. Use the test solution within 1 hour. Separately, weigh accurately about 50 mg (potency) of amoxicillin RS and 25 mg (2 : 1), 12.5 mg (4 : 1) or 7.1 mg (7 : 1) of clavulanic acid RS, add about 70 mL of water, shake to mix well for 60 minutes to dissolve, add water to make 100 mL, and use this solution as the standard solution. Perform the test with each 20 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak areas, A_{T1} and A_{S1}, A_{T2} and A_{S2}, of amoxicillin and clavulanic acid from test solution and the standard solution, respectively.

Potency (μg) of amoxicillin ($C_{16}H_{19}N_3O_5S$)
$$= \text{Potency (μg) of amoxicillin RS} \times \frac{A_{T1}}{A_{S1}}$$

Potency (μg) of clavulanic acid ($C_8H_9NO_5$)
$$= \text{Potency (μg) of clavulanic acid RS} \times \frac{A_{T2}}{A_{S2}}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 to 10 μm in particle diameter).

Mobile phase: Filter a mixture of pH 4.4 phosphate buffer solution and methanol (95 : 5) through a membrane filter with a pore size not exceeding 0.5 μm and use the filtrate as the mobile phase.

Flow rate: 2 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above operating conditions and perform the test; the resolution of amoxicillin and clavulanic acid is NLT 3.5, and the number of theoretical plates and symmetry factor are NLT 550 and NMT 1.5, respectively.

System repeatability: Repeat the test 5 times according to the above conditions with each 20 μL of the standard solution; the relative standard deviation of the peak area is NMT 2.0%

Phosphate buffer solution, pH 4.4—Dissolve 7.8 g of sodium dihydrogen phosphate dihydrate in 900 mL of water, adjust the pH to 4.4 ± 0.1 with phosphoric acid or 10 mol/L sodium hydroxide solution, and add water to make 1000 mL.

Packaging and storage Preserve in tight containers.

Amoxicillin·Clavulanate Potassium Tablets for Oral Suspension
아목시실린·클라불란산칼륨 현탁용 정

Amoxicillin·Clavulanate Potassium Tablets for Oral Suspension contain NLT 90.0% and NMT 120.0% of the labeled amount of amoxicillin ($C_{16}H_{19}N_3O_5S$: 365.41) and clavulanic acid ($C_8H_9NO_5$: 199.16).

Method of preparation Prepare as directed under Tablets to contain Amoxicillin and Clavulanate Potassium in the ratio of 4 : 1 (potency).

Identification The retention times of major peaks obtained from the test solution and the standard solution prepared as directed under the Assay are the same.

Disintegration Perform the test as directed under the Disintegration; disintegration occurs within 3 minutes after starting the test. Use water as the disintegration medium and maintain the temperature at 20 ± 5 ℃.

Uniformity of dosage units Meets the requirements.

Water NMT 9.0% (0.1 g, volumetric titration, direct titration).

Assay Weigh accurately NLT 20 tablets of Amoxicillin·Clavulanate Potassium Tablets for Oral Suspension and powder. Weigh accurately an amount equivalent to about 50 mg (potency) of amoxicillin ($C_{16}H_{19}N_3O_5S$) and about 12.5 mg (potency) of clavulanic acid ($C_8H_9NO_5$), and dissolve in about 70 mL of water by shaking well for 60 minutes. Add exactly 15 mL of the internal standard solution, add water to make exactly 100 mL, filter if necessary, and use this solution as the test solution. Separately, weigh accurately about 50 mg (potency) of amoxicillin RS and 12.5 mg (potency) of clavulanic acid RS, dissolve in about 70 mL of water by shaking well for 60 minutes, and add 15 mL of the internal standard solution. Add water to make exactly 100 mL and use this solution as the standard solution. Perform the test with each 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak area ratios, Q_{T1} and Q_{S1}, Q_{T2} and Q_{S2}, of amoxicillin and clavulanic acid to the internal standard, respectively, from the test and the standard solution.

Amount [mg (potency)] of amoxicillin ($C_{16}H_{19}N_3O_5S$)
= Amount [mg (potency)] of amoxicillin RS
× (Q_{T1} / Q_{S1})

Amount [mg (potency)] of clavulanic acid ($C_8H_9NO_5$)
= Amount [mg (potency)] of clavulanic acid RS
× (Q_{T2} / Q_{S2})

Internal standard solution—Weigh accurately about 0.7 g of sodium benzoate and dissolve in water to make exactly 1000 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: Dissolve 6.3 g of ammonium formate in 750 mL of water, adjust the pH to 6.0 with formic acid or ammonia TS, and add 30 mL of methanol. Add water again to make exactly 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of the internal standard is about 1.5 minutes.

System suitability

Column performance: Proceed with 10 μL of the standard solution according to the above operating conditions and perform the test; clavulanic acid, the internal standard and amoxicillin are eluted in this order with the resolutions between the peaks of the internal standard and clavulanic acid and between the peaks of the internal standard and amoxicillin being NLT 3.9 and 2.0, respectively.

Packaging and storage Preserve in tight containers.

Amoxicillin·Sulbactam Pivoxil Tablets
아목시실린·설박탐피복실 정

Amoxicillin·Sulbactam Pivoxil Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of amoxicillin ($C_{16}H_{19}N_3O_5S$: 365.41) and sulbactam ($C_8H_{11}NO_5S$: 233.24).

Method of preparation Prepare as directed under Tablets to contain Amoxicillin and Sulbactam Pivoxil at a ratio of 1 :1 (potency).

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay ***Amoxicillin and sulbactam pivoxil***—Weigh accurately the mass of NLT 20 tablets of Amoxicillin·Sulbactam Pivoxil Tablets, and powder. Weigh accurately an amount equivalent to about 50 mg (potency) of amoxicillin ($C_{16}H_{19}N_3O_5S$) {about 50 mg of sulbactam ($C_8H_{11}NO_5S$)} according to the labeled potency, and add a mixture of water and methanol (1 :1) to make exactly 100 mL. Filter and use the filtrate as the test solution. Separately, weigh accurately about 50 mg (potency) of

amoxicillin RS and about 50 mg (potency) of sulbactam pivoxil RS, dissolve them in a mixture of methanol and water (1 : 1) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas of amoxicillin and sulbactam pivoxil, A_{T1}, A_{S1}, A_{T2},and A_{S2} in each solution.

$$\text{Potency (μg) of amoxicillin } (C_{16}H_{19}N_3O_5S) = \text{Potency (μg) of amoxicillin RS} \times \frac{A_{T1}}{A_{S1}}$$

$$\text{Potency (μg) of sulbactam } (C_8H_{11}NO_5S) = \textit{Potency (μg) of sulbactam pivoxil RS} \times \frac{A_{T2}}{A_{S2}}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

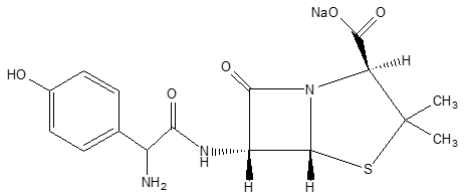
Mobile phase: A mixture of acetonitrile, water and 0.1 mol/L phosphoric acid (50 : 49.2 : 0.8).

Column temperature: 40 °C

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Amoxicillin Sodium
아목시실린나트륨



$C_{16}H_{18}N_3NaO_5S$: 387.39

Sodium (3*S*)-6*b*-[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetamido]-2,2-dimethylpenam-3-carboxylate [*34642-77-8*]

Amoxicillin Hydrate contains NLT 840 μg (potency) of amoxicillin ($C_{16}H_{19}N_3O_5S$: 365.40) per mg, calculated on the anhydrous basis.

Description Amoxicillin Sodium occurs as a white to milky white powder and is odorless or has a slight odor. It is very soluble in water or in methanol, soluble in ethanol(95) and practically insoluble in chloroform or in ether.

Identification Determine the infrared spectra of Amoxicillin Sodium and amoxicillin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve about 0.1 g (potency) each of Amoxicillin Sodium and amoxicillin RS in 0.1 mol/L phosphate buffer solution (pH 7.0)[1)] to make 100 mL, and use these solutions as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 1 μL each of these solutions on the thin-layer chromatographic plate of silica gel for thin-layer chromatography and develop the plate with a mixture of 2-methyl-1-propanol, methylene chloride, formic acid and water (10 : 1 : 1 : 1) as the developing solution. Warm the plate at 100 to 110 °C for 30 minutes, cool at room temperature, and spray evenly a solution obtained by dissolving 0.5 g of fast red GG in 100 mL of 0.1 mol/L sodium hydroxide TS, on the plate and develop the plate in a developing chamber saturated with 25% ammonia water; an orange spot appears on a pale yellow background, and the R_f values of the spots obtained from the test solution and the standard solution are the same.

(3) Amoxicillin Sodium responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between +255° and +285° (0.5 g, calculated on the anhydrous basis, 0.02 mol/L potassium hydrogen phthalate solution, 50 mL).

pH Dissolve 0.3 g of Amoxicillin Sodium in 20 mL of water; the pH of this solution is between 8.5 and 9.5.

Purity (1) ***Clarity and color of solution***—Weigh accurately about 1 g (potency) of Amoxicillin Sodium, transfer into a 50-mL Erlenmeyer flask, dissolve in exactly 20 mL of purified water, and filter. Five minutes after dissolving the filtrate, determine the absorbance of the filtrate at the wavelength of 425 nm as directed under the Ultraviolet-visible Spectroscopy, using purified water as the control solution (the absorbance is NMT 0.1).

(2) ***Heavy metals***—Proceed with 1.0 g of Amoxicillin Sodium according to Method 2 under the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Iodine-consuming substances***—Weigh accurately about 0.1 g (potency) of Amoxicillin Sodium, transfer into a 50-mL glass-stoppered flask, add 5 mL of 0.05 mol/L potassium hydrogen phthalate TS and 20.0 mL of 0.005 mol/L iodine VS, and allow to stand in the dark for 10 minutes. Titrate the excess iodine with 0.01 mol/L sodium thiosulfate VS (A mL) (indicator: 1 mL of starch TS). Separately, put 5 mL of 0.05 mol/L potassium hydrogen phthalate TS and 20.0 mL of 0.005 mol/L iodine VS into a 50-mL glass-stoppered flask, and, without allowing it to stand, titrate the iodine with 0.01 mol/L sodium thiosulfate VS (B mL) (NMT 6.0%).

$$\text{Content (\%) of iodine-consuming substances} = \frac{(B - A) \times 0.372}{Amount\ (mg) of\ Amoxicillin\ Sodium\ taken} \times 100$$

0.372: Amount (mg) of iodine-consuming substances corresponding to Each mL of 0.01 mol/L sodium thiosulfate VS

(4) ***Chloride (as sodium chloride)***—Weigh accurately about 1 g of Amoxicillin Sodium, transfer into a 100-mL beaker, dissolve in 50 mL of distilled water and 5 mL of 4 mol/L nitric acid VS, and titrate potentiometrically with silver nitrate TS (NMT 2.0%).

$$\text{Content (\%) of chloride (as sodium chloride)} = \frac{A \times 5.84}{Amount\ (mg)\ of\ Amoxicillin\ Sodium\ taken} \times 100$$

A: Amount (mL) of silver nitrate TS consumed

(5) ***Dimethylaniline***—Weigh accurately about 1.0 g of Amoxicillin Sodium, add 5 mL of 1 mol/L sodium hydroxide TS and 1 mL of the internal standard solution, centrifuge, if necessary, and use the supernatant as the test solution. Separately, weigh accurately about 50 mg of dimethylaniline, add 2.0 mL of hydrochloric acid, and add water to make 50 mL. Pipet 5.0 mL of this solution and add water to make exactly 250 mL. Pipet 1.0 mL of this solution, add 5.0 mL of 1 mol/L sodium hydroxide TS, add 1.0 mL of the internal standard solution, centrifuge, if necessary, and use the supernatant as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of dimethylaniline to the internal standard from the test solution and the standard solution, respectively (NMT 20 ppm).

$$\text{Content (ppm) of dimethylaniline} = \text{Amount (mg) of dimethylaniline taken} \times \frac{Q_T}{Q_S} \times \frac{Purity\ (\%)\ of\ dimethylaniline}{Amount\ (mg)\ of\ Amoxicillin\ Sodium\ taken} \times 4$$

Internal standard solution—Dissolve 50.0 mg of naphthalene in cyclohexane to make 50 mL. To 5.0 mL of this solution, add cyclohexane to make 100 mL and use this solution as the internal standard solution.

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A column about 2 mm in internal diameter and about 2 m in length, packed with silylated diatomaceous earth for gas chromatography, which is coated with 50% phenyl-50% methylpolysiloxane for gas chromatography equivalent to 3% of the mass of the diatomaceous earth.

Column temperature: 120 °C

Temperatures of the sample injection port and the detector: 150 °C

Carrier gas: Nitrogen

Flow rate: 30 mL/min

(6) ***2-Ethylhexanoic acid***—Dissolve 0.3 g of Amoxicillin Sodium in 4.0 mL of 33% hydrochloric acid, add 1.0 mL of the internal standard solution, shake vigorously for 1 minute to mix, allow the layers to separate, and use the supernatant as the test solution. Dissolve 75.0 g of 2-ethylhexanoic acid in the internal standard solution to make 50 mL. Pipet 1.0 mL of this solution, add 4.0 mL of 33% hydrochloric acid, shake vigorously for 1 minute to mix, allow the layers to separate, and use the supernatant as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of 2-ethylhexanoic acid to the internal standard, respectively; the amount of 2-ethylhexanoic acid is NMT 0.8%.

$$\text{Content (\%) of 2-ethylhexanoic acid} = \frac{Q_T}{Q_S} \times \frac{W_S}{W_T} \times 2$$

*W*s: Amount (g) of Amoxicillin Sodium taken

W_T: Amount (g) of 2-ethylhexanoic acid in the standard solution

Internal standard solution—Weigh accurately 0.1 g of 3-cyclohexyl propionic acid and dissolve in cyclohexane to make 100 mL.

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A glass column about 0.53 mm in internal diameter and about 10 m in length, of which the inner surface is coated with polyethylene glycol 20000-2-nitroterephthalate for gas chromatography (1 μm in thickness).

Column temperature: Maintain at 40 °C for the first 2 minutes, raise the temperature at the rate of 30 °C per minute, keep the temperature constant at 200 °C at 7.3 minutes, and maintain it at 200 °C until at 10.3 minutes.

Sample injection port temperature: 200 °C

Detector temperature: 300 °C

Carrier gas: Helium

Flow rate: 10 mL/min

System suitability

System performance: Proceed with 1 μL each of the test solution and the standard solution according to the above conditions; 2-ethylhexanoic acid and the internal standard are eluted in this order with the resolution between these peaks being NLT 2.0.

Water NMT 3.5% (0.2 g, volumetric titration, direct titration).

Sterility It meets the requirements when Amoxicillin Sodium is used for manufacturing sterile preparations, except for when there is a final sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins Less than 0.25 EU/mg (potency) of amoxicillin, when Amoxicillin Sodium is used for manufacturing sterile preparations.

Assay Weigh accurately about 0.15 g (potency) of Amoxicillin Sodium, dissolve in 5 mL of 0.5 mol/L phosphate buffer solution (pH 7.0) and 5 mL of methanol, add water to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 0.15 g (potency) of amoxicillin RS, proceed in the same manner as in the test solution, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak areas, A_T and A_S, of amoxicillin from the test solution and the standard solution, respectively.

$$\text{Potency (μg) of amoxicillin } (C_{16}H_{19}N_3O_5S_2) = \text{Potency (μg) of amoxicillin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 20 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: A mixture of 0.05 mol/L phosphate buffer solution (pH 4.5) and acetonitrile (85 : 15).

Packaging and storage Preserve in tight containers.

Amoxicillin sodium for Injection
주사용 아목시실린나트륨

Amoxicillin Sodium for Injection is an injection to be dissolved before use. Amoxicillin Sodium for Injection contains NLT 90.0% and NMT 120.0% of the labeled amount of amoxicillin ($C_{16}H_{19}N_3O_5S$: 365.41).

Method of preparation Prepare as directed under Injections, with Amoxicillin Sodium.

Description Amoxicillin Sodium for Injection occurs as a white to milky white powder.

Identification Weigh an amount of Amoxicillin Sodium for Injection, equivalent to 0.1 g (potency) of amoxicillin according to the labeled amount and about 0.1 g (potency) of amoxicillin RS and perform the test as directed under the Identification (2) under Amoxicillin Sodium.

pH Dissolve an amount of Amoxicillin Sodium for Injection, equivalent to 1.5 g (potency) of amoxicillin, in 100 mL of water; the pH of the solution is between 8.5 and 9.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.25 EU per mg (potency) of amoxicillin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Water NMT 3.5% (0.2 g, volumetric titration, direct titration).

Assay Proceed as directed under the Assay under Amoxicillin Sodium. Weigh accurately an amount of Amoxicillin Sodium for Injection, equivalent to 0.15 g (potency) of amoxicillin according to the labeled potency, dissolve in 5 mL of 0.5 mol/L phosphate buffer solution (pH 7.0), add water to make exactly 50 mL, and use this solution as the test solution.

Packaging and storage Preserve in hermetic containers.

Amoxicillin Sodium·Clavulanate Potassium
아목시실린나트륨·클라불란산칼륨

Amoxicillin Sodium·Clavulanate Potassium occurs as a white powder mixed with amoxicillin sodium and clavulanate potassium in a ratio of 5 : 1 (potency). Amoxicillin Sodium·Clavulanate Potassium contains NLT 640 μg (potency) and NMT 775 μg (potency) of amoxicillin ($C_{16}H_{19}N_3O_5S$: 365.41) per mg and NLT 125 μg (potency) and NMT 151 μg (potency) of clavulanic acid ($C_8H_9NO_5$: 199.16) per mg.

Identification (1) Weigh accurately an amount of Amoxicillin Sodium·Clavulanate Potassium, equivalent to about 0.4 g (potency) of amoxicillin ($C_{16}H_{19}N_3O_5S$) {about 80 mg (potency) of clavulanic acid ($C_8H_9NO_5$)}, add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.4 g (potency) of amoxicillin RS and about 80 mg (potency) of clavulanic acid RS, dissolve them in 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed un-

der the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate, prepared by suspending silica gel for thin-layer chromatography (with a fluorescent indicator) in 0.1% ethylenediaminetetraacetic acid disodium salt dihydrate 5% sodium dihydrogen phosphate buffer solution (pH 4.0) and then applying it to a uniform thickness of 0.25 mm, and develop the plate in a developing chamber saturated with a mixture of acetic acid-n-butyl, acetic acid(100), 0.1% ethylenediaminetetraacetic acid disodium salt dihydrate5% sodium dihydrogen phosphate buffer solution (pH 4.0) and n-butanol (10 : 6 : 2 : 1) as the developing solution to a distance of about 10 cm. After air-drying the plate, heat it at 150 °C for 10 minutes, spray evenly iodine starch TS on the plate, and heat it again at 150 °C for 10 minutes; the R_f values of each spot obtained from the test solution and the standard solution are the same.

(2) The retention times of major peaks obtained from the test solution and the standard solution under the Assay are the same.

pH The pH of the 10% solution of Amoxicillin Sodium·Clavulanate Potassium is between 8.0 and 10.0.

Ratio of amoxicillin and clavulanic acid Proceed as directed under the Assay; the potency ratio of amoxicillin and clavulanic acid is between 4.80 : 1 and 5.45 : 1.

Sterility It meets the requirements when Amoxicillin Sodium·Clavulanate Potassium is used for manufacturing sterile preparations, except for when there is a terminal sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins Less than 2.5 EU/mL of amoxicillin when tested as directed in the kinetic chromogenic assay. For this test, weigh an appropriate amount of Amoxicillin Sodium·Clavulanate Potassium, add water for bacterial endotoxins, shake vigorously for 30 minutes to mix to obtain a concentration of 10.0 mg (potency) per mL, and use this solution as the test solution.

Water NMT 2.2% (0.5 g, volumetric titration, direct titration).

Assay ***Amoxicillin Sodium and Clavulanate Potassium***—Weigh accurately an amount of Amoxicillin Sodium·Clavulanate Potassium equivalent to about 0.1 g (potency) of amoxicillin ($C_{16}H_{19}N_3O_5S$) {about 20 mg (potency) of clavulanic acid ($C_8H_9NO_5$)}, dissolve in water to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g (potency) of amoxicillin RS and about 20 mg (potency) of clavulanic acid RS, dissolve in water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_{T1} and A_{S1}, of amoxicillin and A_{T2} and A_{S2}, of clavulanic acid, from each solution.

$$\text{Potency (μg) of amoxicillin } (C_{16}H_{19}N_3O_5S) = \text{Potency (μg) of amoxicillin RS} \times \frac{A_{T1}}{A_{S1}}$$

$$\text{Potency (μg) of clavulanic acid}(C_8H_9NO_5) = \text{Potency (μg) of clavulanic acid RS} \times \frac{A_{T2}}{A_{S2}}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 300 mm in length, packed with octadecylsilanized silica gel for liquid chromatography.

Column temperature: Room temperature

Mobile phase: To 950 mL of 0.1 mol/L phosphate buffer solution (pH 4.0), add 50 mL of methanol.

Flow rate: 2 mL/min

Packaging and storage Preserve in tight containers.

Amoxicillin Sodium·Clavulanate Potassium for Injection
주사용 아목시실린나트륨·클라불란산칼륨

Amoxicillin Sodium·Clavulanate Potassium for Injection is an injection to be dissolved before use. Amoxicillin Sodium·Clavulanate Potassium for Injection contains NLT 90.0% and NMT 120.0% of the labeled amounts of amoxicillin ($C_{16}H_{19}N_3O_5S$: 365.41) and clavulanic acid ($C_8H_9NO_5$: 199.16).

Method of preparation Prepare as directed under Injections, with Amoxicillin Sodium and Potassium Clavulanate.

Description Amoxicillin Sodium·Clavulanate Potassium for Injection occurs as a white to yellowish white powder.

Identification (1) The retention times of the major peaks obtained from the test solution and the standard solution prepared as directed under the Assay are the same.

pH Dissolve an amount of Amoxicillin Sodium·Clavulanate Potassium for Injection, equivalent to 1.0 g (potency) of amoxicillin in 10 mL of water; the pH of the solution is between 8.0 and 10.0.

Water NMT 4.0% (0.2 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.25 EU per mg (potency) of amoxicillin.

Particulate contamination: Visible particles Meets the requirements.

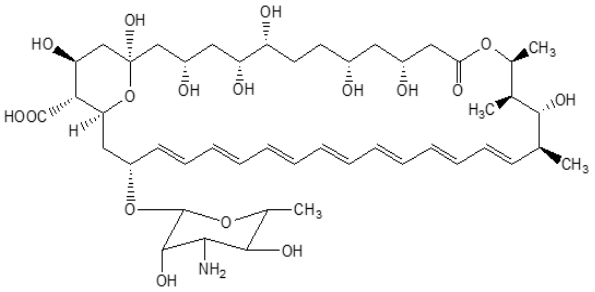
Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Proceed as directed under the Assay under Amoxicillin Sodium·Clavulanate Potassium Tablets. Weigh accurately an amount of Amoxicillin Sodium·Clavulanate Potassium for Injection, equivalent to about 50 mg (potency) of amoxicillin according to the labeled potency, add about 70 mL of water, shake well for 60 minutes to dissolve, and add water to make exactly 100 mL. Filter, if necessary, and use the solution as the test solution. Separately, weigh accurately about 50 mg (potency) of amoxicillin RS and about 10 mg (potency) of clavulanic acid RS, add about 70 mL of water, shake well for 60 minutes to dissolve, and add water to make exactly 100 mL. Use this solution as the standard solution.

Packaging and storage Preserve in hermetic containers.

Amphotericin B
암포테리신B



$C_{47}H_{73}NO_{17}$: 924.08

(1*R*,3*S*,5*R*,6*R*,9*R*,11*R*,15*S*,16*R*,17*R*,18*S*,19*E*,21*E*,23*E*,25*E*,27*E*,29*E*,31*E*,33*R*,35*S*,36*R*,37*S*)-33-[(3-Amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,5,6,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1]nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid [*1397-89-3*]

Amphotericin B is a polyene macrolide substance having antifungal activity produced by culturing *Streptomyces nodosus*.

Amphotericin B contains NLT 840 μg (potency) of amphotericin B ($C_{47}H_{73}NO_{17}$) per mg, calculated on the dried basis.

Description Amphotericin B occurs as a yellow to orange powder.

It is freely soluble in dimethylsulfoxideand practically insoluble in water or ethanol(95).

Identification (1) Dissolve 5 mg of Amphotericin B in 10 mL of dimethylsulfoxide. To 1 mL of this solution, add 5 mL of phosphoric acid; a blue color develops between the two layers, and the solution becomes blue by shaking. And to this solution, add 15 mL of water, and shake to mix; the solution exhibits a yellow to pale yellowish brown color.

(2) Weigh about 25 mg each of Amphotericin B and amphotericin B RS, dissolve in 5 mL of dimethylsulfoxide, and add methanol to make 50 mL. To 1 mL each of these solutions add methanol to make 50 mL. Determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

pH Suspend 0.3 g of Amphotericin B in 10 mL of water; the pH of this suspension is between 3.5 and 6.0.

Purity ***Amphotericin A***—Weigh accurately about 50 mg each of Amphotericin B and amphotericin B RS, dissolve each in exactly 10 mL of dimethylsulfoxide, and add methanol to make exactly 50 mL. Pipet accurately 4 mL each of these solutions, add methanol to make exactly 50 mL, and use these solutions as the test solution and the standard solution (1), respectively. Separately, weigh accurately about 20 mg of nystatin RS, dissolve in 40 mL of dimethylsulfoxide, and add methanol to make exactly 200 mL. Pipet accurately 4 mL of this solution, add methanol to make exactly 50 mL, and use this solution as the standard solution (2). Perform the test as directed under the Ultraviolet-visible Spectroscopy, using a blank test solution prepared in the same manner as the test solution without the addition of Amphotericin B as the control solution. Determine the absorbances at 282 nm and 304 nm from these solutions, and calculate the amount of amphotericin B by the following equation; the amount of amphotericin B for injection is NMT 5%. However, the content (%) of amphotericin B not used for injection is NMT 15%.

$$\text{Content (\%) of amphotericin A} = \frac{W_S \times \{(A_{Sa1} \times A_{T2}) - (A_{Sa2} \times A_{T1})\} \times 25}{W_T \times \{(A_{Sa1} \times A_{Sb2}) - (A_{Sa2} \times A_{Sb1})\}}$$

W_S: Amount (mg) of nystatin RS

W_T: Amount (mg) of Amphotericin B

A_{Sa1}: Absorbance at 282 nm of the standard solution (1)

A_{Sb1}: Absorbance at 282 nm of the standard solution (2)

A_{Sa2}: Absorbance at 304 nm of the standard solution (1)

A_{Sb2}: Absorbance at 304 nm of the standard solution (2)

A_{T1}: Absorbance at 282 nm of the test solution

A_{T2}: Absorbance at 304 nm of the test solution

Loss on drying NMT 5.0% (0.1 g, in vacuum, 60 ℃, 3 hours).

Residue on ignition NMT 0.5% (1 g).

Sterility It meets the requirements when Amphotericin B is used in sterile preparations. However, it is excluded in cases where there is a final sterilization process in the manufacturing of a sterile preparation.

Bacterial endotoxins Less than 1.0 EU per mg (potency) of amphotericin B, when Amphotericin B is used in sterile preparations.

Assay Weigh accurately about 50 mg (potency) of Amphotericin B according to the labeled potency, and dissolve in water to make a solution containing 5 mg (potency) per mL. Pipet a suitable amount of this solution, add the mobile phase to make a solution containing 8 μg (potency) per mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg (potency) of amphotericin B RS, dissolve in methanol to make a solution containing 0.2 mg (potency) per mL, and use this solution as the standard stock solution. Pipet a suitable amount of the standard stock solution, add the mobile phase to make a solution containing 8 μg (potency) per mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of amphotericin B from the test solution and standard solution.

$$\text{Amount [μg (potency)] of amphotericin B}(C_{47}H_{73}NO_{17}) = \text{Amount [μg (potency)] of amphotericin B RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 405 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of 10 mol/L potassium phosphate solution and acetonitrile (66 : 34) (pH 4.8 ± 0.2)

Flow rate: 1.0 mL/min

Packaging and storage Preserve in light-resistant, tight containers and store in a cold place.

Amphotericin B for Injection
주사용 암포테리신B

Amphotericin B for Injection is a preparation for injection which is dissolved before use, and contains NLT 90.0% and NMT 120.0% of the labeled amount of amphotericin B ($C_{47}H_{73}NO_{17}$: 924.08).

Method of preparation Prepare as directed under Injections, with Amphotericin B.

Description Amphotericin B for Injection occurs as a yellow to orange powder or a mass.

Identification Weigh 25 mg (potency) of Amphotericin B for Injection, dissolve in 5 mL of dimethylsulfoxide, and add methanol to make 50 mL. To 1 mL of this solution, add methanol to make 50 mL. Filter as needed. Determine the absorption spectra of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 361 nm and 365 nm, between 380 nm and 384 nm, and between 403 nm and 407 nm.

pH Dissolve an amount of Amphotericin B for Injection equivalent to 1 mg (potency) of amphotericin B, and dissolve in 10 mL of water; the pH of this solution is between 7.2 and 8.0. However, for colloid injectable suspensions, dissolve an amount equivalent to 0.1 g (potency) in 20 mL of water; the pH of this solution is between 6.0 and 7.8.

Purity Clarity and color of solution Dissolve an amount of Amphotericin B for Injection equivalent to 50 mg (potency) of amphotericin B according to the labeled amount in 10 mL of water; the solution is clear and yellow to orange.

Loss on drying NMT 8.0% (0.3 g, in vacuum, 60 ℃, 3 hours). For colloid injectable suspensions, NMT 2.5% (0.1 g, 0.7 kPa, 60 ℃, 3 hours).

Sterility Meets the requirements.

Bacterial endotoxins Less than 3.0 EU per mg (potency) of amphotericin B.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Proceed as directed under the Assay under Amphotericin B.

Packaging and storage Preserve in light-resistant, hermetic containers (in a cold place).

Liposomal Amphotericin B for injection
주사용 리포좀화암포테리신B

Liposomal Amphotericin B for injection is an injection, which is suspended before use. Liposomal Amphotericin B for injection contains NLT 90.0% and NMT 120.0% of the labeled amount of amphotericin B ($C_{47}H_{73}NO_{17}$: 924.08).

Method of preparation Prepare as directed under Injections, with Liposomal Freeze Dried Amphotericin B.

Description Liposomal Amphotericin B for injection occurs as a yellow powder or a mass.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Light scattering factor Add 12 mL of water for injection in Liposomal Amphotericin B for injection, shake to dissolve for NLT 30 seconds, remove the bubbles, and use this solution as the test solution. With this solution, determine the absorbance as directed under the Ultraviolet-visible Spectroscopy at 600 nm to 750 nm for at least every 10 nm. Draw a graph as a straight line regression having the log value of the wavelength as the horizontal axis and the log value of the absorbance as the vertical axis, calculate the absolute value of the slope and use as the scattering factor; the value is NLT 3.6.

pH Dissolve Liposomal Amphotericin B for injection in water to make 4.0 mg (potency) per mL; the pH of the solution is between 5.0 and 6.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 5.0 EU per mg (potency) of Liposomal Amphotericin B for injection.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Water NMT 2.0% (0.5 g, volumetric titration, direct titration).

Assay Weigh accurately an amount of Liposomal Amphotericin B for injection equivalent to 2 mg (potency) of amphotericin B, dissolve in methanol to obtain a solution having known concentration of 20 μg (potency) per mL, and use this solution as the test solution. Separately, weigh an amount of the amphotericin B RS equivalent to about 40 mg (potency) of the amphotericin B, add dimethylsulfoxide, shake well to mix, and prepare a standard stock solution containing 0.4 mg (potency) per mL. Pipet an appropriate amount of this standard stock solution, add methanol to obtain a solution having known concentration of 20 μg (potency) per mL and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and calculate the peak areas A_T and A_S of amphotericin B from the test solution and the standard solution, respectively.

$$\text{Potency (μg) of amphotericin B } (C_{47}H_{73}NO_{17}) = \text{Potency (μg) of amphotericin B RS} \times \frac{A_T}{A_S} \times \frac{1}{20}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 405 nm).

Column: A stainless-steel column about 4.6 mm in internal diameter and about 250 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

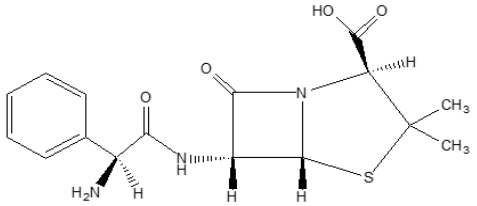
Mobile phase: A mixture of methanol, 2.5 mmol/L ethylenediaminetetraacetic acid disodium salt and acetonitrile (50 : 30 : 25).

Flow rate: 1.5 mL/min

Selection of column: Perform the test according to the above conditions with 20 μL of the standard solution; only use the symmetry factor NMT 2.

Packaging and storage Preserve in hermetic containers.

Anhydrous Ampicillin
암피실린무수물



$C_{16}H_{19}N_3O_4S$: 349.40

(3*S*,5*R*,6*R*)-6-[(2R)-2-Amino-2-phenylacetamido]-2,2-dimethylpenam-3-carboxylic acid [*69-53-4*]

Anhydrous Ampicillin contains NLT 960 μg (potency) and NMT 1005 μg (potency) of ampicillin ($C_{16}H_{19}N_3O_4S$: 349.40) per mg, calculated on the anhydrous basis.

Description Anhydrous Ampicillin occurs as white to pale yellowish white crystals or a crystalline powder.
It is sparingly soluble in water, slightly soluble in methanol, very slightly soluble in ethanol(95), and practically insoluble in acetonitrile.

Identification Determine the infrared spectra of Anhydrous Ampicillin and ampicillin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +280° and +305°(0.5 g calculated on the anhydrous basis, water, 100 mL, 100 mm).

pH Dissolve 1.0 g of Anhydrous Ampicillin in 400 mL of water; the pH of this solution is between 4.0 and 5.5.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Anhydrous Ampicillin according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Anhydrous Ampicillin according to Method 3, and perform the test (NMT 2 ppm).

(3) ***Related substances***—Dissolve 0.05 g of Anhydrous Ampicillin in the mobile phase to make exactly 50 mL, and use this solution as the test solution. Pipet 1 mL of the test solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of each solution by the automatic integration method; the area of each peak other than ampicillin from the test solution is not larger than the peak area of ampicillin from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed according to the operating conditions in the Assay.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution, and add the mobile phase to make exactly 10 mL. Confirm that the peak area of ampicillin obtained from 10 μL of this solution is equivalent to 7 to 13% of the peak area of ampicillin from the standard solution.

System performance: Proceed as directed under the Assay.

System repeatability: Proceed as directed under the Assay.

Time span of measurement: About 10 times the retention time of ampicillin.

(4) ***Dimethylaniline***—Weigh accurately about 1.0 g of Anhydrous Ampicillin, add 5 mL of 1 mol/L sodium hydroxide TS and 1 mL of the internal standard solution, centrifuge if necessary, and use the clear supernatant as the test solution. Separately, weigh accurately about 50 mg of dimethylaniline, and add 2.0 mL of hydrochloric acid and water to make 50 mL. Pipet accurately 5.0 mL of this solution and add water to make exactly 250 mL. Pipet accurately 1.0 mL of this solution, add 5.0 mL of 1 mol/L sodium hydroxide TS and 1.0 mL of the internal standard solution, centrifuge if necessary, and use the clear supernatant as the standard solution Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of dimethylaniline to that of the internal standard from each solution (NMT 20 ppm).

$$\text{Content (ppm) of dimethylaniline} = \text{Amount (mg) of dimethylaniline taken} \times \frac{Q_T}{Q_S} \times \frac{Purity\ (\%)\ of\ dimethylaniline}{Amount\ (mg)\ of\ Anhydrous\ Ampicillin} \times 4$$

Internal standard solution—Dissolve 50.0 mg of naphthalene in cyclohexane to make 50 mL. To 5.0 mL of this solution, add cyclohexane to make 100 mL, and use this solution as the internal standard solution.

Operating conditions

Detector: A flame ionization detector

Column: A column about 2 mm in internal diameter and 2 m in length, packed with diatomaceous earth for gas chromatography coated with 50% phenyl-50% methylpolysiloxane for gas chromatography equivalent to 3% mass of the diatomaceous earth.

Column temperature: 120 °C

Sample injection port, detector temperature: 150 °C

Carrier gas: Nitrogen

Flow rate: 30 mL/min

Water NMT 2.0% (2.5 g, volumetric titration, direct titration).

Sterility It meets the requirements when Anhydrous Ampicillin is used in sterile preparations. However, it is excluded in cases where there is a final sterilization process in the manufacturing of a sterile preparation.

Bacterial endotoxins Less than 0.15 EU per mg (potency) of ampicillin, when Anhydrous Ampicillin is used in sterile preparations.

Assay Weigh accurately about 50 mg (potency) each of Anhydrous Ampicillin and ampicillin RS, dissolve each in exactly 5 mL of the internal standard solution, add the mobile phase to make 50 mL, and use these solutions as the test solution and standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of ampicillin to that of the internal standard from each solution.

Potency (μg) of ampicillin ($C_{16}H_{19}N_3O_4S$)

$$= \text{Potency } (\mu g) \text{ of ampicillin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of guaifenesin in the mobile phase (1 in 200).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 5.94 g of dibasic ammonium phosphate in 850 mL of water, add 100 mL of acetonitrile, adjust the pH to 5.0 with phosphoric acid, and add water to make exactly 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of ampicillin is about 6 minutes.

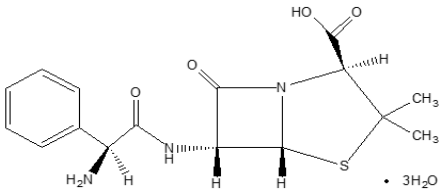
System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; ampicillin and the internal standard are eluted in this order with the resolution being NLT 40.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions under the above operating conditions; the relative standard deviation of the ratios of the peak area of ampicillin to that of internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Ampicillin Hydrate
암피실린수화물



Aminobenzylpenicillin

Ampicillin $C_{16}H_{19}N_3O_4S \cdot 3H_2O$: 403.45

(3*S*,5*R*,6*R*)-6-[(2R)-2-amino-2-phenylacetamido]-2,2-dimethylpenam-3-carboxylic acid trihydrate [*7177-48-2*]

Ampicillin Hydrate contains NLT 960 μg and NMT 1005 μg (potency) of ampicillin ($C_{16}H_{19}N_3O_4S$: 349.40) per mg, calculated on the anhydrous basis.

Description Ampicillin Hydrate occurs as white to pale yellowish white crystals or a crystalline powder.

It is sparingly soluble in water, slightly soluble in methanol, very slightly soluble in ethanol(95), and practically insoluble in acetonitrile.

Identification Determine the infrared spectra of Ampicillin Hydrate and ampicillin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between +280° and +305° (0.5 g calculated on the anhydrous basis, water, 100 mL, 100 mm).

pH Dissolve 1.0 g of Ampicillin Hydrate in 400 mL of water; the pH of this solution is between 3.5 and 5.5.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Ampicillin Hydrate according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Ampicillin Hydrate according to Method 3, and perform the test (NMT 2 ppm).

(3) ***Related substances***—Dissolve 50 mg of Ampicillin Hydrate in the mobile phase to make exactly 50 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas of each solution by the automatic integration method; the area of each peak other than ampicillin from the test solution is not larger than the peak area of ampicillin from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 5.94 g of dibasic ammonium phosphate in 850 mL of water, add 100 mL of acetonitrile, adjust the pH to 5.0 with phosphoric acid, and add water to make exactly 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of ampicillin is about 6 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution, and add the mobile phase to make exactly 10 mL. Confirm that the peak area of ampicillin obtained from 10 μL of this solution is equivalent to 7% to 13% of the peak area of ampicillin from 10 mL of the standard solution.

System performance: Weigh accurately 50 mg

(potency) of ampicillin RS, dissolve in 10 mL of the mobile phase, add 5 mL of a solution of guaifenesin in the mobile phase (1 in 200), add the mobile phase to make 50 mL, and use this solution as the system suitability solution. Proceed with 10 μL of this solution under the above operating conditions; ampicillin and guaifenesin are eluted in this order with the resolution being NLT 40.

System repeatability: Repeat the test 6 times with 10 μL each of the system suitability solution under the above operating conditions; the relative standard deviation of the ratios of the peak area of ampicilin to that of guaifenesin is NMT 1.0%.

Time span of measurement: About 10 times the retention time of ampicillin.

(4) ***Dimethylaniline***—Weigh accurately about 1.0 g of Ampicillin Hydrate, add 5 mL of 1 mol/L sodium hydroxide TS and 1 mL of the internal standard solution, centrifuge if necessary, and use the clear supernatant as the test solution. Separately, weigh accurately about 50 mg of dimethylaniline, and add 2.0 mL of hydrochloric acid and water to make 50 mL. Pipet accurately 5.0 mL of this solution and add water to make exactly 250 mL. Pipet accurately 1.0 mL of this solution, add 5.0 mL of 1 mol/L sodium hydroxide TS and 1.0 mL of the internal standard solution, centrifuge if necessary, and use the clear supernatant as the standard solution Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of dimethylaniline to that of the internal standard from each solution (NMT 20 ppm).

$$\text{Content (ppm) of dimethylaniline} = \text{Amount (mg) of dimethylaniline taken} \times \frac{Q_T}{Q_S} \times \frac{Purity\ (\%)\ of\ dimethylaniline}{Amount\ (mg)\ of\ Ampicillin\ Hydrate} \times 4$$

Internal standard solution—Dissolve 50.0 mg of naphthalene in cyclohexane to make 50 mL. To 5.0 mL of this solution, add cyclohexane to make 100 mL, and use this solution as the internal standard solution.

Operating conditions

Detector: A flame ionization detector

Column: A column about 2 mm in internal diameter and 2 m in length, packed with diatomaceous earth for gas chromatography coated with 50% phenyl-50% methylpolysiloxane for gas chromatography equivalent to 3% mass of the diatomaceous earth.

Column temperature: 120 °C

Sample injection port, detector temperature: 150 °C

Carrier gas: Nitrogen

Flow rate: 30 mL/min

Water Between 12.0% and 15.0% (0.1 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins Less than 0.15 EU per mg (potency) of ampicillin when used in the manufacturing of sterile preparations.

Assay Weigh accurately about 50 mg (potency) each of Ampicillin Hydrate and ampicillin RS, dissolve each in a suitable amount of the mobile phase, add exactly 5 mL of the internal standard solution, add the mobile phase to make 50 mL, and use these solutions as the test solution and standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of ampicillin to that of the internal standard from each solution.

$$\text{Potency (μg) of ampicillin } (C_{16}H_{19}N_3O_4S) = \text{Potency (μg) of ampicillin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of guaifenesin in the mobile phase (1 in 200).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 5.94 g of dibasic ammonium phosphate in 850 mL of water, add 100 mL of acetonitrile, adjust the pH to 5.0 with phosphoric acid, and add water to make exactly 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of ampicillin is about 6 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; ampicillin and the internal standard are eluted in this order with the resolution being NLT 40.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above operating conditions; the relative standard deviation of the ratios of the peak area of ampicillin to that of internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Ampicillin Capsules
암피실린 캡슐

Ampicillin Capsules contain NLT 90.0% and NMT 120.0% of the labeled amount of ampicillin ($C_{16}H_{19}N_3O_4S$: 349.41).

Method of preparation Prepare as directed under Capsules, with Ampicillin.

Identification (1) Take an amount of the contents of Ampicillin Capsules, equivalent to about 10 mg of ampicillin, suspend in 1 mL of water, and add 2 mL of a mixture of 2 mL of Fehling's TS and 6 mL of water; it immediately exhibits a purple color. However, when it contains probenecid, weigh an appropriate amount of Ampicillin Capsules, wash it with chloroform, discard the chloroform layer, and perform the test with the residue.

(2) To 2 mL of a solution of Ampicillin Capsules containing 1 mg of ampicillin per mL, add 0.5 mL of phenol and 5 mL of sodium hypochlorite TS; it gives a persistent odor of benzaldehyde, and an orange precipitate forms within 3 to 5 minutes. However, when it contains probenecid, weigh an appropriate amount of Ampicillin Capsules, wash it with chloroform, discard the chloroform layer, and perform the test with the residue.

Water **Anhydride:** NMT 4.0%. **Hydrate:** Between 10.0% and 15.0% (0.1 g, volumetric titration, direct titration).

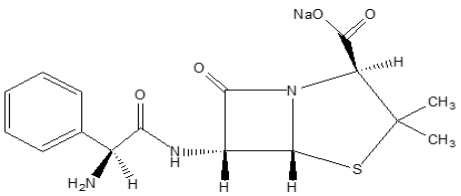
Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Proceed as directed under the Assay under Ampicillin Hydrate. Take NLT 20 capsules of Ampicillin Capsules, weigh accurately the mass of the contents, equivalent to about 50 mg (potency) according to the labeled potency, dissolve in an appropriate amount of the mobile phase, add exactly 5 mL of the internal standard solution, add the mobile phase to make 50 mL, and use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Ampicillin Sodium
암피실린나트륨



Aminobenzylpenicillin Sodium $C_{16}H_{18}N_3NaO_4S$: 371.39
Sodium (3*S*,5*R*,6*R*)-6-[(2R)-2-amino-2-phenylcetamido]-2,2-dimethylpenam-3-carboxylate [*69-52-3*]

Ampicillin Sodium contains NLT 850 μg (potency) and NMT 950 μg (potency) of ampicillin ($C_{16}H_{19}N_3O_4S$: 349.40) per mg, calculated on the anhydrous basis.

Description Ampicillin Sodium occurs as white to pale yellowish white crystals or a crystalline powder.
It is very soluble in water, and sparingly soluble in ethanol(99.5).

Identification (1) Determine the infrared spectra of Ampicillin Sodium and ampicillin sodium RS, previously dried in a desiccator (NMT 0.67 kPa, 60 °C) for 3 hours, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

(2) Ampicillin Sodium responds to the Qualitative Analysis (1) for sodium salt.

Crystallinity Meets the requirements. However, this does not apply to freeze-dried ampicillin sodium.

Optical rotation $[\alpha]_D^{20}$: Between +246° and +272° (1.0 g calculated on the anhydrous basis, water, 100 mL, 100 mm).

pH Dissolve 1.0 g of Ampicillin Sodium in 10 mL of water; the pH of this solution is between 8.0 and 10.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Ampicillin Sodium in 10 mL of water; the solution is clear and colorless to pale yellow.

(2) ***Heavy metals***—Proceed with 1.0 g of Ampicillin Sodium according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Ampicillin Sodium according to Method 1 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 50 mg of Ampicillin Sodium in 50 mL of the mobile phase and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas of each solution by the automatic integration method; the area of each peak other than ampicillin from the test solution is not larger than the peak area of ampicillin from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octa-

decylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 5.94 g of dibasic ammonium phosphate in 850 mL of water, add 100 mL of acetonitrile, adjust the pH to 5.0 with phosphoric acid, and add water to make exactly 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of ampicillin is about 6 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution and add the mobile phase to make exactly 10 mL. Confirm that the peak area of ampicillin obtained from 10 μL of this solution is equivalent to 7 to 13% of the peak area of ampicillin from 10 μL of the standard solution.

System performance: Weigh accurately 50 mg of ampicillin RS, dissolve in 10 mL of the mobile phase, add 5 mL of a solution of guaifenesin in the mobile phase (1 in 200), add the mobile phase again to make 50 mL, and use this solution as the system suitability solution. Proceed with 10 μL of this solution under the above operating conditions; ampicillin and guaifenesin are eluted in this order with the resolution being NLT 35.

System repeatability: Repeat the test 6 times with 10 μL each of the system suitability solutions under the above operating conditions; the relative standard deviation of the ratios of the peak area of ampicillin to that of guaifenesin is NMT 1.0%.

Time span of measurement: About 10 times the retention time of ampicillin.

(5) ***Dimethylaniline***—Weigh accurately about 1.0 g of Ampicillin Sodium, add 5 mL of 1 mol/L sodium hydroxide TS, and shake to dissolve. Add 1 mL of the internal standard solution, mix vigorously for 1 minute, centrifuge, and use the clear supernatant as the test solution. Separately, weigh accurately about 50 mg of dimethylaniline, dissolve in 25 mL of 1 mol/L hydrochloric acid, and add water to make 50 mL. Pipet 5.0 mL of this solution and add water to make exactly 250 mL. Pipet accurately 1.0 mL of this solution, add 5.0 mL of 1 mol/L sodium hydroxide TS and 1.0 mL of the internal standard solution, mix vigorously for 1 minute, centrifuge, and use the clear supernatant as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of dimethylaniline to that of the internal standard from each solution (NMT 20 ppm).

$$\text{Content (ppm) of dimethylaniline} = \text{Amount (mg) of dimethylaniline taken} \times \frac{Q_T}{Q_S} \times \frac{Purity\ (\%)\ of\ dimethylaniline}{Amount\ (mg)\ of\ Ampicillin\ Sodium} \times 4$$

Internal standard solution—Dissolve about 50 mg of naphthalene in cyclohexane to make 50 mL. To 5.0 mL of this solution, add cyclohexane to make 100 mL, and use this solution as the internal standard solution.

Operating conditions

Detector: A flame ionization detector

Column: A column about 0.53 mm in internal diameter and about 30 m in length, coated the inside with 35% phenyl-65% dimethylpolysiloxane for gas chromatography in a thickness of 1.0 μm.

Column temperature: Inject the solution at a constant temperature of about 110 °C, maintain the temperature for 4 minutes, and raise the temperature at the rate of 8 °C per minute to 200 °C, and maintain at a constant temperature of about 200 °C for 5 minutes.

Sample injection port, detector temperature: 250 °C

Carrier gas: Helium

Flow rate: 30 cm/sec

Split ratio: About 1:10.

System suitability

System performance: Proceed with 1 μL of the standard solution according to the above operating conditions; the relative retention time of naphthalene to dimethylaniline is about 1.3, and the signal-to-noise ratio for dimethylaniline is NLT 10.

Water NMT 2.0% (0.2 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, it is excluded in cases where there is a final sterilization process in the manufacturing of a sterile preparation.

Bacterial endotoxins Less than 0.15 EU per mg (potency) of ampicillin when used in the manufacturing of sterile preparations.

Assay Perform the test as directed under the Assay of Ampicillin Hydrate. However, weigh accurately about 50 mg (potency) of Ampicillin Sodium, dissolve in a suitable amount of the mobile phase, add exactly 5 mL of the internal standard solution, add the mobile phase to make 50 mL, and use this solution as the test solution.

System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; ampicillin and the internal standard are eluted in this order with the resolution being NLT 35.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above operating conditions; the relative standard deviation of the ratios of the peak area of ampicillin to that of internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Ampicillin Sodium for Injection
주사용 암피실린나트륨

Ampicillin Sodium for Injection is a preparation for injection which is dissolved before use, and contains NLT 90.0% and NMT 110.0% of the labeled amount of ampicillin ($C_{16}H_{19}N_3O_4S$: 349.41).

Method of preparation Prepare as directed under Injections, with Ampicillin Sodium.

Description Ampicillin Sodium for Injection occurs as pale yellowish white crystals or a crystalline powder.

Identification Perform the test as directed under the Identification for Ampicillin Sodium.

Osmolality Meets the requirements.

pH Dissolve an amount of Ampicillin Sodium for Injection equivalent to 1.0 g (potency) of ampicillin; the pH of this solution is between 8.0 and 10.0.

Purity ***Clarity and color of solution***—Dissolve an amount of Ampicillin Sodium for Injection equivalent to 0.25 g (potency) of ampicillin sodium in 0.75 mL of water; the solution is clear. The absorbance of this solution measured at wavelength 400 nm as directed under the Ultraviolet-visible Spectroscopy is NMT 0.40.

Water NMT 3.0% (0.2 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.075 EU per mg (potency) of ampicillin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately NLT 10 of Ampicillin Sodium for Injection, and weigh accurately the amount equivalent to about 50 mg (potency) according to the labeled potency, add exactly 5 mL of the internal standard solution and then the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg (potency) of ampicillin sodium RS, proceed in the same manner as for the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios of the peak area, Q_T and Q_S of ampicillin to that of the internal standard.

$$\text{Potency (μg) of ampicillin } (C_{16}H_{19}N_3O_4S) = \text{Potency (μg) of ampicillin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of guaifenesin in the mobile phase (1 in 200).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Add 850 mL of water and 100 mL of acetonitrile to 5.9 g of ammonium monohydrogen phosphate, adjust pH to 5.0 by adding phosphoric acid, and add water to make 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of ampicillin is about 6 minutes.

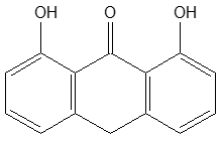
System suitability

System performance: Proceed with 10 μL of the standard solution under the above conditions; ampicillin and the internal standard are eluted in this order with the resolution between these peaks being NLT 26.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above conditions; the relative standard deviation of the peak area ratios of ampicillin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in hermetic containers.

Anthralin
안트랄린



Dithranol $C_{14}H_{10}O_3$: 226.23

1,8-Dihydroxy-10*H*-anthracen-9-one [*1143-38-0*]

Anthralin contains NLT 97.0% and NMT 102.0% of anthralin ($C_{14}H_{10}O_3$), calculated on the dried basis.

Description Anthralin occurs as a yellowish-brown, odorless and tasteless crystalline powder.

It is freely soluble in acetone, chloroform and benzene, sparingly soluble in ethanol(95), ether or acetic acid(100) and insoluble in water. It dissolves in sodium hydroxide

TS.

Identification (1) Determine the absorption spectra of solutions of Anthralin and anthralin RS in chloroform (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Anthralin and anthralin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 178 and 181 ℃ (Method 1).

Purity (1) ***Acidity or alkalinity***—Filtrate of Anthralin suspended in water is neutral when tested with Litmus paper.

(2) ***Chloride***—Weigh 1.0 g of Anthralin and dissolve in 15 mL of water, then filter. Take 5 mL of the filtrate and add nitric acid to make acidic, then add 2 to 3 drops of silver nitrate TS; the distillate of this solution is not thicker than 5 mL of the filtrate which is taken separately and to which nothing is added.

(3) ***Sulfate***—Take 5 mL of the filtrate of (2) and add 3 drops of 3 mol/L hydrochloric acid and 5 drops of barium chloride TS; the suspension of the solution that forms is not thicker than 5 mL of the filtrate which is taken separately and to which nothing is added.

Loss on drying NMT 0.5% (1 g, silica gel, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.25 g of Anthralin, and dissolve in dichloromethane to make exactly 100 mL. Pipet 10 mL of this solution, add dichloromethane to make exactly 100 mL, and mix. Pipet 5 mL of this solution, add 5.0 mL of the internal standard solution, then add the mobile phase to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of anthralin RS and dissolve in dichloromethane to make a solution containing 250 μg per mL. Pipet 5 mL of this solution, add 5.0 mL of the internal standard solution, add the mobile phase to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of anthralin to that of the internal standard.

$$\text{Amount (mg) of anthralin } (C_{14}H_{10}O_3) = C \times \frac{Q_T}{Q_S}$$

C: Concentration of the standard solution (μg/mL)

Internal standard solution—Take a sufficient amount of *o*-nitroaniline and dissolve in a small amount of dichloromethane, then add *n*-hexane to make a solution containing 500 μg per mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 354 nm).

Column: A stainless tube about 4.6 mm in internal diameter and about 25 cm in length, packed with porous silica for liquid chromatography (5 to 10 μm in particle diameter).

Mobile phase: A mixture of *n*-hexane, dichloromethane and acetic acid(100) (82 : 12 : 6).

Flow rate: 2 mL/min

System suitability

System performance: Weigh 10 mg of anthralin RS and 20 mg of danthron and dissolve in dichloromethane to make 100 mL. To 5 mL of this solution, add 5 mL of *n*-hexane and the mobile phase to make 25 mL. Proceed with 10 μL of this solution under the above operating conditions; anthralin and danthron are eluted in this order with the resolution being NLT 1.3.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Anthralin Ointment
안트랄린 연고

Dithranol Ointment

Anthralin Ointment contains NLT 90.0% and NMT 115.0% of the labeled amount of anthralin ($C_{14}H_{10}O_3$: 226.23) when labeled amount of Anthralin in Anthralin Ointment is NLT 0.1%. Anthralin Ointment contains NLT 90.0% and NMT 130.0% of the labeled amount of anthralin ($C_{14}H_{10}O_3$: 226.23) when the labeled amount of Anthralin in Anthralin Ointment is NMT 0.1%.

Method of preparation Prepare as directed under Ointments, with Anthralin.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Assay Weigh accurately about 5 g of Anthralin Ointment, place in a 100-mL beaker, and disperse the ointment by adding 20 mL of dichloromethane and 10 mL of acetic acid(100). Filter the content with dichloromethane using Whatman filter paper No. 4 to 100-mL volumetric flask. Completely wash the precipitate using dichloromethane, then fill with dichloromethane to the gauge line. Pipet an amount equivalent to about 0.5 g of anthralin

($C_{14}H_{10}O_3$), add 2.0 mL of the internal standard solution, then add the mobile phase to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of anthralin RS and dissolve in dichloromethane to prepare a solution containing 0.25 mg per mL. Pipet 2 mL of this solution, add 2.0 mL of the internal standard solution, add the mobile phase to make exactly 25 mL, and use this solution as the standard solution. Perform the test solution with the test solution and the standard solution as directed under the Assay under Anthralin.

$$\text{Amount (mg) of anthralin } (C_{14}H_{10}O_3) = 200 \times \frac{C}{V} \times \frac{Q_T}{Q_S}$$

C: Concentration (mg/mL) of the standard solution
V: Amount (mL) taken of sample

Packaging and storage Preserve in light-resistant, well-closed containers.

Arbekacin Sulfate Injection
아르베카신황산염 주사액

Arbekacin Sulfate Injection is an aqueous injection. It contains NLT 90.0% and NMT 110.0% of the labeled amount of arbekacin ($C_{22}H_{44}N_6O_{10}$: 552.62).

Method of preparation Prepare as directed under Injections, with Arbekacin Sulfate.

Description Arbekacin Sulfate Injection occurs as a clear, colorless liquid.

Identification To 0.2 mL of Arbekacin Sulfate Injection, add 1 mL of water and use this solution as the test solution. Dissolve 10 mg of arbekacin sulfate RS in 1 mL of water and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ammonia water(28), methanol, chloroform and ethanol(95) (7 : 6 : 4 : 1) to a distance of about 12 cm, and air-dry the plate. Spray evenly 0.2% ninhydrin-water saturated 1-butanol TS on the plate and heat at 80 °C for 10 minutes; the principal spots obtained from the test solution and the standard solution are purplish brown and have the same R_f values.

Osmolality Between 0.8 and 1.2 (Injections for intramuscular administration).

pH Between 6.0 and 8.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.50 EU per mg (potency) of amikacin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay ***Cylinder plate method***—(1) Use Bacillus subtilis ATCC 6633 as the test organism.

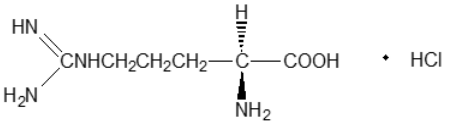
(2) Medium: Agar media for seed and base layer Use the culture medium in (A) (2) (a) ① ⓐ under the Microbial Assays for Antibiotics. In this case, adjust the pH to 7.8 to 8.0 after sterilization.

(3) Standard solution: Weigh accurately about 20 mg (potency) of arbekacin sulfate RS, previously dried, dissolve in diluted phosphate buffer solution (pH 6.0) (1 in 2) to make exactly 50 mL, and use this solution as the standard stock solution. Keep the standard stock solution at 5 to 15 °C and use within 30 days. Pipet an appropriate amount of the standard stock solution, add 0.1 mol/L phosphate buffer solution (pH 8.0), dilute to obtain a solution containing 20 μg (potency) and 5 μg (potency) in 1 mL, and use these solutions as the high concentration standard solution and the low concentration standard solution, respectively.

(4) Test solution: Take exactly equivalent to about 20 mg (potency) of an amount of Arbekacin Sulfate according to the labeled amount, and add water to make exactly 50 mL. Pipet an appropriate amount of this solution, add 0.1 mol/L phosphate buffer solution (pH 8.0), dilute to obtain a solution containing 20 μg (potency) and 5 μg (potency) in 1 mL, and use these solutions as the high concentration test solution and the low concentration test solution, respectively. With these solutions, perform the test according to (A)(8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in hermetic containers.

L-Arginine Hydrochloride
L-아르기닌염산염



Arginine Hydrochloride $C_6H_{14}N_4O_2 \cdot HCl$: 210.66
Arginine hydrochloride [*1119-34-2*]

L-Arginine Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of L-arginine hydrochloride ($C_6H_{14}N_4O_2 \cdot HCl$).

Description L-Arginine Hydrochloride occurs as white crystals or a crystalline powder, which is odorless and has a faint, characteristic taste.
It is freely soluble in water or formic acid, very slightly soluble in ethanol(95), and practically insoluble in ether.

Identification (1) Determine the infrared spectra of L-Arginine Hydrochloride and Arginine hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of L-Arginine Hydrochloride (1 in 50) responds to the Qualitative Analysis for chloride.

pH Dissolve 1.0 g of L-Arginine Hydrochloride in 10 mL of water; the pH of this solution is between 4.7 and 6.2.

Optical rotation $[\alpha]_D^{20}$: Between + 21.5° and + 23.5° (2 g, after drying, 6 mol/L hydrochloric acid TS, 25 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of L-Arginine Hydrochloride in 10 mL of water; the solution is clear and colorless.

(2) ***Sulfate***—Perform the test with 0.6 g of L-Arginine Hydrochloride. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid (NMT 0.028%).

(3) ***Ammonium***—Perform the test with 0.25 g of L-Arginine Hydrochloride. Prepare the control solution with 5 mL of the ammonium standard solution. However, this test is done as directed under the vacuum distillation method.

(4) ***Heavy metals***—Weigh and proceed with 1.0 g of L-Arginine Hydrochloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(5) ***Arsenic***—Proceed with 1.0 g of L-Arginine Hydrochloride according to Method 1 and perform the test (NMT 2 ppm).

(6) ***Related substances***—Dissolve 0.20 g of L-Arginine Hydrochloride in 10 mL of water, and use this solution as the test solution. Pipet 1 mL of this solution and add water to make exactly 10 mL. Pipet 1 mL of this solution, add water to make exactly 25 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethanol(99.5), water, 1-butanol and ammonia water (2 : 1 : 1 : 1) as the developing solvent to a distance of about 10 cm. Dry the thin-layer chromatographic plate at 100 °C for 30 minutes. Spray evenly a solution of ninhydrin in acetone (1 in 50) on the plate and heat at 80 ℃ for 5 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.2% (1 g, 105 ℃, 3 hours).

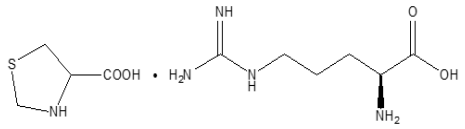
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.1 g of L-Arginine Hydrochloride, previously dried, dissolve in 2 mL of formic acid, add exactly 15 mL of 0.1 mol/L perchloric acid and heat on a steam bath for 30 minutes. After cooling, add 45 mL of acetic acid(100) and titrate the exceeding amount of perchloric acid with 0.1 mol/L sodium acetate VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner.

Each mL of 0.1 mol/L perchloric acid VS
= 10.533 mg of $C_6H_{14}N_4O_2 \cdot HCl$

Packaging and storage Preserve in tight containers.

Arginine Thiazolidine Carboxylate
아르기닌티아졸리딘카르복실산염



$C_{10}H_{21}N_5O_4S$: 307.37
L-Arginine (*R*)-4-thiazolidinecarboxylic acid (1:1), [*97358-56-0*]

Arginine Thiazolidine Carboxylate, when dried, contains NLT 95.0% of arginine thiazolidine carboxylate ($C_{10}H_{21}N_5O_4S$) and NLT 9.89% and NMT 10.94% of sulfur (S: 32.07).

Description Arginine Thiazolidine Carboxylate occurs as a white powder.

Identification Weigh 0.4 g of Arginine Thiazolidine Carboxylate, add water to make 200 mL, filter, and use this solution as the test solution. Dissolve 80 mg of thiazolidinedicarboxylic acid RS and 0.1 g of arginine RS in water to make 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol, chloroform, water and 27% ammonia (40 : 40 : 10 : 10) as the developing solvent to a distance of

about 10 cm, and air-dry the plate. Spray a mixture of a solution prepared by dissolving 300 mg of ninhydrin, 10 mL of acetic acid(100) and 2 mL of collidine in 100 mL of 50% isopropanol aqueous solution, as the coloring agent (should be prepared immediately before use), in this order, as well as 3 mL of 1% copper nitrate-ethanol solution; the R_f value and color of spots obtained from the test solution and the standard solution are the same.

Melting point Between 175 and 185 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 20 g of Arginine Thiazolidine Carboxylate in water to make 100 mL; the solution is clear and colorless.

(2) ***Formaldehyde***—Weigh accurately about 0.1 g of Arginine Thiazolidine Carboxylate, dissolve in 5 mL of water, add 5 mg of chromotropic acid and 5 mL of sulfuric acid. Use this solution as the test solution. Separately, take 20 μg of formaldehyde, proceed in the same manner as the test solution, and use it as the control solution. Compare the color of the test solution and the control solution; the test solution is not more intense than that of the control solution. If needed, perform the test with the test solution and the standard solution under the Ultraviolet-visible Spectroscopy, determine the absorbances at 570 nm, and compare the results (NMT 0.02%).

(3) ***Free thiazolidinedicarboxylic acid***—Weigh accurately 2.0 g of Arginine Thiazolidine Carboxylate, suspend in 100 mL of dimethylformamide, shake well to mix. Again, shake to mix on a steam bath for 10 to 15 minutes and allow to stand for a while. Filter with the G3 glass filter and wash with 30 mL of dimethylformamide several times. To the filtrate, add 50 mL of water and 0.5 mL of phenolphthalein TS, then titrate with 0.1 mol/L sodium hydroxide solution VS. Separately, take 100 mL of dimethylformamide as the blank test solution and proceed with it in the same manner as the test solution to perform the test. Obtain the amount of free thiazolidinedicarboxylic acid (NMT 3.0%).

Each mL of 0.1 mol/L sodium hydroxide
= 13.318 mg of $C_{10}H_{21}N_5O_4S$

pH Between 7.0 and 8.0 (20% aqueous solution).

Loss on drying NMT 1.0% (1.0 g, 40 °C, in vacuum).

Residue on ignition NMT 0.1% (5.0 g).

Assay (1) ***Arginine thiazolidine carboxylate***—Weigh exactly about 0.15 g of Arginine Thiazolidine Carboxylate, previously dried, dissolve in 40 mL of a mixture acetic anhydride and acetic acid(100) for non-aqueous titration (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of methyl violet red TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid
= 10.240 mg of $C_{10}H_{21}N_5O_4S$

(2) ***Sulfur***—Weigh accurately about 0.15 g of Arginine Thiazolidine Carboxylate, previously dried, and perform the test as directed under the Oxygen Flask Combustion with a mixture of 0.1 mL of hydrogen peroxide and 10 mL of water as the absorbent.

Each mL of 0.005 mol/L barium perchlorate VS
= 0.16033 mg of S

Packaging and storage Preserve in tight containers.

Arginine Thiazolidine Carboxylate capsules
아르기닌티아졸리딘카르복실산염 캡슐

Arginine Thiazolidine Carboxylate Tablets contain NLT 95.0% and NMT 105.0% of arginine thiazolidine carboxylate ($C_{10}H_{21}N_5O_4S$: 307.37) of the labeled amount.

Method of preparation Prepare as directed under Capsules, with Arginine Thiazolidine Carboxylate.

Identification Weigh an amount equivalent to 0.4 g of arginine thiazolidine carboxylate according to the labeled amount of Arginine Thiazolidine Carboxylate Capsules, add water to make exactly 200 mL, filter, and use the filtrate as the test solution. Separately, dissolve about 80 mg of thiazolidine carboxylic acid RS and about 0.1 g of arginine RS in water to make 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of methanol, chloroform, water and ammonia water(28) (4 : 4 : 1 : 1), and air-dry the plate. Spray on the plate a mixture of a solution prepared by dissolving 0.3 g of ninhydrin, 10 mL of acetic acid(100) and 2 mL of collidine in 100 mL of 50% isopropanol aqueous solution, as the coloring agent (should be prepared immediately before use), in this order, as well as 3 mL of 1% copper nitrate-ethanol solution; the R_f value and color of spots obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

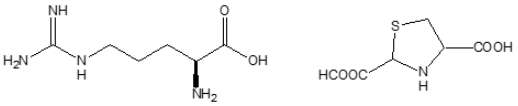
Assay Weigh accurately the mass of the contents of NLT 20 capsules of Arginine Thiazolidine Carboxylate Capsules. Weigh accurately an amount equivalent to about 0.8 g of arginine thiazolidine carboxylate ($C_{10}H_{21}N_5O_4S$), add acetic acid(100), shake well to mix and make exactly 50 mL, and filter the mixture. Pipet 10 mL of the filtrate

and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of methylrosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 10.24 mg of $C_{10}H_{21}N_5O_4S$

Packaging and storage Preserve in tight containers.

Arginine Tidiacicate
아르기닌티디아시케이트



$C_{11}H_{21}O_6N_5S$: 351.38
L-Arginine 1,3-thiazolane-2,4-dicarboxylic acid (1:1), [*30097-06-4*]

Arginine Tidiacicate, when dried, contains NLT 98.5 of argininetidiacicate ($C_{11}H_{21}O_6N_5S$).

Description Arginine Tidiacicate occurs as a white to pale yellow powder.
It is soluble in water, acid and alkali, sparingly soluble in ethanol, and practically insoluble in ether and chloroform

Melting point About 185 °C (with decomposition).

Optical rotation $[a]_D^{20}$: Between -33.0° and -37.5° (after drying, 1 g, 6 mol/L hydrochloric acid, 20 mL, 200 mm).

Identification (1) Put 1 mg of Arginine Tidiacicate in the test tube, add 10 drops of water and 1 mL of 0.02% naphthol ethanol solution (should be prepared immediately before use), then shake to mix well. Next, add 1 mL of 20% sodium hydroxide solution, 20 mg of *N*-bromosuccinimide and 3 mL of water, then shake to mix well. The resulting solution immediately turns orange.

(2) Dissolve 0.2 g of Arginine Tidiacicate in 10 mL of water, and use this solution as the test solution. Separately, dissolve 0.2 g of arginine tidiacicate RS in 10 mL of water and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of *n*-propanol and 20% ammonium hydroxide solution as the developing solvent, and air-dry the plate. Spray a solution obtained by adding 5 mL of 10% acetic acid and ethanol(95) to 0.1 g of ninhydrin to make 50 mL; the R_f value and color of spots obtained from the test solution and the standard solution are the same.

(3) Determine the absorption spectrum of 0.2% aqueous solution of Arginine Tidiacicate as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum absorption at the wavenumbers of between 245 and 250 nm.

pH Between 3.5 and 4.6 (5% aqueous solution).

Purity (1) ***Sulfate***—Dissolve 1 g of Arginine Tidiacicate in hot water, cool it, and then perform the test according to the Sulfate limit test; the resulting solution is not more turbid than the control solution. Add 1 mL of 0.005 mol/L sulfuric acid to the control solution (NMT 0.048%).

(2) ***Arsenic***—Proceed with 1 g of Arginine Tidiacicate according to Method 1 and perform the test (NMT 2 ppm).

(3) ***Heavy metals***—Proceed with 1 g of Arginine Tidiacicate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Loss on drying NMT 0.5% (1.0 g, 80 °C, in vacuum, constant mass).

Residue on ignition NMT 0.1% (1.0 g).

Assay Weigh accurately about 30 mg of Arginine Tidiacicate, and titrate according to the Sulfur assay under the Oxygen Flask Combustion with a mixture of 20 mL of water and 5 drops of hydrogen peroxide as an absorbent. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.005 mol/L barium perchlorate VS
= 1.757 mg of $C_{11}H_{21}O_6N_6S$

Packaging and storage Preserve in tight containers.

Arginine Tidiacicate Capsules
아르기닌티디아시케이트 캡슐

Arginine Tidiacicate Capsules contain NLT 95.0% and NMT 105.0% of arginine tidiacicate ($C_{11}H_{21}O_6N_5S$: 351.38) of the labeled amount.

Method of preparation Prepare as directed under Capsules, with Arginine Tidiacicate.

Identification Weigh an amount of Arginine Tidiacicate Capsules, equivalent to 40 mg of arginine tidiacicate, according to the labeled amount. Wash with about 15 mL of ethyl acetate, transfer quantitatively to a glass-stoppered centrifuge tube, add 20 mL of water, shake vigorously for 10 minutes to extract., and centrifuge for 10 minutes at NLT 3,500 rpm. Collect the water layer, and use this solution as the test solution. Separately, dissolve 20 mg of arginine tidiacicate RS in 10 mL of water,

and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of cellulose with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of phenol, water and ammonia water (75 : 23 : 2) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light; the R_f values and colors of the spots from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the content NLT 20 Arginine Tidiacicate Capsules, and then weigh accurately the amount equivalent to about 40 mg of arginine tidiacicate. Wash with about 20 mL of ethyl ether, transfer quantitatively, add exactly 20 mL of water, and shake vigorously for 10 minutes to extract. Centrifuge at NLT 3,500 rpm for 10 minutes. Collect the water layer, and use this solution as the test solution. Separately, weigh accurately about 40 mg of arginine tidiacicate RS, dissolve in water to make exactly 20 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy using water as a control solution and determine the absorbances, A_T and A_S, at the wavelength of 245 nm.

Amount (mg) of arginine tidiacicate ($C_{11}H_{21}O_6N_5S$)
= Amount (mg) of arginine tidiacicate RS × (A_T / A_S)

Packaging and storage Preserve in well-closed containers.

Arginine Tidiacicate, Thiamine Hydrochloride, Riboflavin and Ascorbic Acid capsules
아르기닌티디아시케이트·티아민염산염·리보플라빈·아스코르브산 캡슐

Arginine Tidiacicate, Thiamine Hydrochloride, Riboflavin and Ascorbic Acid Capsules contain 90.0% to 110.0% of the labeled amount of arginine tidiacicate ($C_{11}H_{21}O_6N_5S$: 351.38) and 90.0% to 150.0% of the labeled amount of thiamine hydrochloride ($C_{12}H_{17}ClN_4OS \cdot HCl$: 337.27), riboflavin ($C_{17}H_{20}N_4O_6$: 376.37) and ascorbic acid ($C_6H_8O_6$: 176.12).

Method of preparation Prepare as directed under Capsules, with Arginine Tidiacicate, Thiamine Hydrochloride, Riboflavin and Ascorbic Acid.

Identification (1) ***Arginine Tidiacicate***—Weigh accurately an amount of Arginine Tidiacicate, Thiamine Hydrochloride, Riboflavin and Ascorbic Acid Capsules, equivalent to 40 mg of arginine tidiacicate, according to the labeled amount. Wash with about 15 mL of chloroform, transfer quantitatively to a glass-stoppered centrifuge tube, add 20.0 mL of water, and shake vigorously for 10 minutes to extract. Then centrifuge at NLT 3,500 rpm for 10 minutes, collect the water layer, and use this solution as the test solution. Separately, dissolve 20 mg of arginine tidiacicate RS in 10 mL of water, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of cellulose with fluorescent indicator for thin-layer chromatography. Then, develop the plate with a mixture of phenol, water and ammonia water (75 : 23 : 2) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light; the R_f values and colors of the spots from the test solution and the standard solution are the same.

(2) ***Thiamine Hydrochloride, Riboflavin and Ascorbic Acid***—Perform the test with the content of Arginine Tidiacicate, Thiamine Hydrochloride, Riboflavin and Ascorbic Acid Capsules as directed under the Analysis for Vitamins.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Arginine Tidiacicate***—Weigh accurately the mass of the content of NLT 20 Arginine Tidiacicate, Thiamine Hydrochloride, Riboflavin and Ascorbic Acid Capsules, and weigh accurately the amount equivalent to about 40 mg of arginine tidiacicate. Wash with about 15 mL of chloroform, transfer quantitatively to a glass-stoppered centrifuge tube, add 20.0 mL of water, and shake vigorously for 10 minutes to extract. Centrifuge at NLT 3,500 rpm for 10 minutes. Collect the water layer, and use this solution as the test solution. Separately, weigh accurately about 40 mg of arginine tidiacicate RS, dissolve in water to make 20 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy using water as a control solution and determine the absorbances, A_T and A_S, at the wavelength of 245 nm.

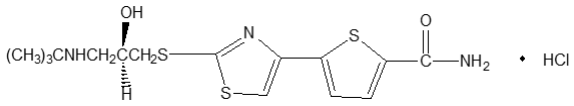
Amount (mg) of arginine tidiacicate ($C_{11}H_{21}O_6N_5S$)
= Amount (mg) of arginine tidiacicate RS × $\frac{A_T}{A_S}$

(2) ***Thiamine Hydrochloride, Riboflavin and Ascorbic Acid Capsules***—Weigh accurately the mass of the content of NLT 20 Arginine Tidiacicate, Thiamine Hydrochloride, Riboflavin and Ascorbic Acid Capsules, and perform the test as directed under the Analysis for

Vitamins.

Packaging and storage Preserve in tight containers.

Arotinolol Hydrochloride
아로티놀롤염산염



and enantiomer

$C_{15}H_{21}N_3O_2S_3 \cdot HCl$: 408.00

5-[2-[3-(*tert*-Butylamino)-2-hydroxypropyl] sulfanyl-1,3-thiazol-4-yl]thiophene-2-carboxamide hydrochloride [*68377-91-3*]

Arotinolol Hydrochloride, when dried, contains NLT 99.0% and NMT 101.0% of arotinolol hydrochloride ($C_{15}H_{21}N_3O_2S_3 \cdot HCl$).

Description Arotinolol Hydrochloride occurs as a white or pale yellow crystalline powder.
It is freely soluble in dimethylsulfoxide, slightly soluble in water or methanol, very slightly soluble in ethanol(99.5) and practically insoluble in ether.
A solution of Arotinolol Hydrochloride in methanol (1 in 125) shows no optical rotation.

Identification (1) Determine the absorption spectra of Arotinolol Hydrochloride and Arotinolol hydrochloride RS in methanol (1 in 75000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectrum of Arotinolol Hydrochloride and Arotinolol hydrochloride RS as directed in the potassium bromide disk method under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Arotinolol Hydrochloride (1 in 200) responds to the Qualitative Analysis (2) for chloride.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Arotinolol Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) **Related substances**—Dissolve 50 mg of Arotinolol Hydrochloride in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution and add methanol to make exactly 100 mL. Pipet 1 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 40 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform, methanol, acetone and ammonia water(28) (30 : 10 : 10 : 1) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.2% (1 g, in vacuum, 105 °C, 4 hours).

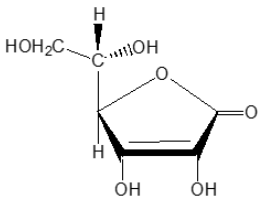
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 1.5 g of Arotinolol Hydrochloride, previously dried, and dissolve in dimethylsulfoxide to make exactly 25 mL. Pipet 5 mL of this solution, add 100 mL of water and 5 mL of sodium hydroxide TS, and extract with 50 mL of dichloromethane three times. Filter the dichloromethane extract solution through a funnel where anhydrous sodium is placed on cotton wool every time. Combine all the dichloromethane extract solution and evaporate to dryness under reduced pressure. Dissolve the residue in 70 mL of acetic acid(100) and titrate with 0.05 mol/L of perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L perchloric acid VS
= 20.400 mg of $C_{15}H_{21}N_3O_2S_3 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Ascorbic Acid
아스코르브산



Vitamin C $C_6H_8O_6$: 176.12

(5*R*)-5-[(1*S*)-1,2-Dihydroxyethyl]-3,4-dihydroxy-2,5-dihydrofuran-2-one [*50-81-7*]

Ascorbic Acid, when dried, contains NLT 99.0% and NMT 101.0% of L-ascorbic acid ($C_6H_8O_6$).

Description Ascorbic Acid occurs as white crystals or a crystalline powder. It is odorless and has a sour taste.
It is freely soluble in water, sparingly soluble in ethanol(95), and practically insoluble in ether.

Melting point—About 190 °C (with decomposition).

Identification (1) Take 5 mL each of the aqueous solution of Ascorbic Acid (1 in 50), and add 1 drop of potassium permanganate TS or 1 to 2 drops of 2,6-dichlorophenolindophenol sodium TS; the color of all test solutions disappears immediately.

(2) Dissolve 0.1 g of Ascorbic Acid in 100 mL of metaphosphoric acid solution (1 in 50). Take 5 mL of this solution, add iodine TS until the solution exhibits a slightly yellow color, add 1 drop of copper sulfate solution (1 in 1000) and 1 drop of pyrrole, and warm at 50 ℃ for 5 minutes; the resulting solution exhibits a blue color.

Optical rotation $[\alpha]_D^{20}$: Between +20.5 and +21.5° (2.5 g, water, 25 mL, 100 mm).

pH Dissolve 1.0 g of Ascorbic Acid in 20 mL of water; the pH of this solution is between 2.2 and 2.5

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Ascorbic Acid in 20 mL of water; the solution is clear and colorless.

(2) ***Heavy metals*—**Weigh 2.0 g of Ascorbic Acid, and add water to make 20 mL. Take 12 mL of this solution, and use this solution as the test solution. Separately, add 2 mL of the test solution to 10 mL of diluted lead standard solution, and use this solution as the control solution. Separately, add 2 mL of the test solution to 10 mL of water, and use this solution as the blank test solution. To 12 mL each of the test solution, the control solution and the blank test solution, add 2 mL of acetate buffer solution (pH 3.5), mix, put 1.2 mL of thioacetamide TS, and mix immediately. Allow it to stand for 2 minutes; the color of the test solution is not more intense than that of the control solution (NMT 10 ppm).

Diluted lead standard solution—Immediately before use, pipet 5 mL of the lead standard solution, and add water to make 50 mL.

System suitability—The control solution exhibits a faint brown color compared to the blank test solution.

(3) ***Copper*—**Weigh 2.0 g of Ascorbic Acid, dissolve in 2 mL of 0.1 mol/L nitric acid, and add 25.0 mL of 0.1 mol/L nitric acid to dilute. Take an appropriate amount of the copper standard solution, dilute with 0.1 mol/L nitric acid, make 0.2, 0.4, and 0.6 ppm, and use these solutions as the standard solution (1), standard solution (2), and standard solution (3). Perform the test with the test solution, the standard solution (1), the standard solution (2), and the standard solution (3) as directed under the Atomic Absorption Spectroscopy, according to the following conditions, and calculate the content of copper in the test solution, using the calibration curve obtained from the standard solution (NMT 5 ppm). Use 0.1 mol/L nitric acid as the blank test solution.

Gas: Air–acetylene
Lamp: Copper hollow cathode lamp
Wavelength: 324.8 nm

Loss on drying NMT 0.2% (1 g, silica gel, 24 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Ascorbic Acid, previously dried, dissolve in 50 mL of metaphosphoric acid solution (1 in 50), and titrate with 0.05 mol/L iodine VS (indicator: 1 mL of starch TS).

Each mL of 0.05 mol/L iodine VS
= 8.806 mg of $C_6H_8O_6$

Packaging and storage Preserve in light-resistant, tight containers.

Ascorbic Acid Injection
아스코르브산 주사액

Vitamin C Injection

Ascorbic Acid Injection is an aqueous solution for injection. Ascorbic Acid Injection contains NLT 95.0% and NMT 115.0% of the labeled amount of ascorbic acid ($C_6H_8O_6$: 176.12).

Method of preparation Prepare as directed under Injections, with Ascorbic Acid.

Description Ascorbic Acid Injection occurs as a clear, colorless liquid.

Identification (1) Take an amount of Ascorbic Acid Injection, equivalent to 0.5 g of ascorbic acid according to the labeled amount, add water to make 25 mL, and perform the test with each 5 mL of the solution as directed under the Identification (1) under Ascorbic Acid.

(2) Take an amount of Ascorbic Acid Injection, equivalent to 5 mg of ascorbic acid according to the labeled amount, add metaphosphoric acid (1 in 50) to make 5 mL, and perform the test with this solution as directed under the Identification (2) under Ascorbic Acid.

(3) Ascorbic Acid Injection responds to the Qualitative Analysis (1) for sodium salt.

pH Between 5.6 and 7.4.

Purity ***Oxalate*—**Take an amount of Ascorbic Acid Injection, equivalent to 50 mg of ascorbic acid, and add water to make 5 mL. Add 0.2 mL of acetic acid(31) and 0.5 mL of calcium chloride TS and allow to stand for 1 minute; it exhibits no turbidity.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.15 EU per mg of

ascorbic acid.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Ascorbic Acid Injection, equivalent to about 0.1 g of L-ascorbic acid ($C_6H_8O_6$), previously diluted with a mixture of metaphosphoric acid and acetic acid TS, if necessary, and add a mixture of metaphosphoric acid and acetic acid TS to make exactly 200 mL. Pipet 2 mL of this solution and proceed as directed under the Assay under Ascorbic Acid Powder.

Each mL of 2,6-dichloroindophenol sodium TS for titration
= A mg of $C_6H_8O_6$

Packaging and storage Preserve in hermetic containers filled with nitrogen.

Ascorbic Acid Powder
아스코르브산 산

Vitamin C Powder

Ascorbic Acid Powder contains NLT 95.0% and NMT 120.0% of the amount of L-ascorbic acid ($C_6H_8O_6$: 176.12).

Method of preparation Prepare as directed under Powders, with Ascorbic Acid Powder.

Identification (1) Weigh an amount equivalent to 0.5 g of ascorbic acid according to the labeled amount of Ascorbic Acid Powder, add 30 mL of water, shake to mix for 1 minute, and filter. Take 5 mL each of filtrate, and perform the test as directed under the Identification (1) of Ascorbic Acid Powder.

(2) Weigh an amount equivalent to 10 mg of amount of Ascorbic Acid Powder, add 10 mL of metaphosphoric acid solution (1 in 50), shake for 1 minute to mix, and filter. Perform the test with 5 mL of filtrate as directed under the Identification (2) of Ascorbic Acid Powder.

Purity ***Rancidity***—Ascorbic Acid Powder has no unpleasant or rancid odor and taste.

Particle size distribution estimation by analytical sieving Meets the requirements.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Weigh accurately an amount equivalent to about 0.1 g of L-ascorbic acid ($C_6H_8O_6$) of Ascorbic Acid Powder, repeat the extraction with metaphosphoric acid-acetic acid TS, combine all the extracts, and filter. Wash with metaphosphoric acid-acetic acid TS, combine filtrate and washings, and add metaphosphoric acid-acetic acid TS again to make exactly 200 mL. Pipet 2 mL of this solution, add 8 mL of metaphosphoric acid-acetic acid TS and 2 mL of hydrogen peroxide TS, shake to mix, and titrate with 2,6-dichlorophenolindophenol sodium TS until a pale red color persists for 5 seconds. Perform a blank test in the same manner and make any necessary correction.

Each mL of 2,6-dichloroindophenol sodium TS for titration
= A mg of $C_6H_8O_6$

However, A is decided by the following standardization of 2,6-dichlorophenolindophenol sodium TS.

2,6-dichlorophenolindophenol sodium TS— Preparation: Dissolve 42 mg of sodium bicarbonate in 50 mL of water, dissolve 50 mg of 2,6-dichlorophenolindophenol sodium, add water to make 200 mL, and filter. This preparation is prepared before use.

Standardization—Weigh accurately about 50 mg of ascorbic acid RS, previously dried in a desiccator (silica gel) for 24 hours, dissolve by adding metaphosphoric acid-acetic acid TS to make 100 mL, pipet 2 mL of this solution, and add 8 mL of metaphosphoric acid-acetic acid TS and 2 mL of hydrogen peroxide TS. Shake to mix, and titrate with 2,6-dichlorophenolindophenol sodium TS for titration until a pale red color persists for 5 seconds. Perform a blank test in the same manner, make any necessary correction, and calculate A mg, the amount of L-Ascorbic acid ($C_6H_8O_6$) equivalent to 1 mL of this test solution.

Packaging and storage Preserve in tight containers.

Ascorbic Acid Tablets
아스코르브산 정

Vitamin C Tablets

Ascorbic Acid Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of L-ascorbic acid ($C_6H_8O_6$: 176.12).

Method of preparation Prepare Ascorbic Acid Tablets as directed under Tablets, with Ascorbic Acid.

Identification (1) Weigh an amount of Ascorbic Acid Tablets, previously powdered, equivalent to 0.5 g of ascorbic acid, according to the labeled amount, add 30 mL of water, shake to mix for 1 minute, and filter. Take 5

mL each of the filtrate, and perform the test as directed under the Identification (1) of Ascorbic Acid.

(2) Take 2 mL of the filtrate obtained from (1), add sodium hydroxide TS to make it neutral, and add 2 drops of uranyl acetate TS; the resulting solution exhibits reddish-brown. Add additional 2 mL of sodium hydroxide TS; the color of the solution turns yellow.

(3) Weigh an amount of Ascorbic Acid Tablets, previously powdered, equivalent to 10 mg of ascorbic acid, according to the labeled amount, add 10 mL of metaphosphoric acid (1 in 50), shake for 1 minute to mix, and filter. Perform the test with 5 mL of the filtrate as directed under the Identification (2) of Ascorbic Acid.

Dissolution Perform the test with 1 tablet of Ascorbic Acid Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take NLT 20 mL of the dissolution medium 45 minutes immediately after the start the Dissolution, and filter through a membrane filter with a pore size of not exceeding 0.8 μm. Take the filtrate and quantify it according to the Assay.

It meets the requirements if the dissolution rate of Ascorbic Acid Tablets in 45 minutes is NLT 75%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Ascorbic Acid Tablets, and powder. Weigh accurately an amount, equivalent to about 0.1 g of L-ascorbic acid ($C_6H_8O_6$), and perform the test as directed under the Assay of Ascorbic Acid.

Packaging and storage Preserve in light-resistant, tight containers.

Ascorbic Acid and Calcium Pantothenate Tablets
아스코르브산·판토텐산칼슘 정

Ascorbic Acid Tablets

Ascorbic Acid and Calcium Pantothenate Tablets contain NLT 90.0% and NMT 150.0% of the labeled amount of ascorbic acid ($C_6H_8O_6$: 176.12) and calcium pantothenate ($C_{18}H_{32}CaN_2O_{10}$: 476.53).

Method of preparation Prepare Ascorbic Acid and Calcium Pantothenate Tablets as directed under Tablets, with Ascorbic Acid and Calcium Pantothenate.

Identification Ascorbic Acid and Calcium Pantothenate Perform the test with Ascorbic Acid and Calcium Pantothenate Tablets as directed under the Analysis for Vitamins.

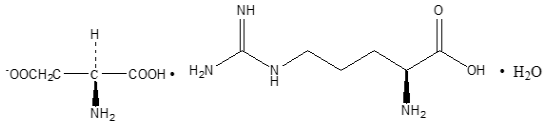
Disintegration Meets the requirements.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Ascorbic Acid and Calcium Pantothenate Weigh accurately the mass of NLT 20 tablets of Ascorbic Acid and Calcium Pantothenate Tablets, and perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in well-closed containers.

L-Aspartate-L-Arginine Hydrate
L-아스파르트산-L-아르기닌수화물



$C_{10}H_{21}N_5O_6 \cdot H_2O$: 325.32

L-Aspartic acid with L-arginine monohydrate (1:1), [*7675-83-4*, anhydrous]

L-Aspartate-L-Arginine Hydrate contains NLT 98.5% and NMT 101.0% of L-arginine-L-aspartate ($C_{10}H_{21}N_5O_6$: 307.30), calculated on the anhydrous basis.

Description L-Aspartate-L-Arginine Hydrate occurs as a white crystalline powder and is absorptive.
It is odorless or has a slightly characteristic odor.
It is freely soluble in water, soluble in hydrochloric acid TS or sodium hydroxide TS, and insoluble in ethanol(95).
The pH of a 10% aqueous solution of L-Aspartate-L-Arginine Hydrate is about 7.

Melting point—Between 225 and 229 ℃ (with decomposition).

Optical rotation $[\alpha]_D^{20}$: Between +25.4° and +27.4° (4 g after drying, 100 mL of 6 mol/L hydrochloric acid, 100 mm).

Identification (1) To 10 mL of a 0.2% aqueous solution of L-Aspartate-L-Arginine Hydrate, add 1 mL of 0.4% ninhydrin-acetone solution, and heat on a steam bath; the resulting solution exhibits a violet color.

(2) Perform the test with L-Aspartate-L-Arginine Hydrate as directed under the Identification and Assay for Amino Acids.

Purity (1) ***Arsenic*—**Proceed with 1.0 g of L-Aspartate-L-Arginine Hydrate according to Method 2 under the Arsenic and perform the test (NMT 2 ppm).

(2) ***Lead*—**Perform the test with 1.0 g of L-Aspartate-L-Arginine Hydrate as directed under the Lead in United States Pharmacopeia (USP) (NMT 20 ppm).

(3) ***Sulfate*—**Perform the test with 1.0 g of L-Aspartate-L-Arginine Hydrate as directed under the Sulfate. Prepare the control solution with 0.1 mL of 0.005

mol/L sulfuric acid (NMT 0.005%).

(4) ***Chloride***—Perform the test with 1.0 g of L-Aspartate-L-Arginine Hydrate as directed under the Chloride. Prepare the control solution with 0.14 mL of 0.01 mol/L hydrochloric acid (NMT 0.05%).

(5) ***Ammonium***—Perform the test with 0.1 g of L-Aspartate-L-Arginine Hydrate as directed under the Ammonium. Prepare the control solution with 2.0 mL of ammonium standard solution (NMT 20 ppm).

(6) ***Iron***—Prepare the test solution with 2.0 g of L-Aspartate-L-Arginine Hydrate according to Method 1 and perform the test according to Method A. Prepare the control solution with 2.0 mL of iron standard solution (NMT 10 ppm).

(7) ***Other amino acids***—Perform the test with L-Aspartate-L-Arginine Hydrate as directed under the Paper Chromatography; the obtained number of spots is the same as the number of spots in the standard solution with no other spots appearing.

Loss on drying NMT 5.5% (1 g, 105 ℃, constant mass).

Assay Weigh accurately about 0.1 g of L-Aspartate-L-Arginine Hydrate, previously dried, dissolve in 20 mL of acetic acid(100) for non-aqueous titration, and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 to 3 drops of methylrosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 10.24 mg of $C_{10}H_{21}N_5O_6$

Packaging and storage Preserve in tight containers.

L-Aspartate-L-Arginine Solution
L-아스파르트산-L-아르기닌 액

L-Aspartate-L-Arginine Solution contains NLT 90.0% and NMT 130.0% of the labeled amount of L-aspartate-L-arginine hydrate ($C_{10}H_{21}N_5O_6 \cdot H_2O$: 325.32).

Method of preparation Prepare as directed under Liquids, with L-Aspartate-L-Arginine Hydrate.

Identification Pipet 1 mL of L-Aspartate-L-Arginine Solution, add water to make 100 mL, and use this solution as the test solution. Separately, dissolve about 0.1 g of L-arginine-L-aspartate RS and dissolve in water to make 50 mL. Use this solution as the standard solution. Spot 5 μL each of the test solution and the standard solution on the plate made of silica gel for thin-layer chromatography. Develop the plate with a saturated vapor of a mixture of n-propyl alcohol and 27% ammonia (64 : 36) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Evenly spray the plate with ninhydrin TS and heat for 5 minutes at 100 ℃; the two spots from the test solution and the standard solution have the same R_f value and same color (R_f value 0.55 : aspartate, R_f value 0.4 : arginine).

pH Between 5.5 and 7.5.

Assay Pipet an amount of L-Aspartate-L-Arginine Solution equivalent to 0.2 g of L-arginine-L-aspartate ($C_{10}H_2N_5O_6$), elute by passing through a Sep-pak C_{18} previously treated by passing 5 mL of methanol and 5 mL of water, add 10 mL of water and elute again. Combine the eluate, add 30 mL of the mobile phase, and add water to make 50.0 mL. Pipet 5.0 mL of L-Aspartate-L-Arginine Solution and add water to make 25.0 mL. Use this solution as the test solution. Separately, weigh accurately about 0.2 g of L-arginine-L-aspartate RS (Dried at 105 ℃ for 4 hours), dissolve in 30 mL of the mobile phase, and add water to make 50.0 mL. Pipet 5.0 mL of this solution, add water to make 25.0 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of L-arginine-L-aspartate.

Amount (mg) of L-arginine-L-aspartate ($C_{10}H_2N_5O_6$)
= Amount (mg) of L-arginine-L-aspartate RS $\times \frac{A_T}{A_S}$

A_T: Sum of peak areas of L-arginine-L-aspartate in the test solution

A_S: Sum of peak areas of L-arginine-L-aspartate in the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 200 nm).

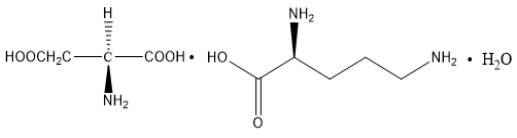
Column: A stainless steel column about 4.6 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: 0.02 mol/L potassium dihydrogen phosphate solution.

Flow rate: 1 mL/min

Packaging and storage Preserve in tight containers.

L-Aspartate-L-Ornithine Hydrate
L-아스파르트산-L-오르니틴수화물



$C_5H_{12}N_2O_2 \cdot C_4H_6NO_4 \cdot H_2O$: 283.28

L-Aspartate with L-ornithine hydrate (1:1), [*3230-94-2*, anhydrous]

L-Aspartate-L-Ornithine Hydrate contains NLT 98.0% and NMT 101.0% of L-ornithine-L-aspartate ($C_9H_{19}N_3O_6$: 265.26), calculated on the anhydrous basis.

Description L-Aspartate-L-Ornithine Hydrate occurs as a white powder. It is odorless or has a slightly characteristic odor.
It is very soluble in water and practically insoluble in methanol or ethanol(95).
The pH of an aqueous solution (1 in 20) of L-Aspartate-L-Ornithine Hydrate is about 6.

Identification To 0.1 g each of L-Aspartate-L-Ornithine Hydrate and L-ornithine-L-aspartate RS, dissolve respective 10 mL of water, use these solutions as the test solution and the standard solution and perform the test as directed under the Paper Chromatography. Spot 5 μL each of the test solution and the standard solution on the paper for chromatography, develop the paper with a mixture of phenol and dilute ammonia TS (3 in 10) (4 : 1) as the developing solvent to a distance of about 20 cm, and air-dry the paper. Spray evenly a solution of ninhydrin in acetone (2 in 100) on the paper, and dry the paper at 90 ℃ for 10 minutes; the spots obtained from the test solution are the same as the spots obtained from the standard solution.

Optical rotation $[\alpha]_D^{20}$: Between +25.0° and +28.0° (2.0 g, calculated on the anhydrous basis, 6 mol/L hydrochloric acid, 25 mL, 200 mm).

Purity (1) ***Clarity and color of solution***—To 0.10 g of L-Aspartate-L-Ornithine Hydrate, dissolve in 10 mL of water; the resulting solution is colorless and practically clear.

(2) ***Chloride***—Perform the test with 0.4 g of L-Aspartate-L-Ornithine Hydrate as directed under the Chloride. Prepare the control solution with 0.7 mL of 0.01 mol/L hydrochloric acid (NMT 0.06%).

(3) ***Sulfate***—Perform the test with 0.5 g of L-Arginine-L-Aspartate-L-Ornithine Hydrate as directed under the Sulfate. Prepare the control solution with 0.5 mL of 0.005 mol/L sulfuric acid (NMT 0.048%).

(4) ***Ammonium***—Perform the test with 0.01 g of L-Aspartate-L-Ornithine Hydrate as directed under the Ammonium. Prepare the control solution with 2.0 mL of ammonium standard solution placed in a flask and proceed in the same manner (NMT 0.05%).

(5) ***Heavy metals***—Proceed with 1.0 g of L-Aspartate-L-Ornithine Hydrate as directed under Method 1 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(6) ***Arsenic***—Proceed with 1.0 g of L-Aspartate-L-Ornithine Hydrate according to Method 2 under the Arsenic and perform the test (NMT 2 ppm).

Water Between 4.0% and 7.0% (0.5 g, water determination, volumetric titration, direct titration).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.2 g of L-Aspartate-L-Ornithine Hydrate, and dissolve in 0.5 mL of water. Add 100 mL of acetic acid(100), shake well to mix, and titrate with 0.1 mol/L perchloric acid VS (indicator: 10 drops of α-naphtholbenzein TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 8.842 mg of $C_5H_{12}N_2O_2 \cdot C_4H_6NO_4$

Packaging and storage Preserve in tight containers.

L-Aspartate-L-Ornithine Injection
L-아스파르트산-L-오르니틴 주사액

L-Aspartate-L-Ornithine Injection contains NLT 90.0% and NMT 130.0% of the labeled amount of L-aspartate-L-ornithine hydrate ($C_9H_{19}N_3O_6 \cdot H_2O$: 283.28).

Method of preparation Prepare as directed under Injections, with L-Aspartate-L-Ornithine Hydrate.

Identification Perform the test with L-Aspartate-L-Ornithine Injection as directed under the Identification and Assay for Amino Acids.

pH Between 5.0 and 7.0.

Assay Pipet an amount of L-Aspartate-L-Ornithine Injection equivalent to 0.1 g of L-ornithine-L-aspartate and perform the test as directed under the Identification and Assay for Amino Acids.

Sterility Meets the requirements.

Bacterial endotoxins Less than 7.5 EU per g of L-ornithine-L-aspartate.

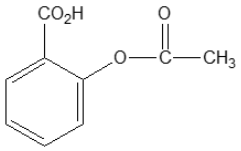
Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Packaging and storage Preserve in hermetic containers.

Aspirin
아스피린



Acetylsalicylic Acid $C_9H_8O_4$: 180.16
2-Acetyloxybenzoic acid [*50-78-2*]

Aspirin, when dried, contains NLT 99.5% and NMT 101.0% of aspirin ($C_9H_8O_4$).

Description Aspirin occurs as a white crystal, grain or a powder. It is odorless and has a slight acidic taste.
It is freely soluble in ethanol(95) or acetone, soluble in ether, and slightly soluble in water.
It dissolves in sodium hydroxide TS or sodium carbonate TS.
It gradually hydrolyzes in moist air to salicylic acid and acetic acid.

Melting point—About 136 °C (bath fluid is heated at 130 °C previously).

Identification (1) Put 0.1 g of Aspirin in 5 mL of water, boil for 5 to 6 minutes, cool, and add 1 to 2 drops of iron(III) chloride TS; the resulting solution exhibits a purple color.

(2) Put 10 mL of sodium carbonate TS in 0.5 g of Aspirin in, boil for 5 minutes, and add 10 mL of dilute sulfuric acid; the odor of acetic acid is perceptible, and a white precipitate is produced. Filter this solution, discard the precipitate, add 3 mL of ethanol(95) and 3 mL of sulfuric acid to the filtrate, and heat; the odor of ethyl acetate is perceptible.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Aspirin in 10 mL of warm sodium carbonate TS; the solution is clear.

(2) ***Salicylic acid***—Dissolve 2.5 g of Aspirin in ethanol(95) to make 25 mL, add 1.0 mL of this solution to a solution prepared by transferring 1 mL of a freshly prepared dilute ammonium iron(III) sulfate TS to a Nessler tube and diluting with water to 50 mL, and allow to stand for 30 seconds; the color of the solution is not more intense than that of the following control solution.

Control solution—Dissolve 0.100 g of salicylic acid in water, and add 1 mL of acetic acid(100) and water to make 1000 mL. Take 1.0 mL of this solution, add to a solution prepared by transferring 1 mL of freshly prepared dilute ammonium iron(III) sulfate TS and 1 mL of ethanol(95) to a Nessler tube and diluting with water to 50 mL, and allow to stand for 30 seconds.

(3) ***Chloride***—Put 75 mL of water in 1.8 g of Aspirin, boil for 5 minutes, cool, add water to make 75 mL, and filter. To 25 mL of the filtrate, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid (NMT 0.015%).

(4) ***Sulfate***—To 25 mL of the filtrate obtained in (3), add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid (NMT 0.040%).

(5) ***Heavy metals***—Dissolve 2.5 g of Aspirin in 30 mL of acetone, add 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 2.5 mL of lead standard solution, 30 mL of acetone, 2 mL of dilute acetic acid and water to make 50 mL (NMT 10 ppm).

(6) ***Readily carbonizable substances***—Weigh 0.5 g of Aspirin, and perform the test. The color of the solution is not more intense than that of the Matching Fluid for Color Q.

Loss on drying NMT 0.5% (3 g, silica gel, 5 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 1.5 g of Aspirin, previously dried, add exactly 50 mL of 0.5 mol/L sodium hydroxide, and boil gently for 10 minutes under a reflux condenser with a carbon dioxide-absorbing tube (soda lime). Cool, and titrate immediately the excess sodium hydroxide with 0.25 mol/L sulfuric acid VS (indicator: 3 drops of phenolphthalein TS). Perform a blank test in the same manner.

Each mL of 0.5 mol/L sodium hydroxide VS
= 45.04 mg of $C_9H_8O_4$

Packaging and storage Preserve in well-closed containers.

Aspirin Tablets
아스피린 정

Acetylsalicylic Acid Tablets

Aspirin Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of aspirin ($C_9H_8O_4$: 180.16).

Method of preparation Prepare Aspirin Tablets as directed under Tablets, with Aspirin.

Identification (1) Weigh an amount of Aspirin Tablets, previously powdered, equivalent to 0.1 g of Aspirin according to the labeled amount, add 10 mL of water, boil for 5 to 6 minutes, cool, and filter. Add 1 to 2 drops of iron(III) chloride TS to the filtrate; it exhibits a purple color.

(2) Weigh an amount of Aspirin Tablets, previously powdered, equivalent to 0.5 g of Aspirin, according to the labeled amount, and extract twice with 10 mL each of

warm ethanol by shaking to mix. Then combine the extracts, and filter. Evaporate the filtrate to dryness, add 10 mL of sodium carbonate TS to the residue, and boil for 5 minutes. Then perform the test as directed under the Identification (2) of Aspirin.

Purity ***Salicylic Acid***—Weigh accurately the mass of NLT 20 tablets of Aspirin Tablets, and powder. Weigh accurately the amount, equivalent to about 1.0 g of aspirin, dissolve in the mobile phase to make exactly 100 mL. Use this solution as the test solution. Separately, weigh exactly about 15 mg of salicylic acid RS and dissolve in the mobile phase to make exactly 100 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 50 mL. Use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Assay (NMT 0.15%).

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Aspirin Tablets, and powder. Weigh accurately an amount equivalent to about 0.25 g of aspirin ($C_9H_8O_4$), add the mobile phase, shake well to mix, add the mobile phase to make exactly 200 mL, and filter. Discard first 10 mL of the filtrate and pipet 2 mL of the subsequent filtrate, add 4.0 mL of the internal standard solution, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg of aspirin RS, previously dried in a desiccator (silica gel) for 5 hours, and dissolve in mobile phase to make exactly 20 mL. Pipet 2 mL of this solution, put 4.0 mL of the internal standard solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S of the peak areas of aspirin to those of the internal standard.

$$\text{Amount (mg) of aspirin } (C_9H_8O_4) = \text{Amount (mg) of aspirin RS} \times \frac{Q_T}{Q_S} \times 10$$

Internal standard solution—Weigh accurately about 10 mg of theophylline RS, dissolve in the mobile phase to make exactly 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 5 to 10 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of 0.085% phosphoric acid and methanol (60 : 40).

Flow rate: 1.0 mL/min

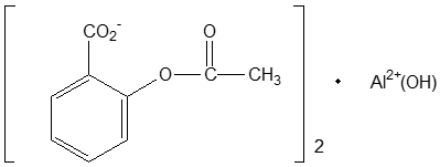
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the internal standard and aspirin are eluted in this order with the resolution being NLT 3.0.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Aspirin Aluminium
아스피린알루미늄



Acetylsalicylic Acid Aluminium

Aluminum acetylsalicylic acid $C_{18}H_{15}AlO_9$: 402.29

Aluminum 2-acetyloxybenzoate hydroxide [*23413-80-1*]

Aspirin Aluminum contains NLT 83.0% and NMT 90.0% of aspirin ($C_9H_8O_4$: 180.16), and NLT 6.0% and NMT 7.0% of aluminum (Al: 26.98), calculated on the anhydrous basis.

Description Aspirin Aluminum occurs as a white, crystalline powder. It is odorless or has a slight acetic acid odor.

It is practically insoluble in water, methanol, ethanol(95) or ether.

It dissolves, with decomposition, in sodium hydroxide TS or sodium carbonate TS.

Identification (1) Put 10 mL of sodium hydroxide TS in 0.1 g of Aspirin Aluminum, and dissolve by warming, if necessary. Neutralize 2 mL of the solution with hydrochloric acid, and add 1 to 2 drops of iron(III) chloride TS; the resulting solution exhibits a purple color.

(2) Determine the absorption spectrum of the test solution obtained in the Assay (1) as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 277 nm and 279 nm.

(3) Put 2 g of Aspirin Aluminum in a platinum crucible, and ignite until charred. To the residue, add 1 g of anhydrous sodium carbonate, and ignite for 20 minutes. After cooling, add 15 mL of dilute hydrochloric acid to the residue, shake to mix, and filter. The filtrate responds

to the Qualitative Analysis for aluminum salt.

Purity (1) ***Salicylate***—Using A_{T2} and A_{S2} obtained in the Assay (1), calculate the amount of salicylate [as salicylic acid ($C_7H_6O_3$: 138.12)] by the following equation; salicylate content is NMT 7.5%, calculated on the anhydrous basis.

$$\text{Amount (mg) of salicylic acid } (C_7H_6O_3) = \text{Amount (mg) of salicylic acid RS} \times \frac{A_{T2}}{A_{S2}} \times \frac{1}{4}$$

(2) ***Heavy metals***—Put 2.0 g of Aspirin Aluminum in a porcelain crucible, cover the crucible loosely, and heat at a low temperature until charred. After cooling, add 2 mL of nitric acid and 1 mL of sulfuric acid to the content of the crucible, heat gently the crucible until white fumes are no longer evolved, then ignite at 500 to 600 °C to incinerate. When the incineration is not completed, add 2 mL of nitric acid and 1 mL of sulfuric acid, and heat gently in the same manner, then ignite at 500 °C to 600 °C to incinerate completely. After cooling, add 2 mL of hydrochloric acid, proceed as directed in Method 2, and perform the test. Prepare the control solution with the same amount as in the preparation of the test solution, and add 2.0ml of lead standard solution and water to make 50 mL (NMT 10 ppm).

(3) ***Arsenic***—Dissolve 1.0 g of Aspirin Aluminum in 15 mL of sodium hydroxide TS, add 1 drop of phenolphthalein TS, and stir to mix until the red color of the solution disappears while adding dropwise hydrochloric acid. Then add again 2 mL of hydrochloric acid, cool with occasional shaking for 10 minutes, and filter with a glass filter (G3). Wash the residue with 5 mL of 1 mol/L hydrochloric acid TS twice, and combine the filtrate and the washings. Use this solution as the test solution, and perform the test (NMT 2 ppm).

Water NMT 4.0% (0.15 g, volumetric titration, direct titration).

Assay (1) ***Aspirin***—Weigh accurately about 0.1 g of Aspirin Aluminum, add 40 mL of sodium fluoride TS, and shake to mix for 5 minutes. Allow the solution to stand for 10 minutes with occasional shaking. Extract the solution with each 20 mL of chloroform six times. Combine all chloroform extracts, and add chloroform to make exactly 200 mL. Pipet 10 mL of this solution, add chloroform to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 90 mg of salicylic acid RS, previously dried in a desiccator (silica gel) for 3 hours, dissolve in chloroform to make exactly 200 mL. Pipet 5 mL of this solution, add chloroform to make exactly 200 mL, and use this solution as the standard solution (1). Then, weigh accurately about 90 mg of aspirin RS, previously dried in a desiccator (silica gel) for 5 hours, and dissolve in chloroform to make exactly 200 mL. Pipet 10 mL of this solution, add chloroform to make exactly 100 mL, and use this solution as the standard solution (2). Perform the test with these solutions as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbances, A_{T1} and A_{S1}, of the test solution and the standard solution (1) at 278 nm, and absorbances, A_{T2} and A_{S2}, of these solutions, at 308 nm, respectively. Then determine the absorbance A_{S3} of the standard solution (2) at 278 nm.

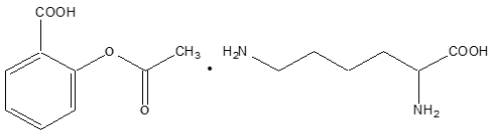
$$\text{Amount (mg) of aspirin } (C_9H_8O_4) = \text{Amount (mg) of aspirin RS} \times \left[\frac{A_{T1} - \frac{A_{T2} \times A_{S1}}{A_{S2}}}{A_{S3}}\right]$$

(2) ***Aluminum***—Weigh accurately about 0.4 g of Aspirin Aluminum, and dissolve in 10 mL of sodium hydroxide TS, and add dropwise 1 mol/L hydrochloric acid TS to adjust the pH to about 1. Add 20 mL of acetic acid-ammonium acetate buffer solution, pH 3.0, and 0.5 mL of Cu-PAN TS to boil, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS. The endpoint is when the color of the solution changes from red to yellow and persists for 1 minute. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L Ethylenediaminetetraacetic acid disodium salt VS
= 1.3491 mg of Al

Packaging and storage Preserve in well-closed containers.

Aspirin DL-Lysine
아스피린리신



$C_6H_{14}N_2O_2 \cdot C_9H_8O_4$: 326.35
2-Acetyloxybenzoate L-lysine (1:1), [62952-06-1]

Aspirin DL-Lysine, when dried, contains NLT 97.0% and NMT 101.0% of aspirin DL-lysine ($C_6H_{14}N_2O_2 \cdot C_9H_8O_4$).

Description Aspirin DL-Lysine occurs as white crystals or a crystalline powder. It is odorless and has a slightly bitter taste.
It is freely soluble in water, slightly soluble in methanol and practically insoluble in ethanol or ether.
An aqueous solution of Aspirin DL-Lysine (1 in 10) shows no optical rotation.

Identification (1) Put 0.2 g of Aspirin DL-Lysine in 5 mL of water, boil for 5 to 6 minutes, cool, and add 1 to 2 drops of iron(II) chloride TS; the resulting solution exhib-

its a reddish purple color.

(2) Add 1 mL of ninhydrin TS to 5 mL of the aqueous solution (1 in 1000) of Aspirin DL-Lysine and heat on a water bath for 2 minutes; the resulting solution exhibits a reddish purple color.

(3) To 1 g of Aspirin DL-Lysine, add 5 mL of dilute hydrochloric acid, shake to mix for 1 minute, filter, and wash the residue on the filter paper with water. Dissolve the residue in 10 mL of sodium carbonate TS, boil for 5 minutes, and add 10 mL of dilute sulfuric acid; the odor of acetic acid is perceptible and a white precipitate is produced. Next, filter the precipitate, add 3 mL of ethanol and 3 mL of sulfuric acid to the filtrate and heat; the odor of ethyl acetate is perceptible.

pH Dissolve 1.0 g of Aspirin DL-Lysine in 10 mL of water; the pH of this solution is between 4.5 and 6.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Aspirin DL-Lysine in 5 mL of water; the solution is clear and colorless.

(2) ***Salicylic acid***—Weigh accurately about 0.1 g of Aspirin DL-Lysine, previously dried, dissolve in 20 mL of a mixture of water, methanol and acetic acid(100) (5 : 3 : 1), and add 10.0 mL of internal standard solution. Then, add again a mixture of water, methanol and acetic acid(100) (5 : 3 : 1) to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 0.05 g of salicylic acid RS, previously dried, and dissolve in methanol to make 50 mL. Pipet 1.0 mL of this solution, add 10.0 mL of the internal standard solution, and add a mixture of water, methanol and acetic acid(100) (5 : 3 : 1) to make 50 mL. Use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid chromatography according to the following conditions, and determine the peak area ratios, QT and QS, of salicylic acid to the peak area of the internal standard, and calculate by the following equation; the amount of salicylic acid is NMT1.0%.

$$\text{Amount (mg) of salicylic acid } (C_7H_6O_3) = \text{Amount (mg) of salicylic acid RS} \times \frac{Q_T}{Q_S} \times \frac{1}{50}$$

◦ *Internal standard solution*—A solution of ethyl paraoxybenzoate in methanol (1 in 1250).

Operating conditions

Detector: Ultraviolet absorption photometer (wavelength: 274 nm).

Column: A stainless steel column with an internal diameter of about 4 mm and a length of about 15 to 30 cm, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of water, methanol and acetic acid(100) (97 : 97 : 6).

Flow rate: Adjust the flow rate so that the retention time of salicylic acid is about 8 minutes.

Selection of column: Proceed with 10 μL of the standard solution according to the above conditions; salicylic acid and the internal standard are eluted in this order, and each peak is completely separated.

(3) ***Ammonium***—Proceed with 0.25 g of Aspirin DL-Lysine according to the Ammonium and perform the test. Prepare the control solution with 5.0 mL of the ammonium standard solution (NMT 0.02%).

(4) ***Heavy metals***—Proceed with 2.0 g of Aspirin DL-Lysine according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Arsenic***—Proceed with 2.0 g of Aspirin DL-Lysine according to the Arsenic and perform the test. (NMT 1 ppm).

(6) ***DL-ε-N-acetyllysine***—Dissolve 2.0 g of Aspirin DL-Lysine and 0.026 g of DL-ε-N-acetyllysine RS in water, respectively, to make 100.0 mL, and use these solutions as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol and water (63 : 37) to a distance of about 10 cm, and air-dry the plate. Spray evenly ninhydrin acetone solution (1 in 50), heat at 80 °C for 5 minutes; the spot of the test solution with the same Rf value as that of the spot from the standard solution is not more intense than the spot from the standard solution.

Loss on drying NMT 1.0% (2 g, silica gel, 24 hours).

Residue on ignition NMT 0.1% (1.0 g).

Particle size estimation by analytical sieving Meets the requirements.

Assay Weigh accurately about 0.1 g of Aspirin DL-Lysine, previously dried, and dissolve in 1 in 20 mL a mixture of water, methanol and acetic acid(100) (5 : 3 : 1). Add 10.0 mL of the internal standard solution, add a mixture of water, methanol and acetic acid(100) (5 : 3 : 1) again to make 50.0 mL, and use this solution as the test solution. Separately, weigh accurately about 0.06 g of aspirin RS, previously dried in a desiccator (silica gel) for 5 hours, dissolve in 10.0 mL of the internal standard solution, add a mixture of water, methanol and acetic acid(100) (5 : 3 : 1) to make 50.0 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid chromatography according to the following conditions, and determine the peak area ratios, QT and QS, of aspirin to the peak area of the internal standard.

Amount (mg) of aspirin DL-lysine (C6H14N2O2·C9H8O4)
= Amount (mg) of aspirin DL-lysine RS × $\frac{Q_T}{Q_S}$ × 1.8114

◦ *Internal standard solution*—A solution of ethyl paraoxybenzoate in methanol (1 in 1250).

Operating conditions

Detector: Ultraviolet absorption photometer (wavelength: 274 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm to 30 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

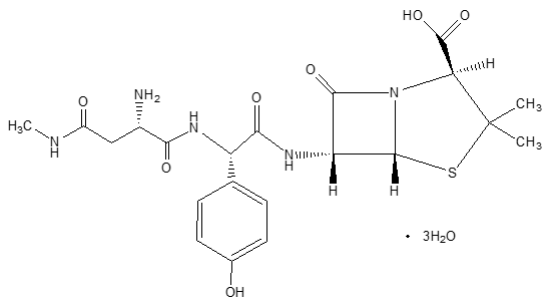
Mobile phase: A mixture of water, methanol and acetic acid(100) (97 : 97 : 6).

Flow rate: Adjust the flow rate so that the retention time of aspirin is about 5 minutes.

Selection of column: Proceed with 10 μL of the standard solution according to the above conditions; aspirin and the internal standard are eluted in this order, and each peak is completely separated.

Packaging and storage Preserve in light-resistant, tight containers at below 6 ℃.

Aspoxicillin Hydrate
아스폭시실린수화물



Aspoxicillin $C_{21}H_{27}N_5O_7S \cdot 3H_2O$
(3*S*,5*R*,6R)-6-{(2*R*)-2-[(2*R*)-2-Amino-4-(methylamino)-4-oxobutanamido]-2-(4-hydroxy-phenyl)acetamido}-2,2-dimethylpenam-3-carboxylic acid trihydrate [*117774-38-6*]

Aspoxicillin Hydrate contains NLT 950 μg (potency) and NMT 1020 μg (potency) of aspoxicillin ($C_{21}H_{27}N_5O_7S$: 493.53) per mg, calculated on the anhydrous basis.

Description Aspoxicillin Hydrate occurs as white crystals or a crystalline powder.
It is freely soluble in *N*,*N*-dimethylformamide, sparingly soluble in water, and practically insoluble in acetonitrile, methanol and ethanol(95).

Identification (1) Determine the absorption spectra of solutions of Aspoxicillin Hydrate and aspoxicillin hydrate RS (1 in 4000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelength.

(2) Determine the infrared absorption spectrum of Aspoxicillin Hydrate and aspoxicillin hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers

Optical rotation $[\alpha]_D^{20}$: Between +170° and +185° (0.2 g, calculated on the anhydrous basis, water, 20 mL, 100 mm).

pH Dissolve 1.0 g (potency) of Aspoxicillin Hydrate in 50 mL of water; the pH of this solution is between 4.2 and 5.2.

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Aspoxicillin Hydrate in 50 mL of water; the solution is clear and colorless.

(2) ***Heavy metals*—**Proceed with 2.0 g of Aspoxicillin Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic*—**Proceed with 2.0 g of Aspoxicillin Hydrate according to Method 5 and perform the test (NMT 1 ppm).

(4) ***Related substances***—Dissolve 0.05 g of Aspoxicillin Hydrate in 10 mL of the mobile phase and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Calculate the peak area of each solution by the automatic integration method; the each peak area other than aspoxicillin from the test solution is NMT 3/10 of the peak area of aspoxicillin from the standard solution. The sum of peak areas other than aspoxicillin from the test solution is NMT the peak area of aspoxicillin from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed under the operating conditions in the Assay.

System suitability

Test for required detectability: Pipet 2 mL of the standard solution and add the mobile phase to make exactly 10 mL. Confirm that the peak area of aspoxicillin obtained from 10 μL of this solution is equivalent to 15 to 25% of the peak area of aspoxicillin obtained from the standard solution.

System performance: Proceed as directed under the system suitability in the Assay.

System repeatability: Repeat the test 6 times

with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of aspoxicillin is NMT 5%.

Time span of measurement: About 6 times of the retention time of aspoxicillin.

Water NLT 9.5% and NMT 13.0% (0.2 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in sterile preparations. However, it is exempt from the requirements when there is a terminal sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins Less than 0.50 EU per mg of aspoxicillin (potency) when used in the manufacturing of sterile preparations.

Assay Weigh accurately an amount of Aspoxicillin and aspoxicillin RS, equivalent to about 0.1 g (potency), dissolve each in a suitable amount of water, add exactly 10 mL of the internal standard solution, add 6.5 mL of acetonitrile and water to make 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios the peak area, Q_T and Q_S of aspoxicillin to that of the internal standard.

$$\text{Potency (μg) of aspoxicillin } (C_{21}H_{27}N_5O_7S) = \text{Potency (μg) of aspoxicillin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—*N*-(3-Hydroxyphenyl)acetamide (1 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: To 130 mL of acetonitrile, add potassium dihydrogen phosphate TS, pH 3.0, to make 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of aspoxicillin is about 3 minutes.

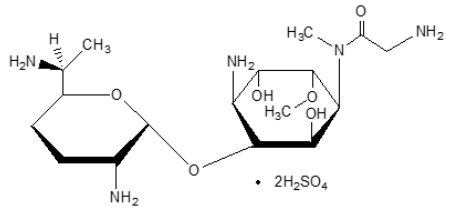
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; aspoxicillin and the internal standard are eluted in this order with the resolution being NLT 8.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above operating conditions; the relative standard deviation of the ratios of the peak area of aspoxicillin to that of the internal standard is NMT 0.8%.

Packaging and storage Preserve in tight containers.

Astromicin Sulfate
아스트로마이신황산염



$C_{17}H_{35}N_5O_6 \cdot 2H_2SO_4$: 601.65

2-Amino-*N*-[(1*S*,2*R*,3*R*,4*S*,5*S*,6*R*)-4-amino-3-[(2*R*,3*R*,6*S*)-3-amino-6-(1-aminoethyl)oxan-2-yl]oxy-2,5-dihydroxy-6-methoxycyclohexyl]-N-methylacetamide disulfate [*72275-67-3*]

Astromicin Sulfate is the sulfate of aminoglycoside substances having antibacterial activity produced by cultivating *Micromonospora olivasterospora*.

Astromicin Sulfate contains NLT 610 μg and NMT 680 μg (potency) of astromicin ($C_{17}H_{35}N_5O_6$: 405.49) per mg, calculated on the anhydrous basis.

Description Astromicin Sulfate occurs as a white to pale yellowish powder or a mass. It is very soluble in water, sparingly soluble in ethylene glycol, and practically insoluble in methanol or ethanol(99.5).
It is hygroscopic.

Identification (1) To 2 mL of an aqueous solution of Astromicin Sulfate (1 in 100), add 2 to 3 drops of barium chloride TS; a white precipitate develops, and it does not dissolve even when dilute nitric acid is added.

(2) Dissolve 10 mg each of Astromicin Sulfate and astromicin sulfate RS in 10 mL of water. To 5 mL of these solutions, add water to make 100 mL, and use these solutions as the test solution and the standard solution. Take 10 μL each of the test solution and the standard solution, and perform the test as directed under the Liquid Chromatography according to the following conditions; the retention time of the astromycin peak obtained from the test solution is the same as that from the standard solution.

Operating conditions

Perform the test with the detector, column, column temperature, reaction coil, reaction coil temperature, mobile phase, reaction reagents, reaction temperature, mobile phase flow rate, and reaction reagent flow rate, following the operating conditions of the Purity (3).

Optical rotation $[\alpha]_D^{20}$: Between +90° and +110° (0.25

g, calculated on the anhydrous basis, water, 25 mL, 100 mm).

pH Dissolve 1.0 g of Astromicin Sulfate in 10 mL of water; the pH of this solution is between 4.5 and 6.5.

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Astromicin Sulfate in 10 mL of water; the solution is clear and colorless to pale yellow.

(2) ***Heavy metals*—**Proceed with 1.0 g of Astromicin Sulfate according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances*—**Dissolve 0.10 g of Astromicin Sulfate in 100 mL of water, and use this solution as the test solution. Pipet 2 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution according to the automatic integration method; the peak areas of the related substances with relative retention times of about 0.1 and about 1.2, relative to the astromycin peak, are not greater than the peak area of the astromycin in the standard solution, and the peak area of the related substance with the relative retention time of about 0.8 is not greater than 2.0 times the peak area of the astromycin in the standard solution. The total area of peaks other than the peak of astromicin is not greater than 3.5 times the peak area of astromicin from the standard solution.

Operating conditions

Detector: A fluorometer (excitation wavelength: 340 nm, fluorescence wavelength: 430 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Reaction coil: A stainless steel column of 0.25 mm in internal diameter and 150 cm in length.

Reaction coil temperature: 50 ℃

Mobile phase: Dissolve 25 mL of sodium 1-heptanesulfonate solution (1 in 1000) and 1 mL of acetic acid(100) in 800 mL of anhydrous sodium sulfate solution (71 in 2000), and add water to make 1000 mL.

Reaction reagents: Dissolve 11.2 g of potassium hydroxide, 0.458 g of polyoxyethylene (23) lauryl ether, 0.300 g of *o*-phthalaldehyde, and 1 mL of 2-mercaptoethanol in 400 mL of boric acid solution (31 in 1000), and add water to make 500 mL.

Reaction temperature: 50 ℃

Mobile phase flow rate: 0.7 mL/min

Reaction reagent flow rate: 0.2 mL/min

System suitability

Test for required detectability: Take 5 mL of the test solution, add water to make 100 mL, and use this solution as the system suitability solution. Pipet 2 mL of this solution, and add water to make exactly 100 mL. Confirm that the peak area of astromicin obtained from 10 μL of this solution is between 1.5% and 2.5% of the peak area of astromicin from the system suitability solution.

System performance: Take 5 mL of the test solution and 2 mL of L-valine solution (1 in 5000), and add 100 mL of water. Proceed with 10 μL of this solution according to the above conditions; L-valine and astromicin are eluted in this order with the resolution being NLT 1.5. Proceed with 10 μL of the system suitability solution according to the above conditions; the symmetry factor for the astromicin peak is NMT 2.0.

System repeatability: Repeat the test 6 times with 10 μL of the system suitability solution according to the above conditions; the relative standard deviation of the peak area of astromicin is NMT 2.0%.

Time span of measurement: About 2 times the retention time of astromicin.

Water NMT 8.0% (0.2 g, volumetric titration, back titration. However, use a mixture of methanol for water determination and ethylene glycol for water determination (1 : 1) instead of methanol for water determination).

Sterility It meets the requirements when used in a sterile preparation. However, it is excluded in cases where there is a final sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins It is less than 0.50 EU per mg of astromicin (potency) when used in the manufacturing of sterile preparations.

Assay ***Cylinder plate method*** (1) Use *Bacillus subtilis* ATCC 6633 as the test organism.

(2) Medium Agar media for seed and base layer Use the culture medium in A) (2) (A) ① (a) under the Microbial Assays for Antibiotics.

(3) Weigh accurately about 25 mg (potency) of each Astromicin Sulfate, and dissolve in a 0.1 mol/L phosphate buffer solution for antibiotics (pH 8.0) to make exactly 25 mL. Pipet an appropriate amount of this solution, add 0.1 mol/L phosphate buffer solution for antibiotics (pH 8.0), dilute it to contain 4 μg (potency) and 1 μg (potency) per mL, and use these solutions as the high concentration test solution and the low concentration test solution, respectively. Separately, weigh accurately about 25 mg (potency) of astromicin sulfate RS, dissolve in diluted hydrochloric acid (1 in 1000) to make exactly 25 mL, and use this solution as the standard stock solution. Store the standard stock solution at 5 °C to 15 °C, and use it within 30 days. Pipet an appropriate amount of the standard stock solution, add 0.1 mol/L phosphate buffer solution for antibiotics (pH 8.0), dilute to contain 4 μg (potency) and 1 μg (potency) in 1 mL, and use these solu-

tions as the high concentration standard solution and the low concentration standard solution, respectively. With these solutions, perform the test according to A)(8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in tight containers.

Astromicin Sulfate for Injection
주사용 아스트로마이신황산염

Astromicin Sulfate for Injection is a preparation for injection which is dissolved before use, and contains NLT 90.0% and NMT 120.0% of the labeled amount of astromicin ($C_{17}H_{35}N_5O_6$: 405.49).

Method of preparation Prepare as directed under Injections, with Astromicin Sulfate.

Description Astromicin Sulfate for Injection occurs as a white to pale yellow powder.

Identification (1) Add 1 mL of ninhydrin TS to 5 mL of aqueous solution of Astromicin Sulfate for Injection (1 in 200), and heat on a steam bath for 5 minutes; the solution exhibits a violet color.

(2) Weigh an appropriate amount of Astromicin Sulfate for Injection, dissolve in water to obtain a solution containing 5 mg (potency) per mL, and use this solution as the test solution. Separately, weigh an appropriate amount of astromicin sulfate RS and dissolve in water to obtain a solution containing 5 mg (potency) per mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with the pellet of a mixture of strong ammonia water, methanol and chloroform (1:1:1) as the developing solvent, and air-dry the plate. Spray the plate evenly with an acetone solution of ninhydrin (1 in 500), and heat at 100 ℃ for 10 minutes; the R_f values of the spots obtained from the test solution and the standard solution are the same.

pH Dissolve Astromicin Sulfate for Injection in water to prepare a solution of 0.1 g (potency) / mL; the pH of the solution is between 5.0 and 7.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.50 EU per mg (potency) of astromicin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Water NMT 5.0% (0.1 g, volumetric titration, direct titration). However, as the solvent, use a mixture of methanol for water determination and ethylene glycol instead of methanol for water determination.

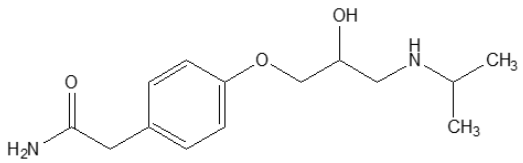
Assay Cylinder plate method (1) Agar media for seed and base layer Use the medium in (A) (1) (a) ① ⓐ under the Microbial Assays for Antibiotics.

(2) ***Test organism***—Use *Bacillus subtilis* ATCC 6633 as the test organism.

(3) Weigh accurately about 0.1 g (potency) according to the labeled potency of Astromicin Sulfate for Injection, dissolve in 0.1 mol/L phosphate buffer (pH 8.0) to prepare a solution containing 1 mg (potency) per mL. Then, pipet an appropriate amount of this solution, dilute with 0.1 mol/L phosphate buffer (pH 8.0) to 4.0 μg and 1.0 μg (potency) per mL, and use these solutions as the high-concentration test solution and the low-concentration test solution, respectively. Separately, weigh accurately about 25 mg (potency) of astromicin sulfate RS, dissolve in diluted hydrochloric acid (1 in 1000) to prepare a standard solution stock solution containing 1 mg (potency) per mL. Keep this standard solution stock solution at 5 °C to 15 °C, and use within 30 days. Pipet an appropriate amount of this standard solution stock solution and dilute with 0.1 mol/L phosphate buffer (pH 8.0) to 4.0 μg and 1.0 μg (potency) per mL, and use these solutions as the high-concentration standard solution and the low-concentration standard solution, respectively. With these solutions, perform the test according to (A) (8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in hermetic containers.

Atenolol
아테놀롤



and enantiomer

$C_{14}H_{22}N_2O_3$: 266.34

2-[4-[2-Hydroxy-3-(propan-2-ylamino)propoxy] phenyl]acetamide [*29122-68-7*]

Atenolol, when dried, contains NLT 99.0% and NMT 101.0% of atenolol ($C_{14}H_{22}N_2O_3$).

Description Atenolol occurs as a white to pale yellowish

white crystalline powder.
It is freely soluble in methanol or acetic acid(100), sparingly soluble in ethanol(99.5) and slightly soluble in water.
A solution of Atenolol in methanol (1 in 25) shows no optical rotation.

Identification (1) Determine the absorption spectra of atenolol and atenolol RS in methanol (5 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar maxima and minima of absorption at the same wavelengths.

(2) Determine the infrared spectrum of Atenolol and atenolol RS, previously dried, as directed in the potassium bromide disk method under the mid-infrared absorption spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 152 and 156 ºC.

Purity (1) ***Chloride*—**Dissolve 1.0 g of Atenolol in 100 mL of 0.15 mol/L nitric acid solution. Use this solution as the test solution. For the control solution, dissolve 1.4 mL of 0.02 mol/L hydrochloric acid TS in 100 mL of 0.15 mol/L nitric acid solution. Add 1 mL of silver nitrate TS to the test solution and control solution and allow to stand for 5 minutes; the turbidity of the test solution is not greater than that of the control solution (NMT 0.1%).

(2) ***Heavy metals*—**Proceed with 1.0 g of Atenolol according to Method 2 under the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances*—**Dissolve 50 mg of Atenolol in 25 mL of the mobile phase and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 200 mL and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; each peak area other than the peak of atenolol from the test solution is not greater than 0.5 times the peak area of atenolol from the standard solution. The total area of the peaks other than the peak of atenolol from the test solution is not greater than the peak area of atenolol from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 226 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 3.4 g of sodium dihydrogen phosphate dihydrate in 1000 mL of water and adjust the pH to 3.0 with phosphoric acid. To 40 mL of this solution, add 9 mL of methanol and 1 mL of tetrahydrofuran. Dissolve 1.0 g of sodium octanesulfonate and 0.4 g of tetrabutylammonium hydrogen sulfate to 1000 mL of this solution.

Flow rate: Adjust the flow rate so that the retention time of atenolol is about 8 minutes.

System suitability

Test for required detectability: Pipet 10 mL of the standard solution and add the mobile phase to make exactly 50 mL. The peak area of atenolol from 10 μL of this solution is between 14% and 26% of the peak area of atenolol from the standard solution.

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; the number of theoretical plates and the symmetry factor of the peak of atenolol are NLT 5000 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 10 μL each of standard solution (1) under the above operating conditions; the relative standard deviation of the peak area of atenolol is NMT 1.0%.

Time span of measurement: About 4 times the retention time of atenolol.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.1 g each of Atenolol and atenolol RS, previously dried, and dissolve in the mobile phase, respectively to make exactly 100 mL. Pipet 5 mL of each solution, add the mobile phase to make exactly 50 mL, then pipet 5 mL of each solution, add the mobile phase to make exactly 50 mL, and use these solutions as the test solution and the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of atenolol.

$$\text{Amount (mg) of atenolol } (C_{14}H_{22}N_2O_3) = \text{Amount (mg) of atenolol RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 226 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Mobile phase: Add 1.1g of sodium 1-heptanesulfonate and 0.71 g of anhydrous sodium dihydrogen phosphate to 700 mL of water and dissolve, add 2 mL of dibutylamine, and adjust to pH 3.0 using 0.8 mol/L phosphoric acid. Add 300 mL of methanol and mix well.

Flow rate: 1.7 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; the number of theoretical plates and the symmetry factor are NLT 5000 and NMT 2.0, respectively.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area is NMT 2.0%

Packaging and storage Preserve in tight containers.

Atenolol Tablets
아테놀롤 정

Atenolol Tablets contain NLT 90.0% and NMT 110.0% of labeled amount of atenolol ($C_{14}H_{22}N_2O_3$: 266.34).

Method of preparation Prepare Atenolol Tablets as directed under Tablets, with Atenolol.

Identification (1) Take an amount of Atenolol Tablets, previously powdered, equivalent to 0.1 g of atenolol, according to the labeled amount, add 15 mL of methanol, mix well and shake for 5 minutes while heating to 50 °C. Filter this solution, evaporate the obtained filtrate to dryness on a steam bath, add 0.1 mol/L hydrochloric acid to the residue, shake while heating, and filter. Add a sufficient amount of 1 mol/L sodium hydroxide TS to the filtrate to make it alkaline, extract with 10 mL of chloroform, remove water from the chloroform layer with anhydrous sodium sulfate, and filter. Evaporate the filtrate to dryness on a steam bath, and dry the residue at 105 °C for 1 hour, and use this as the sample. With the sample and atenolol RS, make them into a fine powder in the same manner, and determine the infrared spectra as directed in the potassium bromide disk method as directed under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention times of the major peaks obtained from the test solution and the standard solution in the Assay are the same.

Dissolution Perform the test with 1 tablet of Atenolol Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take NLT 20 mL of the dissolved solution after 30 minutes from the start of the dissolution test, and filter through a membrane filter with a pore size of NMT 0.8 μm. Add phosphoric acid solution (1 in 1000) to the filtrate so that each mL contains 10 μg of atenolol ($C_{14}H_{22}N_2O_3$) according to the labeled amount, and use this solution as the test solution. Perform the test with the test solution and the standard solution obtained from the Assay as directed under the Assay, and determine A_T and A_S.

Meets the requirements if the dissolution rate of Atenolol Tablets in 30 minutes is NLT 80%.

Dissolution rate (%) with respect to the labeled amount of atenolol ($C_{14}H_{22}N_2O_3$)

$$= \text{Amount (mg) of atenolol RS} \times 900 \times C \times D \times \frac{A_T}{A_S}$$

C: Concentration (mg/mL) of atenolol in the standard solution

D: Dilution factor of the test solution

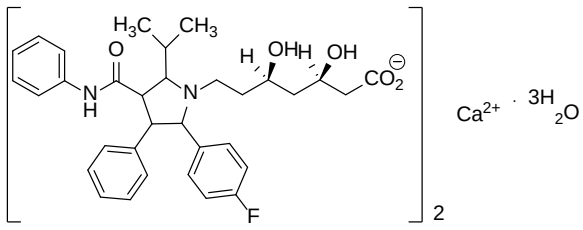
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately NLT 20 tablets of Atenolol Tablets, and powder. Weigh accurately an amount equivalent to about 0.25 g of atenolol ($C_{14}H_{22}N_2O_3$), add the mobile phase, and sonicate for 15 minutes. Make exactly 1000-mL by adding mobile phase, then centrifuge, take exactly 2 mL of the clear supernatant, add the mobile phase to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg of atenolol RS and add the mobile phase to make 100 mL. Take exactly 2 mL of this solution, add the mobile phase to make 50 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the test solution and the standard solution as directed under the Assay of Atenolol.

$$\text{Amount (mg) of atenolol } (C_{14}H_{22}N_2O_3) = \text{Amount (mg) of atenolol RS} \times \frac{A_T}{A_S} \times 10$$

Packaging and storage Preserve in tight containers.

Atorvastatin Calcium Hydrate
아토르바스타틴칼슘수화물



$C_{66}H_{68}CaF_2N_4O_{10}\cdot 3H_2O$: 1209.39

Calcium *bis*{(3*R*,5*R*)-7-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-(phenylcarbamoyl-1*H*-pyrrol-1-yl]-3,5-dihydydroxyheptanoate} trihydrate [*344423-98-9*]

Atorvastatin Calcium Hydrate contains NLT 98.0% and NMT 102.0% of atorvastatin calcium hydrate ($C_{66}H_{68}N_2O_{10}$: 1155.34), calculated on the anhydrous basis.

Description Atorvastatin Calcium Hydrate occurs as a white to pale yellowish crystalline powder.

It is very soluble in methanol, freely soluble in dimethylsulfoxide, and very slightly soluble in water or ethanol(99.5).
It is gradually changed to a yellowish white color by light.
It shows polymorphism.

Identification (1) Determine the absorption spectra of Atorvastatin Calcium Hydrate and atorvastatin calcium hydrate RS in methanol (1 in 62500) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Atorvastatin Calcium Hydrate and avorstatin calcium hydrate RS according to the potassium bromide disk method as directed under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If there is a difference between the spectra of Atorvastatin Calcium Hydrate and avorstatin calcium hydrate RS, recrystallize each, filter and dry the crystals, and repeat measurement using these crystals.

(3) Avostatin Calcium Hydrate made into a paste by adding a small amount of dilute hydrochloric acid responds to the Qualitative Analysis 1) for calcium salt. Further, a mixture of Avostatin Calcium Hydrate with methanol and water (7 : 3) (1 in 250) responds to the Qualitative Analysis (3) for calcium salt.

Optical rotation $[\alpha]_D^{25}$: Between -7° and -10° (0.2 g calculated on the anhydrous basis, dimethylsulfoxide, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Avorstatin Calcium Hydrate and perform the test according to Method 4. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Dissolve 20 mg of Avorstatin Calcium Hydrate in a mixture of acetonitrile and water (1 : 1) to make 20 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of water and acetonitrile (1 : 1) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Measure the peak area of each solution according to the automatic integration method and determine the amounts of related substances; the area of peaks whose relative retention time compared to atorvastatin in the test solution is about 0.8 is NMT 0.3 times the peak area of atorvastatin from the standard solution. Further, the peak areas of atorvastatin in the test solution and peaks other than those whose relative retention time compared to astorvastatin is 0.8 is NMT 0.1 times the peak area of atorvastatin from the standard solution, and the sum of peak areas other than atorvastatin in the test solution is not greater than the atorvastatin peak area from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: Weigh 10.5 g of citric acid monohydrate, dissolve in 900 mL of water, adjust the pH to 5.0 with ammonia water(28), and add water to make 1000 mL. Add 100 mL of acetonitrile and 100 mL of tetrahydrofuran to 400 mL of this solution.

Mobile phase B: A mixture of acetonitrile and tetrahydrofuran (1 : 1).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 40	93	7
40 - 80	93 in 60	7 in 40

Flow rate: Adjust the flow rate so that the retention time of atorvastatin is about 16 minutes.

System suitability

Test for required detectability: Take 5 mL of the standard solution and add a mixture of water and acetonitrile (1 : 1) to make exactly 100 mL. Confirm that the peak area of atorvastatin obtained with 20 μL of this solution is equivalent to NLT 3.5% and NMT 6.5% of the peak area of atorvastatin in the standard solution.

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and symmetry factor of the peak of atorvastatin are NLT 8000 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area for atorvastatin is NMT 2.0%.

Time span of measurement: About 5 times the retention time of atorvastatin after the solvent peak.

Isomer Weigh 10 mg of Avostatin Calcium Hydrate and dissolve in 2.0 mL of methanol, add 2.0 mL of ethanol(99.5), then add hexane to make exactly 10 mL, and use this solution as the test solution. Perform the test with 20 μL of this solution as directed under the Liquid Chromatography according to the following conditions to determine the amount of atorvastatin enantiomer; it is NMT 0.3%.

$$\text{Content (\%) of Atorvastatin enantiomer} = \frac{A_i}{A_T} \times 100$$

A_i: Peak area of atorvastatin enantiomer

A_T: Sum of peak areas of atorvastatin enantiomer and atorvastatin

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with amylose tris(3,5-dimethylphenylcarbamate)-coated silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of hexane, ethanol(99.5) and trifluoroacetic acid (940 : 60 : 1).

Flow rate: 1.0 mL/min

System suitability

System performance: Dissolve an appropriate amount of atorvastatin calcium RS and atorvastatin enantiomer RS in methanol to make concentrations of 5 mg/mL and 37.5 μg/mL, respectively. Take 2.0 mL of this solution, add 2.0 mL of ethanol(99.5), add hexane to make exactly 10 mL, and use this solution as the system suitability solution. Proceed with the system suitability solution according to the above conditions; the resolution between the atorvastatin enantiomer and atorvastatin is NLT 2.0.

Water Between 3.5% and 5.5% (50 mg, coulometric titration).

Assay Weigh accurately about 20 mg each of Atorvastatin Calcium Hydrate and atorvastatin RS (previously measure water in the same manner as Atorvastatin Calcium Hydrate), dissolve by adding a mixture of water and acetonitrile (1 : 1), add exactly 10 mL of the internal standard solution, and then add a mixture of water and acetonitrile (1 : 1) to make 50 mL. Use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, Q_T and Q_S of the atorvastatin to the peak area of the internal standard.

Amount (mg) of atorvastatin calcium ($C_{66}H_{68}CaF_2N_4O_{10}$)
= Amount (mg) of atorvastatin calcium RS,
calculated on the anhydrous basis $\times \frac{Q_T}{Q_S}$

Internal standard solution—Solution of butyl parahydroxybenzoate in a mixture of acetonitrile and water (1 : 1) (1 in 1500).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 10.5 g of citric acid monohydrate in 900 mL of water, adjust the pH to 4.0 with ammonia water(28), and add water to make 1000 mL. Add 270 mL of acetonitrile and 200 mL of tetrahydrofuran to 530 mL of this solution.

Flow rate: Adjust the flow rate so that the retention time of atorvastatin is about 10 minutes.

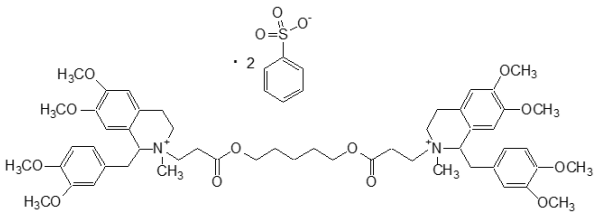
System suitability

System performance: Proceed with 10 μL of the standard solution under the above conditions; the internal standard and atorvastatin are eluted in this order with the resolution being NLT 5.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above conditions; the relative standard deviation of the peak area of atorvastatin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Atracurium Besylate
아트라쿠륨베실산염



$C_{53}H_{72}N_2O_{12}\cdot 2C_6H_5O_3S_2$: 1243.48

2,2'-{1,5-Pentanediyl*bis*[oxy(3-oxo-3,1-propanediyl)]}bis[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroiso-quinolinium] dibenzenesulphonate [*64228-81-5*]

Atracurium Besylate contains NLT 96.0% and NMT 102.0% of atracurium besylate ($C_{53}H_{72}N_2O_{12}\cdot 2C_6H_5O_3S_2$), calculated on the anhydrous basis.

Method of preparation If there is any possibility of alkyl (methyl, ethyl, isopropyl, etc.) benzenesulfonate esters to be included as impurities in the manufacturing process of Atracurium Besylate, precautions must be taken in controlling the starting materials, manufacturing process and intermediates in order to minimize the residue amounts of these impurities in consideration of risk assessment results. If necessary, the manufacturing process may be verified by the test data proving that no quality risk exists in the final drug substance.

Description Atracurium Besylate occurs as a white to yellowish white solid.

It is very soluble in ethanol(95), acetonitrile or dichloromethane and soluble in water.
It is hygroscopic.

Identification (1) Determine the infrared spectra of Atracurium Besylate and atracurium besylate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention times of the major peaks obtained from the 3 isomers obtained from the test solution of the Assay correspond to the retention times of the respective major peaks from the standard solution.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Atracurium Besylate and perform the test according to Method 2. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Methyl benzene sulfonate***—Weigh accurately 0.10 g of Atracurium Besylate and dissolve in mobile phase A of the Assay to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately about 20.0 mg of methyl benezen sulfonate RS and dissolve in the acetonitrile to make exactly 100 mL. Pipet 1.0 mL of this solution, add the mobile phase A to make exactly 200 mL, and the use this solution as the standard solution. Perform the test with 100 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. The peak area of methyl benzene sulfonate from the test solution is not larger than the peak area from the standard solution (0.01%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 217 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with base-deactivated octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A and mobile phase B: Follow the conditions as directed under the Assay.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0	80	20
0 - 5	80	20
5 - 15	80 → 75	20 → 25
15 - 25	75	25
25 - 30	75 → 55	25 → 45
30 - 38	55 → 0	45 → 100
38 - 45	0	100

Flow rate: 1.0 mL/min

System suitability

System performance: Take 1 mL of test solution and 5 mL of 0.02% acetonitrile solution of methyl benzene sulfonate, and add the mobile phase A to make 100 mL. Proceed with this solution according to the above conditions; the resolution between the trans-trans isomer peaks and the methyl benzene sulfonate peaks is NLT 12.0.

System repeatability: Repeat the test 2 times according to the above conditions with the standard solution; the relative standard deviation of the peak area is NMT 12%.

(3) ***Toluene substances***—Weigh accurately about 0.20 g of Atracurium Besylate, dissolve in acetonitrile to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of toluene RS, dissolve in acetonitrile to make exactly 100 mL, then add acetonitrile to 5.0 mL of this solution to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 1 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. The peak area of toluene from the test solution is not larger than the toluene peak area from the standard solution (NMT 0.5%).

Operating conditions

Detector: A flame ionization detector

Column: A stainless steel column about 0.25 mm in internal diameter and about 30 cm in length, packed with 5% phenylmethylsilicone polymer for gas chromatography (0.25 μm in particle diameter).

Column temperature: Inject the sample, hold for 5 minutes at 30 ℃, then heat at a rate of 8 ℃ per minute to 175 ℃. Then heat to 260 ℃ at a rate of 35 ℃ per minute, and hold for NLT 5 minutes at 260 ℃.

Sample injection port temperature: A constant temperature of about 200 ℃.

Detector temperature: A constant temperature of about 260 ℃.

Carrier gas: Helium

Flow rate: 1.0 mL/sec

System suitability

System performance: Weigh accurately 1-butanol, toluene, methanol and 1-propanol, and dissolve in acetonitrile to make 12.0, 7.6, 1.6 and 1.2 μg per mL, respectively. Proceed with 1 μL of this solution according to the above operating conditions; the resolution between the peaks of the two components is NLT 1.0.

System reproducibility: Weigh accurately 1-butanol, toluene, methanol and 1-propanol, and dissolve in acetonitrile to make 12.0, 7.6, 1.6 and 1.2 μg per mL, respectively. Repeat the test with 1 μL each of these solutions according to the above conditions; the relative standard deviation of the peak areas is NMT 15%.

(4) ***Related substances***—Use the test solution in the Assay as the test solution. Add the mobile phase A of

Assay to 1.0 mL of the standard solution of Assay to make exactly 100 mL, and use this solution as the standard solution. Take 20 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the conditions in Assay, and measure the peak areas other than the three major peaks to calculate the amount of each related substance according to the following equation; the amount of laudonasine having the relative retention time of about 0.3 is NMT 0.5%, the amount of other individual related substances is NMT 1.0%, and the amount of total related substances is NMT 3.5%. However, the peak area for laudanosine is obtained by dividing the calculated area by the sensitivity coefficient of 1.9.

$$\text{Content (\%) of each related substance} = 10000 \times \frac{C}{W} \times \frac{A_T}{A_S}$$

A_i: Peak area of each related substance obtained from the test solution

A_S: Peak area of cis-cis isomer obtained from the standard solution

C: Concentration of cis-cis isomer in the standard solution (mg/mL)

W: Weight (mg) of sample taken

System suitability

Repeat the test 2 times with 20 μL each of the standard solution under the conditions of Assay; the relative standard deviation of the peak area of cis-cis isomer is NMT 10%.

Water NMT 5.0% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.1 g each of Atracurium Besylate and atracurium besylate RS, dissolve in mobile phase A to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the total areas, A_T and A_S for the three isomer peaks.

$$\text{Amount (mg) of atracurium besylate } (C_{53}H_{72}N_2O_{12}\cdot 2C_6H_5O_3S_2) = \text{Amount (mg) of atracurium besylate RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless tube about 4.6 mm in internal diameter and about 25 cm in length, packed with base-deactivated octadecylsilanized silica gel for liquid chromatography (3 to 10 μm in particle diameter).

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: Mixture of buffer solution, acetonitrile and methanol (75 : 20 : 5).

Mobile phase B: Mixture of buffer solution, methanol and acetonitrile (50 : 30 : 20).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0	80	20
0 - 5	80	20
5 - 15	80 in 40	20 in 60
15 - 25	40	60
25 - 30	40 in 0	60 in 100

Flow rate: 1.0 mL/min

System suitability

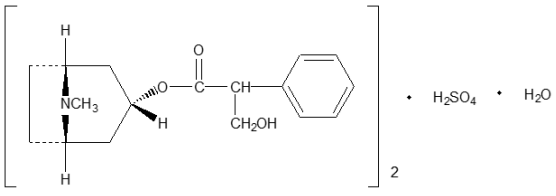
System performance: Perform the test with the standard solution according to the above conditions; the relative retention times for the trans-trans, cis-trans and cis-cis isomer peaks are about 0.8, about 0.9 and 1.0, respectively, and the resolution of the trans-trans isomer peak and cis-trans isomer peak and the resolution of the cis-trans isomer peak and the cis-cis isomer peak are NLT 1.1.

System repeatability: Repeat the test 5 times according to the above conditions with the standard solution; the relative standard deviation of the peaks areas of the isomers is NMT 2.0%.

Buffer solution—Weigh 10.2 g of potassium dihydrogen phosphate, dissolve in 950 mL of water, adjust the pH to 3.1 with phosphoric acid, and add water to make exactly 1000 mL.

Packaging and storage Preserve in light-resistant, tight containers. Preserve in a cold place.

Atropine Sulfate Hydrate
아트로핀황산염수화물



Atropine Sulfate $(C_{17}H_{23}NO_3)_2\cdot H_2SO_4\cdot H_2O$: 694.83

bis[(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl) 3-hydroxy-2-phenylpropanoate] sulfate monohydrate [*5908-99-6*]

Atropine Sulfate Hydrate contains NLT 98.0% and NMT 101.0% of atropine sulfate ($C_{17}H_{23}NO_3\cdot H_3PO_2$),

calculated on the anhydrous basis.

Description Atropine Sulfate Hydrate occurs as a colorless or white, odorless crystalline powder.
It is very soluble in water or acetic acid(100), freely soluble in ethanol(95) and practically insoluble in ether.

Melting point—Dry at between 188 and 194 ℃ (with decomposition), and heat at a rate of about 3 ℃ per minute from 180 ℃.
It is affected by light.

Identification (1) Add 3 drops of fuming nitric acid to 1 mg of Atropine Sulfate Hydrate, evaporate it to dryness on a steam bath, dissolve the residue in 1 mL of *N*,*N*-dimethyl formamide, and add 5 to 6 drops of tetraethylammonium hydroxide TS; the resulting solution exhibits a purple color.

(2) Add 4 to 5 drops of hexchloroplatinic(IV) acid TS to 2 mL of aqueous solution of Atropine Sulfate Hydrate (1 in 50); a non-glossy yellowish white precipitate is formed.

(3) Add 2 mL of ammonia TS to 5 mL of aqueous solution of Atropine Sulfate Hydrate (1 in 25), allow to stand for 2 to 3 minutes, then filter the precipitated crystals, wash it with water, and dry for 4 hours in a desiccator (in vacuum, silica gel); the melting point is 115 ℃ - 118 ℃.

(4) An aqueous solution of Atropine Sulfate Hydrate (1 in 20) responds to the Qualitative Analysis for sulfate.

Optical rotation $[\alpha]_D^{25}$: Between -0.60 and +0.05° (1 g, water, 20 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Atropine Sulfate Hydrate in 10 mL of water; the solution is clear and colorless.

(2) ***Sulfate***—Dissolve 1.0 g of Atropine Sulfate Hydrate in 20 mL of water, add 0.30 mL of 0.02 mol/L sodium hydroxide TS and 1 drop of methyl red - methylene blue TS; the color of the solution is green.

(3) ***Related substances***—Dissolve 0.25 g of Atropine Sulfate Hydrate in 1 mL of diluted hydrochloric acid (1 in 10), then add water to make 15 mL and use this solution as the test solution.

(i) Add 2 to 3 drops of hexachloroplatinic(IV) acid TS to 5 mL of the test solution; no precipitate forms.

(ii) Add 2mL of ammonia TS to 5 mL of the test solution and shake vigorously; the resulting solution is not more turbid than the following control solution.

Control solution—Add 6 mL of dilute nitric acid and water to 0.30 mL of 0.01 mol/L hydrochloric acid to make 50 mL, then add 1 mL of silver nitrate TS; take 7mL of the resulting solution and allow to stand for 5 minutes.

(4) **Hyoscyamine**—Weigh accurately about 1 g of Atropine Sulfate Hydrate, previously dried, and dissolve in water to make exactly 10 mL. Measure the optical rotation at the layer length of 100 mm with this solution; $[\alpha]_D^{20}$ is between -0.60° and + 0.10°.

(5) ***Readily carbonizable substances***—Proceed with 0.20 g of Atropine Sulfate Hydrate and perform the test. The color of this solution is not more intense than that of the Matching Fluid for Color A.

Water Between 2.0% and 4.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately about 0.25 g of Atropine Sulfate Hydrate, add 30 mL of acetic acid(100), dissolve by heating, if necessary, and titrate with 0.05 mol/L perchloric acid VS (indicator: 3 drops of methylrosaniline chloride TS) The endpoint of the titration is when the violet color of this solution turns to blue and then finally to bluish green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L perchloric acid VS
= 33.841 mg of $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4$

Packaging and storage Preserve in light-resistant, tight containers.

Atropine Sulfate Injection
아트로핀황산염 주사액

Atropine Sulfate Injection is a water-based injection and contains NLT 93.0% and NMT 107.0% of the labeled amount of atropine sulfate hydrate [$(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$: 694.83].

Method of preparation Prepare as directed under Injections, with Atropine Sulfate Hydrate.

Description Atropine Sulfate Injection occurs as a clear, colorless liquid.

pH—Between 4.0 and 6.0.

Identification (1) Take an amount of Atropine Sulfate Injection equivalent to 1 mg of atropine sulfate hydrate according to the labeled amount, evaporate it to dryness on a steam bath, and perform the test as directed under the Identification (1) of Atropine Sulfate Hydrate.

(2) Pipet an amount of Atropine Sulfate Injection equivalent to 5 mg of atropine sulfate hydrate according to the labeled amount, evaporate to it dryness on a steam bath, cool, dissolve the residue in 1 mL of ethanol(95) and use this solution as the test solution. If insoluble solids remain, pulverize the residue and allow to stand, and use the clear supernatant as the test solution. Separately, weigh 10 mg of atropine sulfate hydrate RS, dissolve in 2 mL of ethanol(95), and use this solution as the standard

solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of acetone, water and ammonia water(28) (90 : 7 : 3) as the developing solvent to a distance of about 10 cm, and dry the plate at 80 °C for 10 minutes. After cooling, spray evenly Dragendorff TS for spraying; the spots from the test solution and the standard solution exhibit an orange color, and have the same R_f value.

(3) Atropine Sulfate Injection responds to the Qualitative Analysis for sulfate.

Sterility Meets the requirements.

Bacterial endotoxins Less than 75 EU per mg of atropine sulfate hydrate.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Atropine Sulfate Injection equivalent to about 5 mg of atropine sulfate hydrate $[(C_{17}H_{23}NO_3)_2{\cdot}H_2SO_4{\cdot}H_2O]$, add exactly 3 mL of the internal standard solution, then add water to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg of atropine sulfate RS (measure loss on drying beforehand according to the same conditions as for atropine sulfate) and dissolve in water to make exactly 50 mL. Pipet 10 mL of this solution, add 3 mL of the internal standard solution, add water to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of atropine to that of the internal standard, respectively.

Amount (mg) of atropine sulfate hydrate $[(C_{17}H_{23}NO_3)_2{\cdot}H_2SO_4{\cdot}H_2O]$ = Amount (mg) of atropine sulfate RS, calculated on the dried basis $\times \frac{Q_T}{Q_S} \times \frac{1}{5} \times 1.0266$

Internal standard solution—Etilefrine hydrochloride solution (1 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 0.4 g of sodium lauryl sulfate in 500 mL of diluted phosphoric acid (1 in 1000), and adjust pH to 3.0 using sodium hydroxide TS.

Flow rate: Adjust the flow rate so that the retention time of atropine is about 16 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the internal standard and atropine are eluted in this order with the resolution being NLT 3.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio of atropine to the internal standard is NMT 1.5%.

Packaging and storage Preserve in light-resistant, hermetic containers.

Atropine Sulfate Tablets
아트로핀황산염 정

Atropine Sulfate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of atropine sulfate hydrate $[(C_{17}H_{23}NO_3)_2{\cdot}H_2SO_4{\cdot}H_2O$: 694.83].

Method of preparation Prepare Atropine Sulfate Tablets as directed under Tablets, with Atropine Sulfate Hydrate.

Identification (1) Weigh an amount of Atropine Sulfate Tablets, previously powdered, equivalent to 1 mg of atropine sulfate hydrate, according to the labeled amount, add 1 drop of ammonia water(28) and 2 mL of chloroform and mix. Take the chloroform layer separately and evaporate the chloroform on a steam bath. With the residue, perform the test as directed under the Identification (1) of Atropine Sulfate Hydrate.

(2) Weigh an amount of Atropine Sulfate Tablets, previously powdered, equivalent to 5 mg of atropine sulfate hydrate, according to the labeled amount, add 5 mL of ethanol(95), shake to mix, filter using a glass filter, and use the filtrate as the test solution. Separately, weigh 50 mg of atropine sulfate hydrate RS, dissolve in ethanol(95) to make 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 50 μL of the test solution and 10 μL of the standard solution on a plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform and diethylamine (9 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray hexachloroplatinic(IV) acid-potassium iodide TS evenly

on the plate; the spots obtained from the test solution and the standard solution exhibit a violet color and their R_f values are the same.

(3) Atropine Sulfate Tablets responds to the Qualitative Analysis for sulfate.

Disintegration Meets the requirements. However, the time span of test is 15 minutes.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Azathioprine Tablets, and powder. Weigh accurately an amount equivalent to about 1.0 mg of atropine sulfate hydrate [$(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$], put it into a separatory funnel containing 5 mL of buffer solution, pH 9.0, and add 2.0 mL of internal standard solution. Add 1 mol/L sodium hydroxide TS to adjust the pH to 9.0, and extract twice with 10 mL each of dichloromethane. Filter the dichloromethane layer through 1 g of anhydrous sodium sulfate on a pledget of absorbent cotton, evaporate the filtrate with the aid of nitrogen current to dryness, dissolve the residue in 2.0 mL of dichloromethane and use this solution as the test solution. Separately, weigh accurately about 10 mg of Atropine Sulfate Hydrate RS, previously dried at 120 ºC for 4 hours and dissolve in water to make exactly 100 mL. Prepare this solution before use. Transfer exact 10 mL of this solution to a separator, add 2.0 mL of the internal standard solution and 5.0 mL of a pH 9.0 buffer solution and adjust to a pH of 9.0 with 1 mol/L sodium hydroxide. Extract with two 10 mL volumes of dichloromethane, filter the extracts through 1 g of anhydrous sodium sulfate on a pledget of absorbent cotton, evaporate the filtrate with the aid of nitrogen current to dryness, dissolve the residue in 2.0 mL of dichloromethane and use this solution as the standard solution. Perform the test with 1 µL each of the test and the standard solution as directed under Gas Chromatography according to the following conditions and calculate the ratios, Q_T and Q_S, of the peak area of atropine sulfate to that of the internal standard for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of atropine sulfate hydrate } [(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O = \frac{W}{10} \times \frac{Q_T}{Q_S} \times 1.0266$$

W: Amount (mg) of RS, calculated on the dried basis

Internal standard solution—Homatropine hydrobromide solution (5 in 10000); prepare this solution before use.

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A column about 2 mm in internal diameter and about 1.8 m in length, packed with diatomaceous earth for gas chromatography, coated at a rate of 3% with 50% phenyl and 50% methylpolysiloxane.

Column temperature: 225 °C

Carrier gas: Nitrogen

Flow rate: 25 mL/min

System suitability

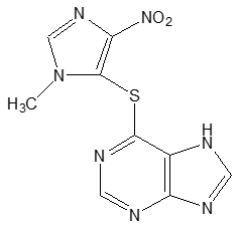
System performance: When the procedure is run with 1 µL of the standard solution under the above operating conditions with the resolution. being NLT 4.0 and with the symmetry factor being NMT 2.0.

System repeatability: Repeat the test 6 times with 1 µL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio is NMT 2.0%.

pH 9.0 Phosphate buffer solution—Dissolve 34.8 g of dibasic potassium phosphate in 900 mL of water, and add 3 mol/L hydrochloric acid TS or 1 mol/L sodium hydroxide TS to adjust the pH to 9.0.

Packaging and storage Preserve in light-resistant, tight containers.

Azathioprine
아자티오프린



$C_9H_7N_7O_2S$: 277.26

6-[(1-methyl-4-nitro-1*H*-imidazol-5-yl)sulfanyl]-7*H*-purine [*446-86-6*]

Azathioprine, when dried, contains NLT 98.5% and NMT 101.0% of azathioprine ($C_9H_7N_7O_2S$).

Description Azathioprine occurs as pale yellow crystals or a crystalline powder. It is odorless.

It is sparingly soluble in *N*,*N*-dimethylformamide and pyridine, very slightly soluble in water and ethanol(99.5), and practically insoluble in chloroform and ether.

It dissolves in sodium hydroxide TS or ammonia TS.

It is gradually colored by light.

Melting point—About 240 °C (with decomposition).

Identification (1) Add 50 mL of water to 10 mg of Azathioprine, and dissolve by warming. To 5 mL of this solution, add 1 mL of dilute hydrochloric acid and 10 mg of zinc powder, and allow to stand for 5 minutes; the resulting solution exhibits a yellow color. Filter this solution; the filtrate responds to the Qualitative Analysis for primary aromatic amines. However, the solution exhibits a red color.

(2) Add 50 mL of water to 10 mg of Azathioprine, and dissolve by warming. To 1 mL of this solution, add 0.5 mL of phosphotungstic acid TS and 0.5 mL of dilute hydrochloric acid; a white precipitate forms.

(3) Prepare the test solution by proceeding with 30 mg of Azathioprine as directed under the Oxygen Flask Combustion, using 20 mL of water as the absorbent. The test solution responds to the Qualitative Analysis (1) for sulfate.

(4) Dissolve 10 mg of Azathioprine in 2 mol/L hydrochloric acid TS to make 100 mL. To 5 mL of this solution, add water to make 50 mL, and determine the absorption spectrum of the resulting solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 278 nm and 282 nm.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Azathioprine in 50 mL of *N*,*N*-dimethylformamide; the solution shows a pale yellow color and is clear.

(2) ***Acid or alkali***—Add 100 mL of water to 2.0 g of Azathioprine, shake well to mix for 15 minutes, centrifuge for 5 minutes at 10,000 revolutions per minute, and filter. Discard the first 20 mL of the filtrate, add 2 drops of methyl red TS to 40 mL of the subsequent filtrate, and use this solution as the test solution (i) To 20 mL of the test solution, add 0.10 mL of 0.02 mol/L hydrochloric acid; the solution exhibits a red color.

(ii) To 20 mL of the test solution, add 0.10 mL of 0.02 mol/L sodium hydroxide; the solution exhibits a yellow color.

(3) ***Sulfate***—To 25 mL of the filtrate obtained in (2), add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid (NMT 0.038%).

(4) ***Heavy metals***—Proceed with 2.0 g of Azathioprine according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Arsenic***—Prepare the test solution with 1.0 g of Azathioprine according to Method 3 and perform the test (NMT 2 ppm).

(6) ***Related substances***—Add 80 mL of the mobile phase to 10 mg of Azathioprine, dissolve by warming, cool, add the mobile phase to make 100 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the sum of pear areas other than azathioprine from the test solution is not larger than 1/2 of the peak area of azathioprine from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 296 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Adjust the pH of 0.05 mol/L potassium dihydrogen phosphate TS (1 in 2) to 2.5 with diluted phosphoric acid (3 in 2000). Add 200 mL of methanol to 800 mL of this solution.

Flow rate: Adjust the flow rate so that the retention time of azathioprine is about 8 minutes.

System suitability

Detection sensitivity: Pipet 5 mL of the standard solution and add water to make exactly 50 mL. Adjust the detection sensitivity so that the peak area of azathioprine obtained from 20 μL of this solution is 8 to 12% of the peak area of azathioprine obtained from the standard solution.

System performance: Dissolve 0.010 g of Azathioprine in 80 mL of water by warming, cool, and add water to make 100 mL. To 2 mL of this solution, add 2 mL of a solution, separately prepared by dissolving 60 mg of benzoic acid in 3 mL of methanol and diluting with water to make 10 mL, and add the mobile phase to make 25 mL. Proceed with 20 μL of this solution under the above operating conditions; azathioprine and benzoic acid are eluted in this order with the resolution being NLT 9.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of azathioprine is NMT 2.0%.

Time span of measurement: About 3 times the retention time of azathioprine after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 °C, 5 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Azathioprine, previously dried, add 80 mL of *N*,*N*-dimethylformamide, and dissolve by warming. After cooling, titrate with 0.1 mol/L tetramethylammonium hydroxide VS (indicator: 1 mL of thymol blue-dimethylformamide TS). The endpoint of the titration is when the color of the solution changes from yellow through yellowish green to bluish green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L tetramethylammonium hydroxide VS
= 27.726 mg of $C_9H_7N_7O_2S$

Packaging and storage Preserve in light-resistant, well-closed containers.

Azathioprine Tablets
아자티오프린 정

Azathioprine Tablets contain NMT 95.0% and NLT 105.0% of the labeled amount of azathioprine ($C_9H_7N_7O_2S$: 277.26).

Method of preparation Prepare Azathioprine Tablets as directed under Tablets, with Azathioprine.

Identification (1) Weigh an amount of Azathioprine Tablets, previously powdered, equivalent to 10 mg of azathioprine, according to the labeled amount, add 50 mL of water, and warm. Shake well to mix, and filter. Perform the test with 5 mL of the filtrate as directed under the Identification (1) of Azathioprine.

(2) With 1 mL of the filtrate from (1), perform the test as directed under the Identification (2) of Azathioprine.

(3) Determine the absorption spectrum of the test solution obtained from the Assay as directed under Ultraviolet-visible Spectroscopy: it exhibits a maximum between 278 nm and 282 nm.

(4) Weigh an amount of Azathioprine Tablets, previously powdered, equivalent to 0.1 g of azathioprine, according to the labeled amount, add 10 mL of ammonia water(28) in methanol (1 in 10). Shake well to mix, filter, and use the filtrate as the test solution. Separately, dissolve 0.1 g of azathioprine RS in 10 mL of ammonia water(28) in methanol (1 in 10), and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, ammonia water(28) in methanol (1 in 10), *n*-butyl formate and 1,2-dichloroethane (15 : 10 : 5 : 2) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values of the spots obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

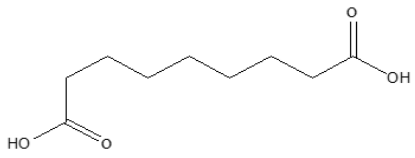
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Azathioprine Tablets, and powder. Weigh accurately an amount equivalent to about 0.1 g of azathioprine ($C_9H_7N_7O_2S$), add 20 mL of dimethylsulfoxide, shake well to mix, add 0.1 mol/L hydrochloric acid TS to make exactly 500 mL, and filter. Discard the first 20 mL of the filtrate, pipet 3 mL of the subsequent filtrate, add 0.1 mol/L hydrochloric acid TS to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of azathioprine RS, previously dried at 105 ℃ for 5 hours, dissolve in 20 mL of dimethylsulfoxide, and add 0.1 mol/L hydrochloric acid TS to make exactly 500 mL. Pipet 3 mL of this solution, add 0.1 mol/L hydrochloric acid TS to make exactly 100 mL, and use this solution as the standard solution. Perform the test with the test solution and standard solution as directed under the Ultraviolet-visible Spectroscopy and determine the absorbances, A_T and A_S, of each solution at the wavelength of 280 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of azathioprine } (C_9H_7N_7O_2S) = \text{Amount (mg) of azathioprine RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in light-resistant, tight containers.

Azelaic Acid
아젤라산



$C_9H_{16}O_4$: 188.22

Nonanedioic acid, [*123-99-9*]

Azelaic Acid contains NLT 98.0% and NMT 102.0% of azelaic acid ($C_9H_{16}O_4$), calculated on the anhydrous basis.

Description Azelaic Acid occurs as a white crystalline powder.
It is freely soluble in ethanol(95), methanol and hot water.

Identification Determine the absorption spectra of Azelaic Acid and azelaic acid RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 105 and 110 ℃.

Purity (1) ***Clarity and color of solution*—**Dissolve 5.0 g of Azelaic Acid in 25 mL of a mixture of tetrahydrofuran and methanol (7 : 3); the solution is colorless and clear.

(2) ***Heavy metals*—**Proceed with 1.0 g of Azelaic Acid as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances*—**Weigh 0.5 g of Azelaic Acid and place in a 50-mL round bottom flask, add 5 mL of toluene and 5.0 mL of boron trifluoride and methanol complex, and chill with a reflux condenser for 5 minutes.

Next, wash the inner wall of the condenser using 5.0 mL of toluene, add 5.0 mL of saturated sodium chloride solution, and shake vigorously to mix. Perform the test with 1 μL of the organic solvent layer as directed under the Gas Chromatography according to the following conditions, and determine each peak area by the automatic integration method; the respective related substances to the total peak area are NMT 2.0%.

Operating conditions

Detector: A flame ionization detector

Column: A glass column about 2 mm in internal diameter and about 1.2 m in length, packed with 125 μm to 149 μm diatomaceous earth for gas chromatography coated at 1% with 33% phenylmethylsilicone polymer.

Column temperature: Between 100 and 210 ℃.

Heating rate: 10 ℃/min.

Carrier gas: Nitrogen

(4) ***Acetone*—**Weigh 5.0 g of Azelaic Acid, add 5.0 mL of internal standard solution, then add dimethylformamide to make 100 mL, and use this solution as the test solution. Separately, weigh accurately 0.2 g of acetone, and add dimethylformamide to make 50 mL. Pipet 5.0 mL of this solution, add 5.0 mL of the internal standard solution, then add dimethylformamide to make 100 mL, and use this solution as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions. Determine the peak area ratios, Q_T and Q_S of acetone to the peak area of the internal standard for each solution; these are NMT 0.5%.

Amount (mg) of acetone in sample
= Amount (mg) of acetone RS × (Q_T / Q_S) × (1 / 10)

Internal standard solution—Solution of dimethylformamide in ethyl benzene (1 in 10000).

Operating conditions

Detector: A flame ionization detector

Column: A glass column about 4 mm in internal diameter and about 1.9 m in length, packed with 80 to 100 mesh diatomaceous earth for gas chromatography coated at 10% with polyethylene glycol 1500.

Column temperature: 85 ℃

Carrier gas: Nitrogen

Flow rate: 45 mL/min

Selection of column: Proceed with 1 μL of the standard solution according to the above conditions; acetone and ethyl benzene are eluted in this order and the peaks are completely separated.

Water NMT 0.5% (1 g, volumetric titration, direct titration).

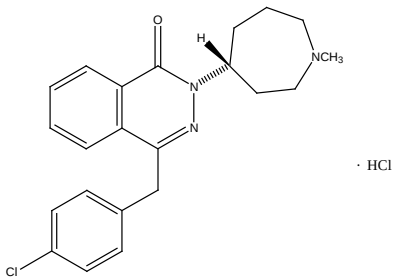
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 1 g of Azelaic Acid, and add 50 mL of a mixture of water and methanol (1 : 1), and dissolve by warming for 5 minutes on a steam bath. Cool and titrate with 0.5 mol/L potassium hydroxide-ethanol VS. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.5 mol/L potassium hydroxide-ethanol VS
= 47.06 mg of $C_9H_{16}O_4$

Packaging and storage Preserve in light-resistant, tight containers.

Azelastine Hydrochloride
아젤라스틴염산염



and enantiomer

Azelastine HCl $C_{22}H_{24}ClN_3O \cdot HCl$: 418.36

4-[(4-Chlorophenyl)methyl]-2-(1-methylazepan-4-yl)phthalazin-1-one hydrochloride [*79307-93-0*]

Azelastine Hydrochloride contains NLT 98.5% and NMT 101.0% of azelastine hydrochloride ($C_{22}H_{24}ClN_3O \cdot HCl$), calculated on the dried basis.

Description Azelastine Hydrochloride occurs as a white crystalline powder.

It is soluble in ethanol(99.5), slightly soluble in water and practically insoluble in ether, *n*-hexane or toluene.

Identification (1) Determine the infrared spectra of Azelastine Hydrochloride and azelastine hydrochloride RS as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) A solution of Azelastine Hydrochloride (1 in 50) responds to the Qualitative Analysis (2) for chloride.

Optical rotation $[\alpha]_D^{20}$: Between -0.05 and +0.05° (after drying, 1.0 g, dichloromethane, 20 mL, 100 mm).

Purity (1) ***Acidity and alkali*—**Add 0.2 mL of bromothymol blue TS to 10 mL of aqueous solution of Azelastine Hydrochloride (1 in 100), and then add 0.1 mol/L hydrochloric acid or 0.1 mol/L sodium hydroxide; the solution does not change in color.

(2) ***Heavy metals*—**Proceed with 1.0 g of Azelastine Hydrochloride according to Method 2 and perform the

test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic*—**Proceed with 1.0 g of Azelastine Hydrochloride according to Method 3 and perform the test (NMT 2 ppm).

(4) ***1-methyl-4-(2-benzoylhydrazino)azepan*—** Weigh accurately 0.1 g of Azelastine Hydrochloride, dissolve in 12 mL of methanol, and add water to make exactly 20 mL. Use this solution as the test solution. Separately, weigh accurately 5.0 mg of 1-methyl-4-(2-benzoylhydrazino) azepan RS, dissolve in 60% methanol to make exactly 100 mL, then add 60% methanol to 5.0 mL of the solution to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. The area of the peak for 1-methyl-4-(2-benzoylhydrazino)azepan from the test solution is not greater than the major peak area from the standard solution (NMT 0.1%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: Dissolve sodium octanesulfonate in a mixture of methanol, water and acetic acid(100) (60 : 40 : 1) to make 0.02 mol/L.

Flow rate: 1.5 mL/min

(5) ***Related substances*—**Weigh 50 mg of Azelastine Hydrochloride, dissolve exactly in 100 mL of the mobile phase, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; each peak area other than the peak of azelastine from the test solution is not greater than 1/10 of the peak area of azelastine from the standard solution. Additionally, the sum of the peaks other than the peak of azelastine in the test solution is not greater than 1/2 of the peak area of azelastine from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of water, acetonitrile and perchloric acid (660 : 340 : 1).

Flow rate: Adjust the flow rate so that the retention time of azelastine is about 10 minutes.

System suitability

Test for required detectability: Pipet 5 mL of the standard solution, add the mobile phase to make exactly 50 mL, and use this solution as the system suitability solution. Confirm that the peak area of azelastine obtained from 20 μL of this solution is within the range between 7% and 13% of the peak area of azelastine in the standard solution.

System performance: Proceed with 20 μL of the standard solution under the above operating conditions; the number of theoretical plates and symmetry factor of the peak of azelastine are NLT 5000 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions; the relative standard deviation of the peak area of azelastine is NMT 1.0%.

Loss on drying NMT 1.0% (1 g, 105 ℃, constant mass).

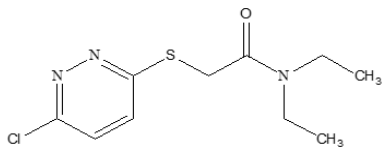
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Azelastine Hydrochloride, dissolve in 5 mL of anhydrous formic acid, add 30 mL of acetic anhydride and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 41.84 mg of $C_{22}H_{24}ClN_3O \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Azintamide
아진타미드



$C_{10}H_{14}ClN_3OS$: 259.76

2-[(6-Chloro-3-pyridazinyl)thio]-*N*,*N*-diethylacetamide, [*1830-32-6*]

Azintamide contains NLT 98.0% and NMT 101.0% of azintamide ($C_{10}H_{14}ClN_3 \cdot 2HCl$: 259.76), calculated on the anhydrous basis.

Description Azintamide occurs as a white, crystalline powder. It is odorless.

It is freely soluble in alcohol, acetone and benzene, and slightly soluble in water.

Melting point—Between 98 and 100 ℃.

Identification (1) Use a solution of Azintamide in 4% ethanol as the test solution. Use 4% ethanol solution of azintamide RS as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Next, develop the plate with a mixture of chloroform and ethanol(95) (20 : 1) as the developing solvent, and air-dry the plate. Spray with a mixture of 10 mL of 0.1% potassium permanganate solution and 1 mL of 0.1 mol/L sodium hydroxide or expose to ultraviolet rays (main wavelength 250 nm); the spot of the test solution exhibits an Rf value and color corresponding to that of the standard solution.

(2) Suspend a small amount of Azintamide in 5 mL of water, add dimethylaminobenzaldehyde TS (saturated solution of 1% hydrochloric acid), and boil; the solution changes color.

Purity (1) ***Clarity and color of solution***—The color of a 10% ethanol solution of Azintamide is not more intense than the color of a mixture prepared by adding 15 μL of the standard iron(III) chloride solution and 5 μL of the standard ferric chloride cobalt solution to 10 mL of 1% hydrochloric acid.

(2) ***Heavy metals***—Proceed with 1.0 g of Azintamide and perform the test according to Method 2. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Sulfate***—Proceed with 1.0 g of Azintamide, and perform the test according to Sulfate. Prepare the control solution with 0.63 mL of 0.005 mol/L sulfuric acid (NMT 0.03%).

(4) ***Chloride***—Dissolve 2.0 g of Azintamide in water to make 100 mL; take 25 mL of this solution, and perform the test according to the Chloride. Prepare the control solution with 0.5 mL of 0.01 mol/L hydrochloric acid (NMT 0.035%).

(5) ***Other organic substances***—Perform the test according to the Identification (1); there are no spots other than the principal spot (amount spotted: 0.5 μL).

Water NMT 0.5% (1 g, volumetric titration, direct titration).

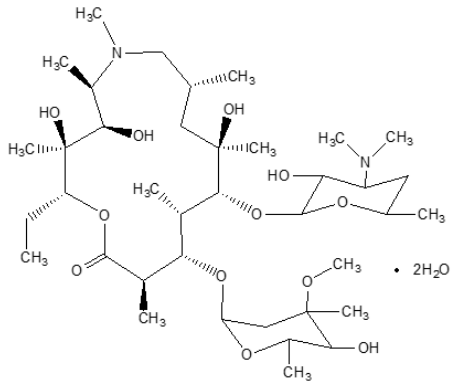
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Azintamide, add ethanol(95), and shake to dissolve, and then add ethanol(95) to make exactly 250 mL. Pipet 5 mL of this solution, and add ethanol(95) to make exactly 100 mL. Pipet 25 mL of this solution, add ethanol(95) to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.2 g of azintamide RS, proceed as directed within the same manner as the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, at 250 nm as directed under the Ultraviolet-visible Spectroscopy, using ethanol(95) as the control solution.

Amount (mg) of azintamide ($C_{10}H_{14}ClN_3OS$)
= Amount (mg) of azintamide RS × (A_T / A_S)

Packaging and storage Preserve in tight containers.

Azithromycin Hydrate
아지트로마이신수화물



Azithromycin $C_{38}H_{72}N_2O_{12}\cdot 2H_2O$: 785.02
(2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-2-Ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo-11-{[3,4,6-trideoxy-3-(dimethyl-amino)-β-D-xylo]oxy}-1-oxa-6-azacyclo-pentadec-13-yl 2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranoside dihydrate [*117772-70-0*]

Azithromycin Hydrate is a derivative of erythromycin.

Azithromycin Hydrate contains NLT 945 μg and NMT 1030 μg (potency) of azithromycin ($C_{38}H_{72}N_2O_{12}$: 748.98) per mg, calculated on the anhydrous basis.

Description Azithromycin Hydrate occurs as a white crystalline powder.
It is freely soluble in methanol or ethanol(99.5) and practically insoluble in water.

Identification Determine the infrared spectra of Azithromycin Hydrate and azithromycin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit the same intensities of absorption at the same wave numbers.

Crystallinity Meets the requirements, except where it is labeled as amorphous, most of the particles do not exhibit birefringence and extinction positions.

Optical rotation $[\alpha]_D^{20}$: Between -45° and -49° (0.4 g, calculated on the anhydrous ethanol basis, ethanol(99.5), 20 mL, 100 mm).

pH Dissolve 0.2 g of Azithromycin Hydrate in 10 mL of 50% methanol solution; the pH of this solution is between 9.0 and 11.0.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Azithromycin Hydrate and perform the test according to Method 2. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—(i) Total related substances: Test as directed under the Assay. The test solution and operating conditions are as follows: Weigh accurately about 33 mg of Azithromycin Hydrate, dissolve by adding 5 mL of acetonitrile, and then add a mixture of 0.02 mol/L potassium dihydrogen phosphate solution and acetonitrile (71 : 29) adjusted the pH to 8.0 with 10 mol/L potassium hydroxide TS to make 100 mL. Use this solution as the test solution. Take 50 μL of the test solution and perform the test as directed under the Liquid Chromatography according to the following conditions, and measure the peak areas of azithromycin and the respective related substances (total related substances NMT 5.5%).

$$\text{Total content (\%) of related substances} = \frac{Sum\ of\ total\ peak\ areas\ other\ than\ the\ principal\ peak}{Sum\ of\ total\ peak\ areas} \times 100$$

Operating conditions

Mobile phase: Adjust the pH of the mixture of 0.02 mol/L potassium dihydrogen phosphate solution and acetonitrile (75 : 25) to 11.0 using 10 mol/L potassium hydroxide TS.

Flow rate: 1.2 mL/min

Time span of measurement: About 80 min.

(ii) Erythromycin A iminoether: Weigh an appropriate amount of Azithromycin Hydrate, dissolve in a mixture of chloroform and methanol (1 :1) to make 25 mg per mL, and use this solution as the test solution. Separately, weigh accurately 2.5 mg of erythromycin A iminoether RS, dissolve in a mixture of chloroform and methanol (1 : 1) to make 0.125 mg per mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 50 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, hexane and diethylamine (15 : 5 : 2) as the developing solvent, then heat the plate at 100 ℃ for 10 minutes. Spray evenly a solution of 1.5 mL sulfuric acid added to 3 g of vanillin dissolved in 100 mL of ethanol(95), then heat again at 100 ℃ for 10 minutes; the spots other than the principal spot from the test solution are not more intense than the principal spot from the standard solution.

Water Between 4.0% and 5.0% (0.4 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg (potency) each of Azithromycin Hydrate and azithromycin RS, dissolve each in a mixture of methanol and water (4 : 1), add exactly 2 mL each of internal standard solution, and then add a mixture of methanol and water (4 : 1) to make 50 mL. Use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios of the peak area, Q_T and Q_S, of azithromycin to that of the internal standard.

$$\text{Potency (μg) of azithromycin } (C_{38}H_{72}N_2O_{12}) = \text{Potency (μg) of azithromycin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of 4,4'-bis(diethylamino)benzophenone in methanol (3 in 8000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 50 °C.

Mobile phase: Dissolve 1.11 g of potassium dihydrogen phosphate and 5.88 g of dibasic potassium phosphate in 750 mL of water, adjust pH to 7.5 with potassium hydroxide TS, then add water to make 1000 mL. Add 800 mL of methanol to 200 mL of this solution.

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the internal standard and azithromycin are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions under the above operating conditions; the relative standard deviation of the peak area ratios of azithromycin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Azithromycin for Syrup
시럽용 아지트로마이신

Azithromycin for Syrup is a preparation for Syrup, which is suspended before use, and contains NLT 90.0% and NMT 120.0% of the labeled amount of Azithromycin ($C_{38}H_{72}N_2O_{12}$: 748.99).

Method of preparation Prepare as directed under Syrups, with Azithromycin Hydrate.

Identification (1) The retention time of the major peak obtained in the test solution corresponds to that in the standard solution, as obtained in the Assay.

(2) Weigh accurately an appropriate amount each of the contents of Azithromycin for Syrup and azithromycin RS, dissolve in a mixture of chloroform and methanol (1 : 1) to obtain a solution containing 1 mg (potency) per mL, and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 50 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of hexane, ethyl acetate and diethylamine (150 : 50 : 20), and heat the plate at 100 ℃ for 10 minutes. Then, dissolve 3 g of vanillin in 100 mL of ethanol(95). Spray the solution which contains 1.5 mL of sulfuric acid and 100 mL of ethanol with 3 g of vanillic acid dissolved in it evenly on the plate and heat the plate again at 100 ℃ for 10 minutes; the black spot of the test solution shows the same Rf value as the spot obtained from the standard solution.

pH Dissolve an amount of Azithromycin for Syrup, equivalent to 0.4 g (potency) of azithromycin in 10 mL of water; the pH of the solution is 9.0 to 11.0.

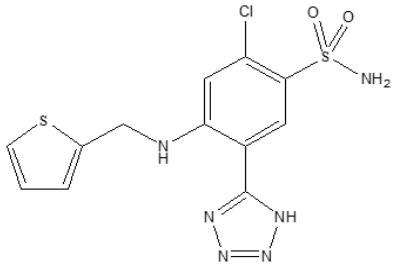
Water NMT 1.5% (0.5 g, volumetric titration, direct titration).

Uniformity of dosage units (distribution) Meets the requirements.

Assay Proceed as directed under the Assay under Azithromycin Hydrate. Weigh accurately a suitable amount of Azithromycin for Syrup, equivalent to 50 mg (potency) of azithromycin, dissolve in a mixture of methanol and water (4 : 1), add exactly 2 mL of the internal standard solution, and add a mixture of methanol and water (4 : 1) to make exactly 50 mL. Use this solution as the test solution. Separately, weigh accurately 50 mg (potency) of azithromycin RS, dissolve in a mixture of methanol and water (4 : 1), add exactly 2 mL of the internal standard solution, and add a mixture of methanol and water (4 : 1) to make exactly 50 mL. Use this solution as the standard solution.

Packaging and storage Preserve in tight containers.

Azosemide
아조세미드



$C_{12}H_{11}ClN_6O_2S_2$: 370.84

2-Chloro-5-(1*H*-tetrazol-5-yl)-4-[(2-thienylmethyl)amino]benzenesulfon amide; 2-Chloro-5-(2*H*-tetrazol-5-yl)-N^4-2-thenylsulfanilamide, [*27589-33-9*]

Azosemide, when dried, contains NLT 99.0% and NMT 101.0% of azosemide ($C_{12}H_{11}ClN_6O_2S_2$: 370.84).

Description Azosemide occurs as a white to yellowish white crystalline powder.
It is odorless and has a bitter taste.
It is freely soluble in dimethyl formamide, slightly soluble in methanol or ethanol(95), very slightly soluble in ether, and practically insoluble in water.
It dissolves in sodium hydroxide TS.
It is gradually changed to yellow by light.

Melting point—About 220 ℃ (with decomposition).

Identification (1) Weigh 10 mg of Azosemide, and dissolve in 10 mL of methanol, then add 10 mL of 2 mol/L hydrochloric acid to 1 mL of this solution, heat for 15 minutes on a steam bath with a reflex condenser, and cool; the solution responds to the Qualitative Analysis for primary aromatic amines. However, the solution exhibits a red to reddish purple color.

(2) Add 0.5 g of sodium carbonate to 0.1 g of Azosemide, mix, and carefully dissolve. The gas generated changes moistened red litmus paper to blue. Break down the cooled melt with a rod, add 10 mL of water, and mix, then filter. Take 4 mL of the filtrate, and add 2 drops of hydrogen peroxide(30), 5 mL of dilute hydrochloric acid (1 in 9) and 2 to 3 drops of barium chloride TS; a white precipitate is formed.

(3) Take 4 mL of the filtrate of (2), and add 5 mL of dilute nitric acid and 3 drops of silver nitrate TS; a white precipitate is formed.

(4) Dissolve 30 mg of Azosemide in dilute sodium hydroxide TS to make 100 mL. Pipet 2 mL of this solution, add dilute sodium hydroxide TS to make 100 mL, and determine the absorption spectra as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima

between 235 nm and 237 nm, between 272 nm and 276 nm, and between 324 nm and 330 nm.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Azosemide in 50 mL of dilute sodium hydroxide TS; the solution is colorless to light yellow and clear. Determine the absorbance using this solution at wavelength 400 nm; it is NMT 0.1.

(2) ***Chloride***—Weigh 1.0 g of Azosemide, and add 60 mL of dilute sodium hydroxide TS, warm to dissolve, then add 0.5 mL nitric acid, and filter. Pipet 30 mL of the filtrate, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test as directed in Chloride. Prepare the control solution by adding 6 mL of dilute nitric acid and water to 0.45 mL of 0.01 mol/L hydrochloric acid solution to make 50 mL (NMT 0.032%).

(3) ***Sulfate***—Weigh 0.15 g of Azosemide, and dissolve in 10 mL of dilute sodium hydroxide TS, then add 1 mL nitric acid, and filter. Add 2 mL of barium chloride TS to the filtrate, and allow it to stand for 10 minutes; the solution does not become turbid.

(4) ***Heavy metals***—Proceed with 1.0 g of Azosemide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(5) ***Arsenic***—Proceed with 2.0 g of Azosemide as directed under Method 3 under the Arsenic and perform the test (NMT 1 ppm).

(6) ***Primary aromatic amines***—Weigh 20 mg of Azosemide, dissolve in 5 mL of dimethylformamide, add 12 mL of water, 1.0 mL of sodium nitrite solution (1 in 200) and 2.0 mL of dilute hydrochloric acid (1 in 10), and shake to mix while cooling in iced water. Allow it to stand for 3 minutes, add 1.0 mL of ammonium sulfamate TS, shake thoroughly to mix, and then allow to stand for 3 minutes. Add 1.0 mL of *N*-naphthylethylenediamine hydrochloride (1 in 200), shake well to mix, add dimethylformamide to make exactly 50 mL, and use this solution as the test solution. Separately, take 5 mL of dimethylformamide, cool, and then proceed in the same way as the test solution. Use this solution as the control solution. Perform the test as directed under the Ultraviolet-visible Spectroscopy and determine the absorbance at the wavelength of 540 nm within 60 minutes; the absorbance is NMT 0.15 (NMT 0.34%).

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

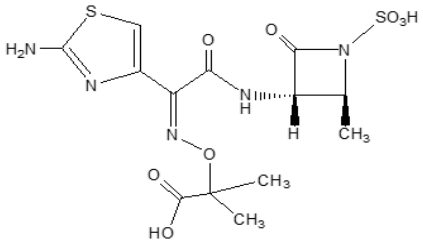
Assay Weigh accurately about 0.6 g of Azosemide, previously dried, dissolve in 50 mL of dimethylformamide, and titrate with 0.1 mol/L potassium hydroxide-ethanol VS (indicator: 10 drops of thymol blue-dimethylformamide TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L potassium hydroxide-ethanol VS

= 37.08 mg of $C_{12}H_{11}ClN_6O_2S_2$

Packaging and storage Preserve in light-resistant, tight containers.

Aztreonam
아즈트레오남



$C_{13}H_{17}N_5O_8S_2$: 435.43

2-({[(1*Z*)-1-(2-Amino-1,3-thiazol-4-yl)-2-{[(2*S*,3*S*)-2-methyl-4-oxo-1-sulfoazetidin-3-yl]amino}-2-oxoethylidene]amino}oxy)-2-methyl-propanoic acid [*78110-38-0*]

Aztreonam contains NLT 920 μg and NMT 1030 μg (potency) of aztreonam ($C_{13}H_{17}N_5O_8$: 435.43) per mg, calculated on the anhydrous basis.

Description Aztreonam occurs as a white to yellowish white crystalline powder.
It is freely soluble in dimethylsulfoxide, slightly soluble in water or methanol, and very slightly soluble in ethanol(95).

Identification (1) Determine the absorption spectra of aqueous solutions of Aztreonam and aztreonam RS (3 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelength.

(2) With deuterated methyl sulfoxide solution of Aztreonam (1 in 10), measure ^1H according to Nuclear Magnetic Resonance Spectroscopy; multiplet signals are exhibited at around 1.5 ppm and singlet signals are exhibited at around 7.0 ppm, and the area intensity ratio of each signal is 9 : 1.

Optical rotation $[\alpha]_D^{20}$: Between -26° and -32° (0.25 g calculated on the anhydrous basis, 50 mL of water, 100 mm).

pH Dissolve 0.1 g (potency) of Aztreonam in 20 mL of water; the pH of this solution is between 2.2 and 2.8.

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g of Aztreonam in 20 mL of water; the solution is clear, and colorless to pale yellow.

(2) ***Heavy metals***—Proceed with 2.0 g of Aztreonam according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard

solution (NMT 10 ppm).

(3) ***Arsenic***—Prepare the test solution with 1.0 g of Aztreonam according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Weigh accurately about 40 mg (potency) of Aztreonam, dissolve in water to make 100 mL, and use this solution as the test solution. Pipet 2 mL of this solution, dissolve in the water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions. Determine the peak area of each peak from the test solution and the standard solution; the area of each peak other than for aztreonam in the test solution is not greater than the peak area for aztreonam in the standard solution. The total area of the peaks other than the peak of aztreonam from the test solution is not greater than 2.5 times the peak area of aztreonam from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed under the operating conditions in the Assay.

System suitability

Test for required detectability: Pipet 5 mL of the standard solution and add water to make exactly 10 mL. Use this solution as the system suitability solution. Pipet 1 mL of the system suitability solution and add water to make exactly 10 mL; confirm that the peak area of aztreonam from 25 μL of this solution is 7% to 13% of the peak area of aztreonam from the system suitability solution.

Detection sensitivity: Adjust so that the height of the aztreonam peak is 10 mm to 20 mm when testing using 25 μL of the standard solution.

System performance: Proceed with 25 μL of the standard solution of the Assay according to the above conditions; the internal standard and aztreonam are eluted in this order with the resolution being NLT 4.

System repeatability: Repeat the test 6 times with 25 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area for aztreonam is NMT 2.0%.

Time span of measurement: About 4 times the retention time of aztreonam after the solvent peak

Water NMT 2.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Sterility It meets the requirements when used in a sterile preparation (excluding cases wherein a terminal sterilization step is included in the preparation process for the sterile preparation). Provided, dissolve 8g of arginine in 200 mL of washings, heat, and autoclave at 121 ℃, and then cool. To this solution, add 10.0 g of Aztreonam and use this solution as the test solution.

Bacterial endotoxins Less than 0.10 EU per mg (potency) of aztreonam when used in the manufacturing of sterile preparations.

Assay Weigh accurately about 20 mg (potency) each of Aztreonam and aztreonam RS, dissolve in 70 mL water, add exactly 10 mL of internal standard solution, and then add water to make 100 mL. Use these solutions as the test solution and the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios of peak area, Q_T and Q_S, of the aztreonam to that of the internal standard.

$$\text{Potency (μg) of aztreonam } (C_{22}H_{22}N_5O_8S_2) = \text{Potency (μg) of aztreonam RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—4-aminobenzoic acid solution (1 in 6250).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 1.7 g of tetrabutylammonium hydrogen sulfate in 300 mL of water, adjust the pH to 3.0 with dibasic sodium phosphate TS, and add water to make 1000 mL. Add 350 mL of methanol to 650 mL of this solution.

Flow rate: Adjust the flow rate so that the retention time of aztreonam is about 8 minutes.

System suitability

System performance: Proceed with 25 μL of the standard solution according to the above conditions; the internal standard and aztreonam are eluted in this order with the resolution being NLT 4.

System repeatability: Repeat the test 6 times with 25 μL each of the standard solutions as directed under the above conditions. The relative standard deviation of the peak area ratio of aztreonam to the internal standard is NMT 1.5%.

Packaging and storage Preserve in light-resistant, tight containers.

Aztreonam for Injection
주사용 아즈트레오남

Aztreonam for Injection is a preparation for injec-

tion which is dissolved before use, and contains NLT 93.0% and NMT 107.0% of the labeled amount of aztreonam ($C_{13}H_{17}N_5O_8S_2$: 435.43).

Method of preparation Prepare as directed under Injections, with Aztreonam.

Description Aztreonam for Injection occurs as a white to yellowish white mass or a powder.

Identification (1) Dissolve an amount of Aztreonam for Injection equivalent to 6 mg (potency) of aztreonam according to the labeled amount, dissolve in 1 mL of hydroxylamine hydrochloride-ethanol TS, allow to stand for 3 minutes, and add 1mL of acidic ammonium iron(III) sulfate TS and shake to mix; the solution exhibits a reddish brown color.

(2) Dissolve an amount of Aztreonam for Injection equivalent to 3 mg (potency) of aztreonam according to the labeled amount in 100 mL of water. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 289 nm and 293 nm.

pH Dissolve an amount of Aztreonam for Injection equivalent to 1.0 g (potency) of aztreonam according to the labeled amount in 10 mL of water; the pH of this solution is between 4.5 and 7.0.

Purity ***Clarity and color of solution***—Dissolve an amount of Aztreonam for Injection equivalent to 1.0 g (potency) of aztreonam according to the labeled amount in 10 mL of water; the solution is clear. Perform the test as directed under the Ultraviolet-visible Spectroscopy; the absorbance of the solution at 450 nm is NMT 0.06.

Water NMT 2.0% (0.5 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.10 EU per mg (potency) of aztreonam.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

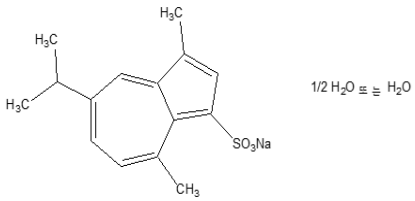
Assay Take a number of units equivalent to about 5 g (potency) of aztreonam, dissolve the contents of each in water, and transfer to a 100-mL volumetric flask. Wash each container with water, combine the washings and the solution prepared previously, and add water to make exactly 100 mL. Pipet 10 mL of this solution, and add water to make exactly 50 mL. Pipet 2 mL of this solution, add exactly 10 mL of the internal standard solution, add water to make exactly 100 mL, and use this solution as the standard solution. Separately, weigh accurately about 20 mg (potency) of aztreonam RS, dissolve in water, add 10 mL of the internal standard solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test as directed under the Assay for Aztreonam below.

$$\text{Potency (mg) of aztreonam } (C_{13}H_{17}N_5O_8S_2) = \text{Potency (mg) of aztreonam RS} \times \frac{Q_T}{Q_S} \times 250$$

Internal standard solution—4-aminobenzoic acid solution (1 in 6250).

Packaging and storage Preserve in light-resistant, well-closed containers.

Soluble Azulene
수용성아줄렌



Azulene Sodium Sulfonate

$C_{15}H_{17}NaO_3S \cdot 1/2H_2O$: 309.35

$C_{15}H_{17}NaO_3S \cdot H_2O$: 318.36

3,8-Dimethyl-5-(1-methylethyl)-1-azulenesulfonic acid sodium salt, [*6223-35-4, inorganic*]

Soluble Azulene, when dried, contains NLT 98.5% and NMT 101.5% of sodium azulenesulfonate ($C_{15}H_{17}NaO_3S \cdot 1/2H_2O$).

Description Soluble Azulene occurs as dark blue crystals or a crystalline powder, and is odorless and tasteless. It is soluble in methanol, sparingly soluble in water or acetic acid(100), slightly soluble in ethanol, and practically insoluble in acetic anhydride, ether or hexane.

Identification (1) To 5 mL of a aqueous solution of Soluble Azulene (1 in 200), add 1 mL of barium chloride TS; a blue precipitate is produced.

(2) To 1 mL of an aqueous solution of Soluble Azulene (1 in 200), add 0.5 mL of hydrochloric acid; the solution gradually changes to a pale yellow color or is decolorized.

(3**)** With phosphate buffer solution, pH 7.0, of Soluble Azulene, determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelengths of between 567 nm and 571 nm.

pH Between 6.0 and 9.0 (0.5% aqueous solution).

Absorbance $E_{1cm}^{1\%}$: Between 19.85 and 20.65 (20 mg, after drying, phosphate buffer solution (pH 7.0), 100 mL).

Purity (1) ***Clarity and color of solution***—To 0.1 g of Soluble Azulene, add 20 mL of water, shake to mix for 5 minutes, and filter; there is no residue on the filter paper.

(2) ***Heavy metals***—Proceed with 1.0 g of Soluble Azulene according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 0.40 g of Soluble Azulene according to Method 3 and perform the test (NMT 5 ppm).

(4) ***Guaiazulene***—Add 10 mL of hexane to 0.10 g of Soluble Azulene, shake to mix for 5 minutes, and filter. With the filtrate, determine the transmission rate as directed under the Ultraviolet-visible Spectroscopy at a wavelength of 605 nm; it is NLT 95.0%.

Loss on drying NMT 3.5% (0.5 g, silica gel, 24 hours).

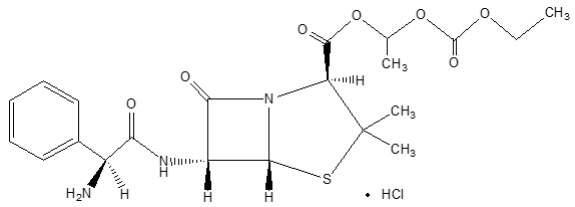
Water Between 2.5% and 3.5% (after drying, 2 g).

Assay Weigh accurately about 0.3 g of Soluble Azulene, previously dried, dissolve in 25 mL of acetic acid(100), add 25 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 30.936 mg of $C_{15}H_{17}NaO_3S \cdot 1/2H_2O$

Packaging and storage Preserve in light-resistant, tight containers.

Bacampicillin Hydrochloride
바캄피실린염산염



$C_{21}H_{27}N_3O_7S \cdot HCl$: 501.98

1-Ethoxycarbonyloxyethyl(2*S*,5*R*,6*R*)-6-[[(2*R*)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate hydrochloride [*37661-08-8*]

Bacampicillin Hydrochloride contains NLT 626 μg (potency) of ampicillin ($C_{16}H_{19}N_3O_4S$: 349.40) per mg, calculated on the anhydrous basis.

Description Bacampicillin Hydrochloride occurs as a white to pale yellow crystalline powder with a characteristic odor.

It is freely soluble in methanol or ethanol(99.5) and is soluble in water.

Identification (1) Determine the absorption spectra of solutions of Bacampicillin Hydrochloride and bacampicillin hydrochloride RS in methanol (1 in 1000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Bacampicillin Hydrochloride and bacampicillin hydrochloride RS as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Bacampicillin Hydrochloride (1 in 50) responds to the Qualitative Analysis for chloride.

Optical rotation $[\alpha]_D^{20}$: Between +140° and +170° (0.1 g, calculated on the anhydrous basis, ethanol(99.5), 25 mL, 100 mm).

pH Dissolve 0.2 g of Bacampicillin Hydrochloride in 10 mL of water; the pH of this solution is between 3.0 and 5.0.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Bacampicillin Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Bacampicillin Hydrochloride according to Method 3 and perform the test (NMT 2 ppm).

(3) ***Free ampicillin*—**Weigh accurately about 0.1 g of Bacampicillin Hydrochloride, transfer to a separatory funnel, and dissolve in exactly 15 mL of water cooled with ice. Add 10 mL of 0.05 mol/L phosphate buffer solution, pH 7.0, cooled with ice, shake, add 25 mL of chloroform cooled with ice, shake, and discard the chloroform layer. Proceed with two 25 mL portions of chloroform in the same manner. Centrifuge the water layer, filter the clear supernatant, and use the filtrate as the test solution. Separately, weigh accurately about 20 mg of ampicillin RS, dissolve in water, and make exactly 100 mL. Pipet 5 mL of this solution, add 10 mL of 0.05 mol/L phosphate buffer solution, pH 7.0, and water to make exactly 25 mL. Pipet 10 mL each of the test solution and the standard solution, add exactly 2 mL of sodium hydroxide TS, allow to stand for exactly 15 minutes, and add exactly 2 mL of 1 mol/L hydrochloric acid TS, 10 mL of 0.3 mol/L potassium hydrogen phthalate buffer solution, pH 4.6, and 10 mL of 0.005 mol/L iodine solution. Allow to stand for 20 minutes while protected from light, and titrate each solution with 0.01 mol/L sodium thiosulfate VS. The endpoint of the titration is when

the solution becomes colorless. Separately, pipet 10 mL each of the test solution and the standard solution, add exactly 10 mL of 0.3 mol/L potassium hydrogen phthalate buffer solution, pH 4.6, and 10 mL of 0.005 mol/L iodine solution, and perform a blank test in the same manner and make any necessary correction. When consumptions (mL) of 0.005 mol/L iodine for the test solution and the standard solution are V_T and V_S, respectively, the amount of ampicillin is NMT 1.0%.

$$\text{Content (\%) of liberated ampicillin} = \frac{V_T}{V_S} \times \frac{Potency\ (mg)\ in\ \text{ampicillin RS taken}}{Amount\ (mg) of\ Bacampicillin\ Hydrochloride} \times 20 \times 100$$

0.3 mol/L potassium hydrogen phthalate buffer solution, pH 4.6—Weigh 61.26 g of potassium hydrogen phthalate, dissolve in about 800 mL of water, adjust the pH to 4.6 with sodium hydroxide TS, and add water to make 1000 mL.

(4) ***Dimethylaniline***—Weigh accurately about 1.0 g of Bacampicillin Hydrochloride, add 5 mL of 1 mol/L sodium hydroxide TS and 1 mL of the internal standard solution, centrifuge if necessary, and use the clear supernatant as the test solution. Separately, weigh accurately about 50 mg of dimethylaniline, add 2.0 mL of hydrochloric acid, and add water to make 50 mL. Pipet 5.0 mL of this solution and add water to make exactly 250 mL. Pipet 1.0 mL of this solution, add 5.0 mL of 1 mol/L sodium hydroxide TS and 1.0 mL of the internal standard solution, centrifuge if necessary, and use the clear supernatant as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the ratios, QT and QS, of the peak area of dimethylaniline to that of the internal standard in the test solution and the standard solution, respectively (NMT 20 ppm).

$$\text{Content (ppm) of dimethylaniline} = \text{Amount (mg) of dimethylaniline taken} \times \frac{Q_T}{Q_S} \times \frac{Purity\ (\%) of\ dimethylaniline}{Amount\ (mg) of\ Bacampicillin\ Hydrochloride\ taken} \times 4$$

Internal standard solution—Dissolve 50.0 mg of naphthalene in cyclohexane to make 50 mL. Pipet 5.0 mL of this solution, add cyclohexane to make 100 mL, and use this solution as the internal standard solution.

Operating conditions

Detector: A flame ionization detector

Column: A column about 2 mm in internal diameter and about 2 m in length, packed with diatomaceous earth for gas chromatography coated with 50% phenyl-50% methtyl polysiloxane for gas chromatography equivalent to 3% of the mass.

Column temperature: 120 °C

Sample injection port, detector temperature: 150 °C

Carrier gas: Nitrogen

Flow rate: 30 mL/min

Water NMT 1.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 1.5% (1 g).

Assay Weigh accurately about 40 mg (potency) each of Bacampicillin Hydrochloride and bacampicillin hydrochloride RS, dissolve in water to make exactly 100 mL each, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of bacampicillin.

$$\text{Potency (μg) of ampicillin } (C_{16}H_{19}N_3O_4S) = \text{Potency (μg) of bacampicillin hydrochloride RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Sample injection port temperature: Constant temperature of about 4 ℃.

Mobile phase: To 500 mL of 0.02 mol/L sodium dihydrogen phosphate, add 0.02 mol/L sodium hydrogen phosphate to adjust the pH to 6.8. To 500 mL of this solution, add 500 mL of acetonitrile.

Flow rate: 1 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the number of theoretical plates of bacampicillin peak is NLT 2000.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of peak areas of bacampicillin is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Bacampicillin Hydrochloride Granules
바캄피실린염산염 과립

Bacampicillin Hydrochloride Granules contain NLT 90.0% and NMT 120.0% of labeled amount of ampicillin ($C_{16}H_{19}N_3O_4S$: 349.41).

Method of preparation Prepare as directed under Granules, with Bacampicillin Hydrochloride.

Identification Weigh an appropriate amount of Bacampicillin Hydrochloride Granules according to the labeled potency, add ethanol to dilute to a concentration of 2 mg (potency) per mL, and use this solution as the test solution. Separately, weigh an appropriate amount of bacampicillin hydrochloride RS, add ethanol to make a solution containing 2 mg (potency) per mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate using a mixture of dichloromethane, ethanol and chloroform (10 : 1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly ninhydrin-ethanol solution on the plate; the R_f values of the spots obtained from the test solution and the standard solution are the same.

Particle size distribution estimation by analytical sieving Meets the requirements.

Disintegration Meets the requirements.

Uniformity of dosage units (distribution) Meets the requirements.

Water NMT 2.0% (0.5 g, volumetric titration, direct titration).

Assay Weigh accurately about 40 mg (potency) of pulverized Bacampicillin Hydrochloride Granules according to the labeled potency, dissolve in water to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 40 mg (potency) of bacampicillin hydrochloride RS, dissolve in water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of bacampicillin, A_T and A_S, in each solution.

Amount [mg (potency)] of ampicillin ($C_{16}H_{19}N_3O_4S$)
= Amount [mg (potency)] of bacampicillin hydrochloride RS
$\times (A_T / A_S)$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Sample injection port temperature: A constant temperature of about 4 °C.

Mobile phase: To 500 mL of 0.02 mol/L sodium dihydrogen phosphate, add 0.02 mol/L sodium hydrogen phosphate to adjust the pH to 6.8. To 500 mL of this solution, add 500 mL of acetonitrile.

Flow rate: 1 mL/min.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the number of theoretical plates for bacampicillin peak is NLT 3000 plates.

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area for bacampicillin is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Bacampicillin Hydrochloride Tablets
바캄피실린염산염 정

Bacampicillin Hydrochloride Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of ampicillin ($C_{16}H_{19}N_3O_4$: 349.41).

Method of preparation Prepare as directed under Tablets, with Bacampicillin Hydrochloride.

Identification Weigh an appropriate amount of bacampicillin hydrochloride and an appropriate amount of bacammycin hydrochloride RS according to the labeled amount of Bacampicillin Hydrochloride Tablets, dissolve in ethanol(95) to contain 2 mg per mL; and use these solutions as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of these solutions on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate using a mixture of methylene chloride, chloroform and ethanol (10 : 1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray 0.3% ninhydrin methanol solution evenly onto the plate; the spots from the test solution and the standard solution have the same R_f values.

Water NMT 2.0% (0.5 g, volumetric titration, direct titration).

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Bacampicillin Hydrochloride Tablets, and powder. Weigh accurately an amount of this powder, equivalent to about 56 mg of ampicillin ($C_{16}H_{19}N_3O_4S$), dissolve in water to make exactly 100 mL, and use this solution as the test solution. Weigh accurately about 80 mg (potency) of bacampicillin hydrochloride RS, dissolve in water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of bacampicillin.

$$\text{Potency (μg) of ampicillin } (C_{16}H_{19}N_3O_4S) = \text{Potency (μg) of bacampicillin hydrochloride RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: To 500 mL of 0.02 mol/L sodium dihydrogen phosphate, add 0.02 mol/L sodium hydrogen phosphate to adjust the pH to 6.8. To 500 mL of this solution, add 500 mL of acetonitrile.

Flow rate: 1 mL/min

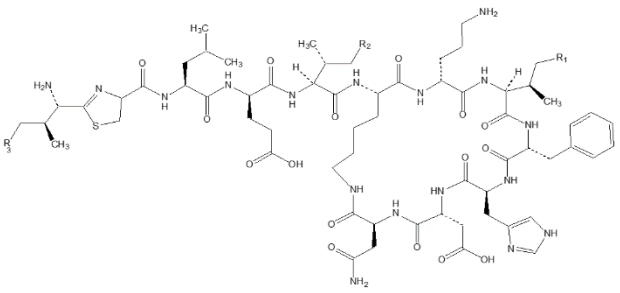
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the number of theoretical plates for bacampicillin peak is NLT 3000 plates.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of peak areas of bacampicillin is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Bacitracin
바시트라신



	R_1	R_2	R_3
Bacitracin A:	CH_3	CH_3	CH_3
Bacitracin B_1:	CH_3	CH_3	H
Bacitracin B_2:	H	CH_3	CH_3
Bacitracin B_3:	CH_3	H	CH_3

[*1405-87-4*]

Bacitracin is a mixture of peptide-based compounds in which the main component is bacitracin A, having anti-bacterial activity, obtained from the culture of *Bacillus subtilis* or *Bacillus licheniformis*.

Bacitracin contains NLT 60 units (potency) of bacitracin A ($C_{66}H_{103}N_{17}O_{16}S$: 1422.69) per mg, calculated on the dried basis.

Description Bacitracin occurs as a white to pale brown powder.
It is freely soluble in water and slightly soluble in ethanol(99.5).

Identification (1) To 3 mL of Bacitracin aqueous solution (1 in 100), add 3 mL of 4-dimethylaminobenzaldehyde TS, and shake until a deep red to purple color appears. Then, add some drops of sodium nitrite solution (1 in 100) and shake; the resulting solution exhibits a green to dark green color.

(2) Dissolve 60 mg each of Bacitracin and bacitracin RS in 10 mL of water and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 1 μL each of the test solutions and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, acetic acid(100), water, pyridine and ethanol(99.5) (30 : 15 : 10 : 6 : 5) (as the developing solvent) to a distance of about 10 cm, and air-dry the plate. Spray evenly a ninhydrin TS on the plate and heat at 110 ℃ for 5 minutes; the R_f values of spots obtained from the test solution and the standard solution are the same.

pH Dissolve 1 g of Bacitracin in 10 mL of water; the pH of this solution is between 5.5 and 7.5.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Bacitracin as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 0.15 g of Bacitracin in 0.05 mol/L sulfuric acid TS to make 100 mL. To 2 mL of this solution, add 0.05 mol/L sulfuric acid TS to make 10 mL, and use this solution as the test solution. Determine the absorbances A_1 and A_2 of the test solution at the wavelengths 252 nm and 290 nm as directed under the Ultraviolet-visible Spectroscopy; the A_2/A_1 is NMT 0.20.

Loss on drying NMT 5.0% (1.0 g, in vacuum, 60 ℃, 3 hours).

Residue on ignition NMT 1.0% (1 g).

Sterility In case of use for manufacturing of sterile preparations, it meets the requirements. It is excluded if there is a final sterilization process included in the manufacturing process of the sterile preparations.

Bacterial endotoxins In case of use for manufacturing of sterile preparations, less than 0.01 EU per mg (potency) as bacitracin.

Bacitracin content ratio Weigh accurately an appropriate amount of Bacitracin, dissolve in the mobile phase to obtain a solution having known concentration of 2.0 mg per mL, and use this solution as the test solution. Perform the test with 100 μL each of the mobile phase, the test solution and the detection limit solution as directed under the bacitracin content ratio section under Bacitracin Zinc. The amount of bacitracin A is NLT 40.0%, and the amount of active bacitracin (bacitracin A, B_1, B_2 and B_3) is NLT 70.0%. Also, the amount of all peaks flown out before the bacitracin B_1 peak (initial efflux peptide) is NMT 20.0%, and the amount of bacitracin F is NMT 6.0%. The peak in the test solution that is smaller than the bacitracin A obtained from the detection limit solution and the peak appearing in the mobile phase are excluded.

Assay ***Cylinder plate method*** (1) ***Medium*—**Agar media for seed and base layer Use the culture media under the Microbial Assays for Antibiotics A)(2)(A)⑥ⓐ.

(2) ***Test organism*—**Use *Micrococcus luteus* ATCC 10240 as the test organism.

(3) Weigh accurately about 400 units (potency) of Bacitracin, dilute with 1% phosphate buffer (pH 6.0) to obtain solutions having known concentrations of 2.0 and 0.5 units (potency) per mL, respectively, and use these solutions as the high-concentration test solution and the low-concentration test solution, respectively. Separately, weigh accurately about 400 units (potency) of bacitracin RS, dilute with 1% phosphate buffer (pH 6.0) to obtain a solution containing 5 units (potency) per mL, and use this solution as the standard stock solution. Keep the standard stock solution at NMT 10 ℃ and use it within 2 days. Pipet an appropriate amount of the standard stock solution, dilute with 1% phosphate buffer (pH 6.0) to obtain solutions having known concentrations of 2.0 and 0.5 units (potency) per mL, respectively, and use these solutions as the high-concentration standard solution and the low-concentration standard solution. With these solutions, perform the test as directed under the Microbial Assays for Antibiotics, A) (8).

Packaging and storage Preserve in tight containers (in a cold place).

Bacitracin Ointment
바시트라신 연고

Bacitracin Ointment contains NLT 90.0% and NMT 120.0% of the labeled amount of bacitracin A ($C_{66}H_{103}N_{17}O_{16}S$: 1421.77).

Method of preparation Prepare as directed under Ointments, with Bacitracin.

Identification Weigh about 5 g of Bacitracin Ointment, place in a beaker, wash 2 to 3 times with 20 mL of chloroform each, and discard the washings. Dissolve in a small amount of ethanol(95), evaporate to dryness, and perform the test with the residue as directed under the Identification for Bacitracin.

Water NMT 1.0% (1.0 g, volumetric titration, direct titration).

Assay ***Cylinder plate method***—Perform the test according to the Assay under Bacitracin. Weigh accurately an amount of Bacitracin Ointment, equivalent to 500 to 2000 units (potency) according to the labeled potency, place in a separatory funnel, add 50 mL of ether, and shake to mix until it is homogeneous. Extract 3 times with 25 mL each of 1% phosphate buffer solution, pH 6.0, combine the extracts, and add 1% phosphate buffer solution, pH 6.0, to make 100 mL. Pipet an appropriate amount of this solution, dilute with 1% phosphate buffer solution, pH 6.0, to the concentration of (3), and use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Bacitracin·Neomycin Sulfate·Polymyxin B Sulfate Ointment
바시트라신·네오마이신황산염·폴리믹신B황산염 연고

Bacitracin·Neomycin Sulfate·Polymyxin B Sulfate Ointment contains NLT 90.0% and NMT 120.0% of the labeled amounts of bacitracin, neomycin ($C_{23}H_{46}N_6O_{13}$: 614.65) and polymyxin B.

Method of preparation Prepare as directed under Ointments, with Bacitracin, Neomycin Sulfate and Ploymixin B Sulfate.

Identification Weigh appropriate amounts of Bacitracin·Neomycin Sulfate·Polymyxin B Sulfate Ointment and reference standards of each component, dissolve in 0.1 mol/L phosphate buffer solution, pH 8.0, to make solutions containing 1 mg (potency) or 200 units (potency) per mL, and use these solutions as the test solution

and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution onto a thin-layer chromatographic plate made of silica gel for thin-layer chromatography, and develop the plate with a mixture of 1-butanol, acetic acid(100) and water (60 : 20 : 20) as the developing solvent. Air-dry the plate and evenly spray a solution of 1% ninhydrin butanol solution mixed with a small amount of pyridine; the spots obtained from the test solution and the standard solution have the same R_f values.

Water NMT 1.0% (1 g, volumetric titration, direct titration).

Assay (1) ***Cylinder plate method for bacitracin—*** Perform the test as directed under the Assay for Bacitracin Ointment.

(2) ***Cylinder plate method for neomycin sulfate—*** Perform the test as directed under the Assay for Neomycin Sulfate. Weigh accurately an amount of Bacitracin·Neomycin Sulfate·Polymyxin B Sulfate Ointment, equivalent to about 10 mg (potency) of neomycin according to the labeled potency, place in a separatory funnel, add 100 mL of ether, and shake well to mix. Extract with 50 mL of 0.1 mol/L phosphate buffer solution, pH 8.0, while mixing well, and collect the buffer solution layer. Repeat this procedure 2 times using 20 mL each of 0.1 mol/L phosphate buffer solution, pH 8.0, combine all of the buffer solution layers, add 50 mL of butanol to this combined buffer solution layer, shake to mix, and discard the butanol layer. Repeat the procedure 2 more times using 25 mL each of butanol, discard the butanol layers, and collect the buffer solution layers. Add 0.1 mol/L phosphate buffer solution, pH 8.0, to make exactly 100 mL, pipet an appropriate amount of the resulting solution, dilute with 0.1 mol/L phosphate buffer solution, pH 8.0, to the concentration of ③, and use this solution as the test solution.

(3) ***Cylinder plate method for polymyxin B sulfate—*** ① Medium

(A) Agar medium for seed layer

Pancreatin digest of casein	17.0g
Glucose	2.5 g
Papain digest of soybean	3.0 g
Agar	13.0 to 20.0 g

Weigh the above amount of substances, add purified water to make 1000 mL, and adjust the pH after sterilizing to between 7.2 and 7.3 with sodium hydroxide TS

(B) Agar media for base layer

Pancreatin digest of casein	17.0 g
Papain digest of soybean	3.0 g
Sodium chloride	5.0g
Glucose	2.5g

Weigh the above amount of substances, add purified water to make 1000 mL, and adjust the pH after sterilizing to between 7.2 and 7.3 with sodium hydroxide TS

(C) Agar medium for transferring test organism

Peptone	6.0g
Glucose	1.0g

Weigh the above amount of substances, add purified water to make 1000 mL, and adjust the pH after sterilizing between 6.5 and 6.6 with sodium hydroxide TS

② Test organism—Use *Bordetella bronchiseptica* ATCC 4617 as the test organism.

③ Suspension of test organism—Culture the test organism in the agar medium for transferring test organism for 16 to 24 hours at 32 to 37 ℃, subculture NLT 3 times, then inoculate the test organism in a slanted agar medium and culture for 16 to 24 hours at 32 to 37 ℃, suspend in an appropriate amount of sterile purified water to produce a suspension whose transmittance is 60% at a wavelength of 660 nm when measured using a photoelectric photometer. Store the suspension at below 15 ℃ and use within 3 days. For the Assay, dissolve 0.13 mL of this adjusted suspension beforehand, place it in 100 mL of agar medium for the seed layer cooled to 48 ℃, and use this solution as the suspension of the test organism.

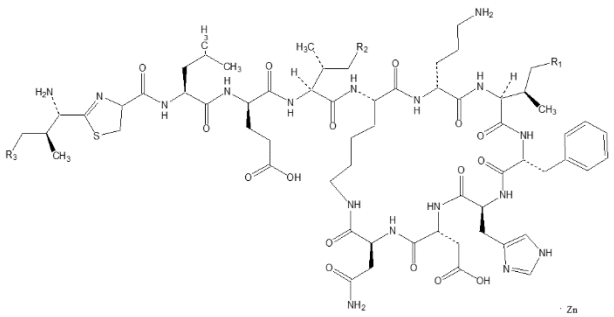
④ Weigh accurately an amount of Bacitracin·Neomycin Sulfate·Polymyxin B Sulfate Ointment, equivalent to about 8000 to 20000 units (potency) of polymyxin B sulfate according to the labeled potency, place in a separatory funnel, add 20 mL of ether, shake to mix, then extract with 20 mL of 10% phosphate buffer solution, pH 6.0. Then extract 2 times with 10 mL each of 10% phosphate buffer solution, pH 6.0, combine all of the buffer solution layers, then add 10% phosphate buffer solution, pH 6.0, to make exactly 50 mL. Pipet an appropriate amount of this solution, dilute with 10% phosphate buffer solution, pH 6.0, to contain 100.0 and 25.0 units (potency) per mL, and use these solutions as the high-concentration test solution and the low-concentration test solution. Separately, weigh accurately about 20000 to 30000 units (potency) of polymyxin B sulfate RS and dissolve in 10% phosphate buffer solution, pH 6.0, to prepare a standard stock solution containing 1000 units (potency) per mL. For the Assay, pipet an appropriate amount of the standard stock solution, dilute with 10% phosphate buffer solution, pH 6.0, to contain 100.0 and 25.0 units (potency) per mL, respectively, and use these solutions as the high-concentration standard solution and the low-concentration standard solution. With these solutions, perform the test according to (A) ⑧ under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in tight containers.

Dibasic potassium phosphate	2.5 g
Agar	13.0 to 20.0 g

Polysorbate 80 10.0g Sodium chloride 5.0g

Bacitracin Zinc
바시트라신아연



	R_1	R_2	R_3
Bacitracin A:	CH_3	CH_3	CH_3
Bacitracin B_1:	CH_3	CH_3	H
Bacitracin B_2:	H	CH_3	CH_3
Bacitracin B_3:	CH_3	H	CH_3

[*1405-89-6*]

Bacitracin Zinc contains NLT 65 units (potency) of bacitracin A ($C_{66}H_{103}N_{17}O_{16}S$: 1422.69) per mg, calculated on the dried basis. Also, Bacitracin Zinc contains NLT 4.0% and NMT 6.0% of zinc (Zn: 65.41), calculated on the dried basis.

Description Bacitracin Zinc occurs as a white to pale yellow powder. It has no or slight odor and a bitter taste. It is slightly soluble in water or alcohol, very slightly soluble in ether, and practically insoluble in chloroform. It is hygroscopic.

Identification Dissolve an appropriate amount of Bacitracin Zinc in 0.1 mol/L hydrochloric acid TS to obtain a solution having a known concentration of 500 units per mL, and use this solution as the test solution. Separately, weigh an appropriate amount of bacitracin zinc RS to obtain a solution having a known concentration of 500 units per mL and use this solution as the standard solution. Perform the test with 10 μL each of the test solutions and the standard solutions as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol, 2-propanol, dichloromethane, ammonium hydroxide and water (4 : 2 : 2 : 1 : 5) to a distance of about 15 cm, and dry the plate at 105 ℃ for 10 minutes. Spray evenly a 0.2% ninhydrin-butanol solution on the plate and heat at 105 ℃ for 5 minutes; the spots obtained from the test solution and the standard solution exhibit a dark purple color and have the same R_f value.

pH The pH of the saturated solution of Bacitracin Zinc is between 6.0 and 7.5.

Loss on drying NMT 5.0% (0.1 g, in vacuum, 60 ℃, 3 hours).

Sterility In case of use for manufacturing of sterile preparations, it meets the requirements. It is excluded if there is a final sterilization process included in the manufacturing process of the sterile preparations.

Bacitracin zinc content ratio Weigh accurately an appropriate amount of Bacitracin Zinc, dissolve in the diluent to obtain a solution having a known concentration of 2.0 mg per mL, and use this solution as the test solution. Perform the test with 100 μL each of the diluents, the test solution and the detection limit solution as directed under the Liquid Chromatography according to the following conditions and determine the peak area of the respective solutions according to the automatic integration method. Obtain the amount of bacitracin A according to the following equation (1); it is NLT 40.0%. Obtain the amount of active bacitracin (bacitracin A, B_1, B_2 and B_3) according to the following equation (2); it is NLT 70.0%. Obtain the amount of all peaks flown out before the bacitracin B_1 peak (initial efflux peptide) according to the following equation (3); it is NMT 20.0%. Obtain the amount of bacitracin F according to the following equation (4); it is NMT 6.0%. The peak in the test solution that is smaller than the bacitracin A obtained from the detection limit solution and the peak appearing in the diluent are excluded.

$$\text{Amount of bacitracin A} = \frac{A_\text{A}}{A_\text{T}} \times 100 \quad (1)$$

A_A: Peak area of bacitracin A obtained from the test solution

A_T: Sum of areas of all peaks obtained from the test solution

$$\text{Content (\%) of active bacitracin} = \frac{A_\text{A}}{A_\text{T}} \times \frac{A_\text{A} + A_\text{B1} + A_\text{B2} + A_\text{B3}}{A_\text{T}} \times 100 \quad (2)$$

A_A, A_B1, A_B2, A_B3: Peak areas of bacitracin A, B_1, B_2, and B_3, respectively

A_T: Sum of areas of all peaks obtained from the test solution

$$\text{Content (\%) of initial efflux peptide} = \frac{A_\text{i}}{A_\text{T}} \times 100 \quad (3)$$

A_i: Sum of areas of all peaks flown out before the bacitracin B_1 peak

A_T: Sum of areas of all peaks obtained from the test solution

$$\text{Content (\%) of bacitracin F} = \frac{A_\text{F}}{A_\text{A}} \times 100 \quad (4)$$

A_F: Peak area of bacitracin F

A_A: Peak area of bacitracin A

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of methanol, water, phosphate buffer (pH 6.0) and acetonitrile (26 : 15 : 5 : 2).

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 100 μL of the peak verification solution according to the above conditions at the wavelength 300 nm and verify the location of the bacitracin F peak having a relative retention time of about 2.4. Change the wavelength to 254 nm, and proceed with 100 μL of the system suitability solution according to the above conditions to verify the active portions of bacitracin (bacitracin A, B_1, B_2 and B_3), initial efflux peptide flown out before the bacitracin B_1, and bacitracin F, based on the relative retention time. The relative retention times for bacitracin C_1, C_2, C_3, B_1, B_2, B_3 and F are about 0.5, 0.6, 0.6, 0.7, 0.7, 0.8 and 2.4. Also, the ratio of peak versus valley (*H*v/*H*p) is NMT 1.2, where *H*v is the height of the valley, at which the bacitracin B_1 peak is separated from the bacitracin B_2 peak from the baseline and *H*p is the height of the bacitracin B_1 peak from the baseline.

Time span of measurement: About 3 times the retention time of bacitracin A

Diluent—Dissolve 40 mg of ethylenediaminetetraacetic acid disodium salt dihydrate in 1000 mL of water and adjust pH to 7.0 with dilute sodium hydroxide TS.

System suitability solution—Weigh accurately an appropriate amount of bacitracin zinc RS and dissolve in the diluent to a known concentration of about 2.0 mg/mL.

Detection limit solution—Dilute the system suitability solution with water to known concentration of about 0.01 mg/mL.

Peak verification solution—Heat the system suitability solution on a steam bath for about 30 minutes and cool to room temperature.

Phosphate buffer (pH 6.0)—Dissolve 34.8 g of dibasic potassium phosphate in 1000 mL of water, and adjust pH to 6.0 with a solution made by dissolving 27.2 g of potassium dihydrogen phosphate in 1000 mL of water.

Assay (1) ***Bacitracin***—Standard curve method 1) Medium Agar media for seed and base layer Use the culture media under the Microbial Assays for Antibiotics A)(2)(A)⑥ⓐ.

2) ***Test organism***—Use *Micrococcus luteus* ATCC 10240 as the test organism.

3) Weigh accurately an appropriate amount of Bacitracin Zinc and dilute with 0.01 mol/L hydrochloric acid TS to obtain a solution having a known concentration of 100 units (potency) per mL. Pipet an appropriate amount of this solution, dilute with 1% phosphate buffer (pH 6.0) to obtain a solution having a known concentration of 1.00 unit (potency) per mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of bacitracin RS, dilute with 0.01 mol/L hydrochloric acid TS to obtain a solution having a known concentration of 100 units (potency) per mL, and use this solution as the standard stock solution. Pipet an appropriate amount of this standard stock solution, dilute with 1% phosphate buffer (pH 6.0) to obtain solutions having known concentrations of 0.64, 0.80, 1.00, 1.25 and 1.56 units (potency) per mL, and use them as the standard solutions. Use the solution having known concentration of 1.00 unit (potency) per mL as the standard intermediate diluent. Perform the test with the test solution, the standard solution and the standard intermediate diluent as directed under the Microbial Assays for Antibiotics, B)(4).

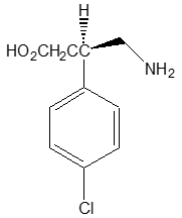
(2) ***Zinc***—Weigh accurately about 0.2 g (potency) of Bacitracin Zinc and dissolve in 0.01 mol/L hydrochloric acid TS to make 100 mL. Pipet 2 mL of this solution, add 0.001 mol/L hydrochloric acid TS to make exactly 200 mL, and use this solution as the test solution. Separately, weigh accurately about 3.11 g of zinc oxide, add 80 mL of 1 mol/L hydrochloric acid TS, warm to dissolve, and cool to room temperature. Then, add water to make exactly 250 mL. Pipet an appropriate amount of this solution, dilute with 0.001 mol/L hydrochloric acid TS to obtain solutions having known concentrations of 0.5, 1.5 and 2.5 μg of zinc per mL, and use these solutions as the standard solutions. Perform the test with the test solution and the standard solutions as directed under the Atomic Absorption Spectroscopy. Determine the absorbances of the test solution and the standard solutions at the wavelength 213.8 nm, using the 0.001 mol/L hydrochloric acid TS as the blank test solution, to obtain the concentration of zinc according to the calibration curve.

$$\text{Content (\%) of zinc} = \frac{C \times 100000}{W \times (100 - m)}$$

C: Concentration (μg/mL) of zinc in the test solution
W: Amount (mg) of Bacitracin Zinc taken
m: Loss on drying (%) of the sample

Packaging and storage Preserve in tight containers.

Baclofen
바클로펜



and enantiomer

$C_{10}H_{12}ClNO_2$: 213.66

(*RS*)-4-Amino-3-(4-chlorophenyl)butanoic acid [*1134-47-0*]

Baclofen contains NLT 98.5% and NMT 101.0% of baclofen ($C_{10}H_{12}$ $ClNO_2$), calculated on the anhydrous basis.

Description Baclofen occurs as a white to pale yellowish white crystalline powder.
It is freely soluble in acetic acid(100), slightly soluble in water, very slightly soluble in methanol and ethanol(95), and practically insoluble in ether.
It is soluble in dilute hydrochloric acid.

Identification (1) To 5 mL of an aqueous solution of Baclofen (1 in 1000), add 1 mL of ninhydrin TS, and heat on a steam bath for 3 minutes; the resulting solution turns a bluish purple color.

(2) Determine the absorption spectra of solutions of Baclofen and baclofen RS in 0.1 mol/L hydrochloric acid TS (1 in 2000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Perform the test with Baclofen as directed under the Flame Coloration (2); it exhibits a green color.

Purity (1) ***Chloride***—Dissolve 0.5 g of Baclofen in 50 mL of acetic acid(100) and add water to make 100 mL. To 10 mL of this solution, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. To 0.30 mL of 0.01 mol/L hydrochloric acid, add 5 mL of acetic acid(100), 6 mL of dilute nitric acid and water to make 50 mL (NMT 0.21%). Use this solution as the control solution.

(2) ***Heavy metals*—**Proceed with 2.0 g of Baclofen according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Baclofen according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 50 mg of Baclofen in 50 mL of the mobile phase and use this solution as the test solution. Pipet 1.0 mL and 1.5 mL of this solution, add the mobile phase to each to make exactly 100 mL, and use these solutions as the standard solution (1) and (2). Perform the test with 25 μL each of the test solution, the standard solution (1) and (2) as directed under the Liquid Chromatography according to the following conditions. Determine the peak height of each solution; each peak height of peaks other than baclofen obtained from the test solution is not higher than peak height of baclofen from the standard solution (1) and the sum of these peak heights is not higher than the peak height of baclofen from the standard solution (2).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 268 nm).

Column: A stainless steel column about 4 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: A mixture of methanol and diluted acetic acid(100) (1 in 900) (3 : 2).

Flow rate: Adjust the flow rate so that the retention time of baclofen is about 4 minutes.

System suitability

Test for required detectability: Adjust so the peak height of baclofen obtained from 25 μL of the standard solution (1) is between 5 mm to 10 mm.

System performance: Dissolve 0.40 g of Baclofen and 5 mg of methyl *p*-hydroxybenzoate in 200 mL of the mobile phase. To 10 mL of this solution, add the mobile phase to make 100 mL. Proceed with 25 μL of this solution according to the above conditions; baclofen and methyl *p*-hydroxybenzoate are eluted in this order with the resolution between these peaks being NLT 5.

System repeatability: Repeat the test 6 times with 25 μL each of the standard solution (1) according to the above conditions; the relative standard deviation of the baclofen peak height is NMT 3.0%.

Time span of measurement: About 3 times the retention time of baclofen after the solvent peak.

Water NMT 1.0% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.3% (1 g).

Assay Weigh accurately about 0.5 g of Baclofen, dissolve in 80 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of methylrosaniline chloride TS). The endpoint of titration is when the violet color changes to blue and then to greenish blue. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 21.366 mg of $C_{10}H_{12}ClNO_2$

Packaging and storage Preserve in well-closed containers.

Baclofen Tablets
바클로펜 정

Baclofen Tablets contain NLT 93.0% and NMT 107.0% of baclofen ($C_{10}H_{12}ClNO_2$: 213.66).

Method of preparation Prepare as directed under Tablets, with Baclofen.

Identification (1) Take a portion of powdered Baclofen Tablets, equivalent to 10 mg of baclofen according to the labeled amount, add 10 mL of water, shake well to mix, and filter. To 5 mL of the filtrate, add 1 mL of ninhydrin TS, and perform the test as directed under the Identification (1) of Baclofen.

(2) Take a portion of powdered Baclofen Tablets, equivalent to 25 mg of baclofen according to the labeled amount, add 50 mL of 0.1 mol/L hychloric acid TS, shake for 15 minutes to mix, and filter. Determine the absorption spectrum of the filtrate as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima 257 nm to 261 nm, 264 nm to 268 nm and 272 nm to 276 nm.

(3) Weigh a portion of powdered Baclofen Tablets, equivalent to 10 mg of baclofen according to the labeled amount, and add 2 mL of a mixture of methanol and acetic acid(100) (4 : 1). After shaking well to mix, centrifuge, and use the clear supernatant as the test solution. Separately, dissolve 10 mg of baclofen RS in 2 mL of a mixture of methanol and acetic acid(100) (4 : 1), and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Next, develop the plate with a mixture of 1-butanol, water and acetic acid(100) (4 : 1 : 1) (as the developing solvent) to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values of the spots obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 tablet of Baclofen Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 500 mL of water as the dissolution medium. Take NLT 20 mL of the dissolved solution 45 minutes after starting the dissolution test, filter through a membrane filter with a pore size of not exceeding 0.8 μm, and discard the first 10 mL of the filtrate. Take exactly V mL of the subsequent filtrate, add water to make exactly V' mL of a solution containing about 10 μg of baclofen ($C_{10}H_{12}ClNO_2$) per mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of baclofen RS (previously measured the water content), and dissolve in water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 220 nm as directed under the Ultraviolet-visible Spectroscopy. Meets the requirements if the dissolution rate of Baclofen Tablets for 45 minutes is NLT 70%.

Dissolution rate (%) for the labeled amount of baclofen ($C_{10}H_{12}ClNO_2$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 50$$

W_S: Amount (mg) of baclofen RS, calculated on the anhydrous basis

C: Labeled amount of baclofen ($C_{10}H_{12}ClNO_2$) in 1 tablet

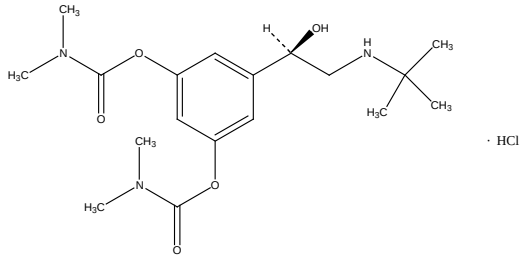
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass NLT 20 tablets of Baclofen Tablets, and powder. Weigh accurately a portion of this powder, equivalent to about 50 mg of baclofen ($C_{10}H_{12}ClNO_2$), add 130 mL of 0.1 mol/L hydrochloric acid TS, shake to mix for 10 minutes, add 0.1 mol/L hydrochloric acid TS to make exactly 200 mL, and centrifuge. Take exactly 10 mL of the clear supernatant, add 2 drops of phenolphthalein TS, neutralize it with dilute sodium hydroxide TS, add water to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 0.25 g of the baclofen TS (previously measured the water content), and dissolve in 0.1 mol/L hydrochloric acid TS to make exactly 100 mL. Take exactly 10 mL of this solution and add 0.1 mol/L hydrochloric acid TS to make exactly 100 mL. Take accurately 10 mL of this solution, add 2 drops of phenolphthalein TS, neutralize with dilute sodium hydroxide TS, add water to make exactly 50 mL, and use this solution as the standard solution. Take accurately 2 mL of the test solution and the standard solution, add 4 mL of ninhydrin-tin(II) chloride TS to each, and shake to mix. Heat on a steam bath for 20 minutes, and immediately shake vigorously for 2 minutes to mix. After cooling, add a mixture of water and 1-propanol (1 : 1) to each to make exactly 25 mL. With these solutions, perform the test as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbances, A_T and A_S, of each solution obtained from the test solution and the standard solution at the wavelength of 570 nm, using a solution, prepared with 2 mL of water in the same procedure, as a control solution.

Amount (mg) of baclofen ($C_{10}H_{12}ClNO_2$)
= Amount (mg) of baclofen RS,
as calculated on the anhydrous basis $\times \frac{A_T}{A_S} \times \frac{1}{5}$

Packaging and storage Preserve in well-closed containers.

Bambuterol Hydrochloride
밤부테롤염산염



and enantiomer

$C_{18}H_{29}N_3O_5 \cdot HCl$: 403.90

(*RS*)-[3-[2-(*tert*-Butylamino)-1-hydroxyethyl]-5-(dimethylcarbamoyloxy)phenyl] *N,N*-dimethyl-carbamate hydrochloride [*81732-46-9*]

Bambuterol Hydrochloride contains NLT 98.5% and NMT 101.5% of bambuterol hydrochloride ($C_{18}H_{29}N_3O_5 \cdot HCl$), calculated on the dried basis.

Description Bambuterol Hydrochloride occurs as a white crystalline powder.
It is freely soluble in water and soluble in ethanol(95).
It shows polymorphism.

Identification (1) Determine the infrared spectra of Bambuterol Hydrochloride and bambuterol hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the spectra, perform the following: dissolve Bambuterol Hydrochloride and bambuterol hydrochloride RS in a mixture of acetone and water (6:1) by shaking, allow the mixture to stand in an ice bath, dry the resulting precipitate in vacuum at 50 ℃, and re-determine the spectra.

(2) An aqueous solution of Bambuterol Hydrochloride (1 in 50) responds to the Qualitative Analysis (2) for chloride.

Optical rotation $[\alpha]_D^{20}$: Between -0.10° and +0.01° (0.4 g calculated on the anhydrous basis, water, 20 mL, 100 mm).

Purity (1) ***Acidity or alkalinity***—Dissolve 4.0 g of Bambuterol Hydrochloride in water to make exactly 20 mL. Add 0.2 mL of methyl red TS and 0.2 mL of 0.01 mol/L hydrochloric acid to 10 mL of this solution; the solution exhibits a red color. Then, add 0.4 mL of 0.01 mol/L sodium hydroxide; the solution exhibits a yellow color.

(2) ***Related substances***—Weigh 5.0 mg of Bambuterol Hydrochloride, dissolve in the mobile phase to make exactly 10 mL. Use this solution as the test solution. Separately, dissolve 1.0 mg of formoterol fumarate hydrate RS in the mobile phase to make exactly 10 mL. Mix 0.8 mL of this solution and 0.4 mL of the test solution and add the mobile phase to make 100 mL. Use this solution as the standard solution (1). Add the mobile phase to 1.0 mL of the test solution to make exactly 50 mL, and add the mobile phase to 2.0 mL of this solution to make exactly 20 mL. Use this solution as the standard solution (2). Use the mobile phase as the blank test solution. Perform the test with 20 μL each of the blank test solution, test solution, and standard solution as directed under the Liquid Chromatography according to the following conditions. The area of each peak other than the major peak obtained from the test solution is not greater than the area of the major peak obtained from the standard solution (2) (NMT 0.2%), and the total area of all peaks other than the major peaks is not greater than 3 times the area of the major peak obtained from the solution (NMT 0.6%). Exclude any peaks from the blank test solution and any peaks with an area not greater than 0.25 times the area of the major peak from the standard solution (2).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with base-deactivated octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 1.3 g of sodium octanesulfonate in 430 mL of a mixture of methanol and acetonitrile (75 : 25). Mix this solution and 570 mL of phosphate buffer solution.

Flow rate: 1.5 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution (2) according to the above conditions to adjust the height of the major peak to about 50% of full scale. Proceed with 20 μL of the standard solution (1) according to the above conditions; the retention times of formoterol and bambuterol are about 7 minutes and about 9 minutes respectively, with the resolution being NLT 5.0.

Time span of measurement: 1.5 times the retention time of bambuterol.

Phosphate buffer solution—Dissolve 6.90 g of sodium dihydrogen phosphate monohydrate in water to make 1000 mL, and adjust the pH to 3.0 with 5 w/v% phosphoric acid.

Water NMT 0.5% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

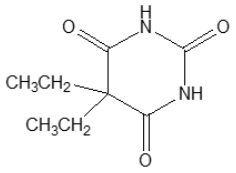
Assay Weigh accurately about 0.32 g of Bambuterol Hydrochloride, dissolve in 50 mL of ethanol(95), add 5 mL of 0.01 mol/L hydrochloric acid, mix, and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration

under the Titrimetry). Determine the endpoint between the two inflection points. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 40.39 mg of $C_{18}H_{29}N_3O_5 \cdot HCl$

Packaging and storage Preserve in well-closed containers.

Barbital
바르비탈



$C_8H_{12}N_2O_3$: 184.19
5,5-Diethyl-1,3-diazinane-2,4,6-trione [*57-44-3*]

Barbital, when dried, contains NLT 99.0% and NMT 101.0% of barbital (C8H12N2O3).

Description Barbital occurs as colorless to white crystals or a crystalline powder.
It is freely soluble in acetone or pyridine, soluble in ethanol(95), sparingly soluble in ether, and slightly soluble in water or chloroform.
It is soluble in sodium hydroxide TS or ammonia TS.
The pH of the saturated solution of Barbital is between 5.0 and 6.0.

Identification (1) Add 10 mL of sodium hydroxide TS to 0.2 g of Barbital and boil; the gas produced changes a moistened litmus paper to blue.

(2) Dissolve 50 mg of Barbital in 5 mL of diluted pyridine (1 in 10), add 0.3 mL of copper(II) sulfate TS, shake to mix, and allow to stand for 5 minutes; a purple precipitate is formed. To this, add 5 mL of chloroform and mix; the chloroform layer exhibits a purple color. Separately, weigh 50 mg of Barbital, dissolve in 2 to 3 drops of ammonia-ammonium chloride buffer solution, pH 10.7 and 5 mL of diluted pyridine (1 in 10), and add 5 mL of chloroform and 0.3 mL of copper(II) sulfate TS; a purple precipitate is formed in the water layer, and this precipitate is insoluble in chloroform when shaken to mix.

(3) Add 0.1 g of anhydrous sodium carbonate and 4 mL of water to 0.4 g of Barbital, and shake to mix. To this solution, add 0.3 g of 4-nitrobenzyl chloride in 7 mL of ethanol(95), heat on a water bath with a reflux condenser for 30 minutes, and allow to stand for 1 hour. Filter the precipitated crystals. Wash the crystals with 7 mL of sodium hydroxide TS and a small volume of water, recrystallize with a mixture of ethanol(95) and chloroform (1 : 1), and dry at 105 ℃ for 30 minutes; the melting point is between 192 and 196 ℃

Melting point Between 189 and 192 ℃.

Purity (1) ***Clarity and color of solution—*** Dissolve 0.5 g of Barbital in 5 mL of sodium hydroxide TS; the solution is colorless and clear.

(2) ***Chloride—***Dissolve 0.30 g of Barbital in 20 mL of acetone, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution as follows; to 0.30 mL of 0.01 mol/L hydrochloric acid , add 20 mL of acetone, 6 mL of dilute nitric acid, and water to make 50 mL (NMT 0.035%).

(3) ***Sulfate—***Dissolve 0.40 g of Barbital in 20 mL of acetone, add 1 mL of dilute hydrochloric acid and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution as follows; to 0.40 mL of 0.005 mol/L sulfuric acid, add 20 mL of acetone, 1 mL of dilute hydrochloric acid, and water to make 50 mL (NMT 0.048%).

(4) ***Heavy metals—***Proceed with 1.0 g of Barbital as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of the standard lead solution (NMT 20 ppm).

(5) ***Readily carbonizable substances—*** Weigh 0.5 g of Barbital and perform the test. The color of the solution is not more intense than that of Matching fluids for color A.

Loss on drying NMT 1.0% (0.5 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Barbital, previously dried, dissolve in 5 mL of ethanol(95) and 50 mL of chloroform, and titrate with 0.1 mol/L potassium hydroxide-ethanol VS (indicator: 1 mL of alizarin yellow GG-thymolphthalein TS). The endpoint of titration is when the yellow color of the solution changes from pale blue through to violet. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L potassium hydroxide-ethanol VS
= 18.419 mg of $C_8H_{12}N_2O_3$

Packaging and storage Preserve in well-closed containers.

Barium Sulfate
황산바륨

Barium Sulfate $BaSO_4$: 233.39
Barium(2+) sulfate [*7727-43-7*]

Description Barium Sulfate occurs as a white powder. It

is odorless and tasteless.
It is practically insoluble in water, ethanol(95), or ether and insoluble in hydrochloric acid, nitric acid, or sodium hydroxide TS.

Identification (1) Transfer 0.5 g of Barium Sulfate into a crucible, add 2 g each of anhydrous sodium carbonate and anhydrous potassium carbonate, mix well, and fuse by heating. After cooling, transfer into hot water, filter while stirring to mix, and add hydrochloric acid to the filtrate. The resulting solution responds to the Qualitative Analysis for sulfate.

(2) Wash hot water insoluble residue (1) with water, dissolve in 2 mL of acetic acid(31), and filter if necessary. Magnesium Glycerophosphate responds to the Qualitative Analysis for barium salt.

Purity (1) ***Acidity or alkalinity***—To 1.0 g of Barium Sulfate, add 20 mL of water, and shake well to mix for 5 minutes; the resulting solution is neutral.

(2) ***Phosphate***—To 1.0 g of Barium Sulfate, add 3 mL of nitric acid and 5 mL of water, and boil for 5 minutes. After cooling, add water to make the initial volume, filter with the filter paper washed with dilute nitric acid, add the same volume of ammonium molybdate TS, and allow to stand at 50 to 60 ℃ for 1 hour; a yellow precipitate does not form.

(3) ***Sulfide***—Transfer 10 g of Barium Sulfate into a 250-mL Erlenmeyer flask, add 10 mL of dilute hydrochloric acid and water to make 100 mL, and boil for 10 minutes; the produced gas does not change moistened lead acetate paper to black.

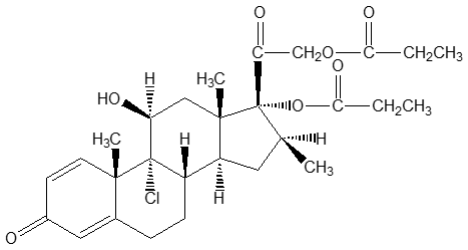
(4) ***Heavy metals***—To 5.0 g of Barium Sulfate, add 2.5 mL of acetic acid(100) and 50 mL of water, and boil for 10 minutes. After cooling, add 0.5 mL of ammonia TS and water to make 100 mL, and filter. Perform the test with 50 mL of the filtrate as the test solution. Prepare the control solution by adding 2.5 mL of lead standard solution, acetic acid(100), 0.25 mL of dilute Ammonia TS acid, and water to make 50 mL (NMT 10 ppm).

(5) ***Arsenic***—Prepare the test solution with 2.0 g of Barium Sulfate according to Method 1 and perform the test (NMT 1 ppm).

(6) ***Hydrochloric acid solubles and soluble barium salt—***Cool the solution from (3), add water to make 100 mL, and filter. Evaporate 50 mL of the filtrate to dryness on a steam bath. To the residue, add 2 drops of hydrochloric acid and 10 mL of warm water, filter with filter paper for quantitative analysis, wash with 10 mL of warm water, and combine the filtrate and the washings. Again, evaporate to dryness, and dry the residue at 105 ℃ for 1 hour; the amount of the residue is NMT 15 mg. If there is residue, add 10 mL of water, shake to mix, filter, and add 0.5 mL of dilute sulfuric acid to the filtrate. Allow to stand for 30 minutes; the resulting solution is not turbid.

Packaging and storage Preserve in well-closed containers.

Beclomethasone Dipropionate
베클로메타손디프로피오네이트



$C_{28}H_{37}ClO_7$: 521.04
(8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*S*,17*R*)-9-Chloro-11-hydroxy-10,13,16-trimethyl-3-oxo-17-[2-(propanoyloxy)ethanoyl]-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-yl propanoate [*5534-09-8*]

Beclomethasone Dipropionate, when dried, contains NLT 97.0% and NMT 103.0% of beclomethasone dipropionate ($C_{28}H_{37}ClO_7$).

Description Beclomethasone Dipropionate occurs as a white to pale yellow powder. It is odorless.
It is freely soluble in chloroform, soluble in methanol, sparingly soluble in ethanol(95) or 1,4-dioxane, slightly soluble in ether, and practically insoluble in water.

Melting point—About 208 °C (with decomposition).

Identification (1) Dissolve 2 mg of Beclomethasone Dipropionate in 2 mL of sulfuric acid; the solution exhibits a yellowish color initially, and it gradually turns orange to dark reddish brown. To this solution, carefully add 10 mL of water; the color of the solution turns bluish green, and a flocculent precipitate is formed.

(2) Dissolve 10 mg of Beclomethasone Dipropionate in 1 mL of methanol, add 1 mL of Fehling's TS, and heat; a red to reddish brown precipitate is formed.

(3) Weigh 20 mg of Beclomethasone Dipropionate and use a mixture of 1 mL of sodium hydroxide TS and 20 mL of water as the absorbent. Prepare the test solution, as directed under the Oxygen Flask Combustion; the test solution responds to the Qualitative Analysis for chloride.

(4) Determine the infrared spectra of Beclomethasone Dipropionate and beclomethasone dipropionate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If there is any difference between the spectra, perform the following: dissolve each of Beclomethasone Dipropionate and beclomethasone dipropionate RS in ethanol(95), evaporate ethanol(95), and perform the test with the residue in the same manner.

Optical rotation $[\alpha]_D^{20}$: Between + 108° and + 115° (0.1

g, previously dried, ethanol(95), 10 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 0.5 g of Beclomethasone Dipropionate according to Method 2 and perform the test. Prepare the control solution with 1.5 mL of lead standard solution (NMT 30 ppm).

(2) ***Related substances***—Dissolve 20 mg of Beclomethasone Dipropionate in 5 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin-layer chromatography. Spot 5 μL each of the test solution and the standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of toluene, methanol, and water (100 : 25 : 1) (as the developing solvent) to a distance of about 15 cm, and allow to air-dry the plate. Spray evenly alkaline blue tetrazolium TS on the plate; the spots other than the principal spot from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 0.5% (0.5 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately, about 20 mg each of Beclomethasone Dipropionate and Beclomethasone Dipropionate RS, previously dried, and dissolve each in methanol to make exactly 50 mL. Pipet 10 mL each of the test solution and the standard solution, add exactly 10 mL of the internal standard solution to each, and then add methanol to make 50 mL. Use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution, as directed under the Liquid Chromatography to the following conditions, and calculate the peak area ratios of beclomethasone dipropionate to the internal standard for the test solution and the standard solution, Q_T and Q_S, respectively.

Amount (mg) of beclomethasone dipropionate ($C_{28}H_{37}ClO_7$)
= Amount (mg) of beclomethasone dipropionate RS × $\frac{Q_T}{Q_S}$

Internal standard solution—A solution of testosterone dipropionate in the methanol (1 in 4000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 20 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μ*m* in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: A mixture of acetonitrile and water (3:2).

Flow rate: Adjust the flow rate so that the retention time of beclomethasone dipropionate is about 6 minutes.

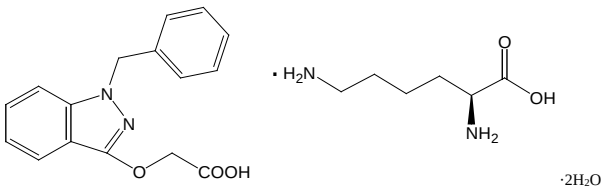
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; beclomethasone dipropionate and the internal standard are eluted in this order with the resolution between these peaks being NLT 8.

System repeatability: Perform the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio of beclomethasone dipropionate to the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Bendazac Lysine Hydrate
벤다작리신수화물



$C_{22}H_{28}N_4O_5 \cdot 2H_2O$: 464.52

L-Lysine 2-[[1-(phenylmethyl)-1*H*-indazol-3-yl] oxy]acetate (1:1) dihydrate, [*81919-14-4*]

Bendazac Lysine Hydrate, when dried, contains NLT 98.0% and NMT 102.0% of bendazac lysine ($C_{22}H_{28}N_4O_5$: 428.49).

Description Bendazac Lysine Hydrate occurs as a white to pale brown crystalline powder. It has a slight, characteristic odor.

It is soluble in water, sparingly soluble in methanol, slightly soluble in ethanol, and practically insoluble in chloroform and ether.

Identification (1) Dissolve 5 g of Bendazac Lysine Hydrate in 100 mL of water, heat to 80 ℃, and add 15 mL of 1 mol/L hydrochloric acid while shaking to mix. Shake well to mix and allow the precipitate to stand at 80 ℃ for 15 minutes. Filter immediately without cooling and wash the residue several times with distilled water. Dry the filtered precipitate under reduced pressure of 2.67 kPa at 105 ℃ and transfer 10 mg of the precipitate to a test tube. Add 2 - 3 drops of thionyl chloride and evaporate to dryness. Add 2 drops of a saturated ethanolic solution of hydroxylamine hydrochloride and 2 drops of 0.5 mol/L potassium hydroxide ethanolic solution to alkalify. Heat on a steam bath for 2 minutes and add 0.5 mol/L hydrochloric acid to acidify. To this solution, add an aqueous solution of 1% iron(III) chloride; the resulting solution exhibits a reddish brown color.

(2) Transfer 2 mL of a 1.5 mg/mL aqueous solution of Bendazac Lysine Hydrate to a test tube, add 0.5 mL of pyridine and 1 mL of a mixture of an aqueous solution of 0.5% pyridine-2-aldehyde and 0.1 mol/L cobalt nitrate (2 : 1), prepared before use, heat on a steam bath for 3 minutes, and cool; the resulting solution exhibits a violet color.

(3) Determine the absorption spectrum of the test solution in the Assay as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelength of about 306 nm.

(4) Determine the infrared spectra of Bendazac Lysine Hydrate and bendazac lysine hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

pH Dissolve 3.5 g of Bendazac Lysine Hydrate in 100 mL of water; the pH of this solution is between 5.5 and 7.5.

Melting point Between 179 and 184 °C.

Optical rotation $[\alpha]_D^{20}$: Between +4.2° and +4.6° (drying, 3.5 g, water, 100 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—A 3.2% aqueous solution of Bendazac Lysine Hydrate is clear.

(2) ***Chloride***—Transfer 1.8 g of Bendazac Lysine Hydrate to a 100-mL volumetric flask, dissolve in 75 mL of water, add 18 mL of 10% nitric acid, dilute with water to volume, mix, and filter. Take 33.3 mL of the filtrate and perform the test as directed under the Chloride. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid (NMT 0.015%).

(3) ***Sulfate***—Transfer 1.8 g of Bendazac Lysine Hydrate to a 100-mL volumetric flask, dissolve in 75 mL of water, add 18 mL of 10% nitric acid, dilute with water to volume, mix, and filter. Take 33.3 mL of the filtrate and perform the test as directed under the Sulfate. Prepare the control solution with 0.5 mL of 0.005 mol/L sulfuric acid (NMT 0.040%).

Loss on drying NMT 8.20% (1 g, 105 ℃).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.5 g of Bendazac Lysine Hydrate, previously dried, dissolve in 20 mL of 0.1 mol/L sodium hydroxide solution with shaking, and add water to make 200 mL. Pipet 2.0 mL of this solution, add water to make 200 mL, and use this solution as the test solution. Separately, weigh accurately about 0.5 g of bendazac lysine hydrate RS, previously dried, proceed in the same manner as the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbances, A_T and A_S, at the wavelength of 306 nm, respectively.

Amount (mg) of bendazac lysine ($C_{22}H_{28}N_4O_5$)
= Amount (mg) of bendazac lysine hydrate RS× $\frac{A_T}{A_S}$

Packaging and storage Preserve in tight containers.

Bendazac Lysine Tablets
벤다작리신 정

Bendazac Lysine Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of bendazac lysine hydrate ($C_{22}H_{28}N_4O_5 \cdot 2H_2O$: 464.52).

Method of preparation Prepare as directed under Tablets, with Bendazac Lysine Hydrate.

Identification Weigh an amount of Bendazac Lysine Tablets, equivalent to 20 mg of bendazac lysine hydrate according to the labeled amount, add 20 mL of methanol, shake to dissolve, and use the filtrate as the test solution. Separately, weigh 10 mg of bendazac lysine hydrate RS, dissolve in 10 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Next, develop the plate with a mixture of toluene, methyl ethyl ketone, and acetic acid(100) (45 : 45 : 4) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the color and R_f values of the spots obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

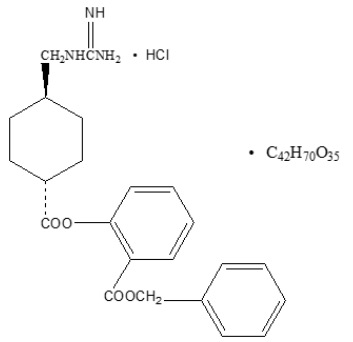
Assay Weigh accurately the mass of NLT 20 tablets of Bendazac Lysine Tablets, and powder. Weigh accurately an amount, equivalent to 0.5 g of bendazac lysine hydrate ($C_{22}H_{28}N_4O_5 \cdot 2H_2O$), add 20 mL of 0.1 mol/L sodium hydroxide solution, shake to dissolve, add water to make 200 mL, and filter. Pipet 2.0 mL of the filtrate, add water to make 200 mL, and use this solution as the test solution. Separately, weigh accurately about 0.5 g of bendazac lysine hydrate RS, proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Perform the test using the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, measure the absorbance A_T and A_S at a wavelength of 306 nm.

Amount (mg) of bendazac lysine hydrate
($C_{22}H_{28}N_4O_5 \cdot 2H_2O$)

= Amount (mg) of bendazac lysine hydrate RS× $\frac{A_T}{A_S}$

Packaging and storage Preserve in tight containers.

Benexate Hydrochloride Betadex
베넥세이트염산염베타덱스



$C_{23}H_{27}N_3O_4 \cdot HCl \cdot C_{42}H_{70}O_{35}$: 1580.94

β-Cyclodextrin trans-phenylmethyl 2-[[[4-[[(aminoiminomethyl)amino]methyl]cyclohexyl]carbonyl]oxy]benzoate hydrochloride (1:1:1), [*91574-91-3*]

Benexate Hydrochloride Betadex contains NLT 97.5% and NMT 101.5% of benexate hydrochloride betadex ($C_{23}H_{27}N_3O_4 \cdot C_{42}H_{70}O_{35}$: 1580.94), calculated on the anhydrous basis.

Description Benexate Hydrochloride Betadex occurs as a white crystalline powder. It is odorless and has a bitter taste.

It is soluble in water, slightly soluble in acetic acid(100), very slightly soluble in methanol or ethanol, and practically insoluble in acetonitrile, ether or chloroform.

Melting point—About 221℃ (with decomposition).

Identification (1) To 4 mL of an aqueous solution of Benexate Hydrochloride Betadex (1 in 500), add 0.5 mL of a solution of α-naphthol in ethanol (1 in 50), 1 mL of diacetyl TS, and 5 mL of water to, then add 1 mL of sodium hydroxide TS, shake to mix, and allow to stand for 30 minutes; the solution exhibits a red color.

(2) Weigh 0.2 g of Benexate Hydrochloride Betadex, add 20 mL of methanol, shake to mix. Filter the residue to collect, wash 3 times with 2 mL each of methanol, dry the residue at 105 ℃ for 1 hour, then dissolve in 5 mL of water, by heating if necessary. After cooling, add 2 mL of iodine TS, heat the resulting precipitate on a steam bath to dissolve, and then allow to stand at room temperature, 1 ~ 30 ℃; yellowish brown precipitates are formed.

(3) Determine the absorption spectrum of Benexate Hydrochloride Betadex as directed in the potassium bromide disk method under the Mid-infrared spectroscopy; it exhibits absorption at the wavenumbers of about 2930 cm^{-1}, 1725 cm^{-1}, 1664 cm^{-1}, 1153 cm^{-1}, 1077 cm^{-1} and 1026 cm^{-1}.

(4) An aqueous solution of Benexate Hydrochloride Betadex (1 in 50) responds to the Qualitative Analysis 1) for chloride.

Optical rotation $[\alpha]_D^{20}$: Between +107 and +114° (0.5 g calculated on the anhydrous basis, water, 50 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Benexate Hydrochloride Betadex in 10 mL of water; the solution is colorless.

(2) ***Heavy metals***—Proceed with 2.0 g of Benexate Hydrochloride Betadex as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Benexate hydrochloride***—Weigh accurately 0.5 g of Benexate Hydrochloride Betadex, transfer it into a 50-mL volumetric flask, add 30 mL of acetonitrile, and allow to stand for 5 minutes with occasional shaking. Add 5.0 mL of internal standard solution, add acetonitrile again to make 50 mL and filter. Pipet 10.0 mL of this solution and add water to make 20 mL. Use this solution as the test solution. Separately, weigh accurately about 0.1 g of benexate hydrochloride betadex RS and dissolve in acetonitrile to make 50 mL. Pipet 5.0 mL of this solution, add 5.0 mL of internal standard solution, add 50 mL of acetonitrile again to make 50 mL, and then filter. Pipet 10.0 mL of this solution and add water to make 20 mL. Use this solution as the standard solution. Perform the test with 20 μL each of the test solution and standard solution as directed under the Liquid Chromatography under Assay. Determine the ratio of the peak area, Q_T and Q_S, of benexate hydrochloride to the peak area of the internal standard for each solution; the percentage of the amount of benexate hydrochloride is NMT 1.0%.

$$\text{Content (\%) of benexate hydrochloride } (C_{23}H_{27}N_3O_4 \cdot HCl) = \frac{\text{Amount (mg) of benexate hydrochloride RS, calculated on the anhydrous basis}}{\text{Amount (mg) of sample, calculated on the anhydrous basis}} \times \frac{Q_T}{Q_S} \times 10$$

Internal standard solution—A solution of phenyl benzoate in acetonitrile (1 in 1000).

(4) ***Benzyl salicylate***—Use the solution obtained from Assay as the test solution. Separately, weigh accurately about 20 mg of benzyl salicylate RS and dissolve in a mixture of water and acetonitrile (1 : 1) to make 100 mL. Pipet 5.0 mL of this solution, and add a mixture of water and acetonitrile (1 : 1) to make 50 mL. Weigh 10.0 mL of the resulting solution, add 10.0 mL of the internal standard solution, and then add a mixture of water and acetonitrile (1 : 1) to make 50 mL. Use this solution as the standard solution. Perform the test with 10 μL each of

the test solution and standard solution as directed under the Liquid Chromatography under Assay, and determine the ratio of the peak areas, Q_T and Q_S, of benzyl salicylate to that of the internal standard in each solution; the amount of benzyl salicylate is NMT 0.2%.

$$\text{Content (\%) of benzyl salicylate } (C_{14}H_{12}O_3 : 228.25) = \frac{\text{Amount (mg) of benzyl salicylate RS, calculated on the anhydrous basis}}{\text{Amount (mg) of sample, calculated on the anhydrous basis}} \times \frac{Q_T}{Q_S}$$

Internal standard—A solution of phenyl benzoate in a mixture of water and acetonitrile (1:1) (1 in 400).

(5) **R*elated substances***—Weigh 0.2 g of Benexate Hydrochloride Betadex, dissolve it in 10 mL of a mixture of water and acetonitrile (3 : 1). Use this solution as the test solution. Separately, weigh 4.0 mg of trans-4-guanidinomethylcyclohexanecarboxylic acid hydrochloride RS, and dissolve in a mixture of water and acetonitrile (3 : 1) to make 100 mL. Use this solution as the standard solution. Spot 5 μL each of the test solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, water, and acetic acid (3 : 1 : 1) as the developing solvent to a distance of about 10 cm and air-dry the plate. Evenly spray a solution of 8-oxyquinoline in acetone (1 in 1000) on the plate, air-dry it again, and then evenly spray bromine-sodium hydroxide TS to the plate; the spots other than the principal spot from the test solution are not more intense than those from the standard solution.

Water NMT 5.0% (0.2 g, volumetric titration, back titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.15 g of Benexate Hydrochloride Betadex, dissolve in 30 mL of a mixture of water and acetonitrile (1 : 1), add 10.0 mL of internal standard solution, and then add a mixture of water and acetonitrile (1 : 1) to make 50 mL. Use this solution as the test solution. Separately, weigh accurately about 90 mg of benexate hydrochloride betadex RS, dissolve in a mixture of water and acetonitrile (1 : 1), add 20.0 mL of internal standard solution, and then add a mixture of water and acetonitrile (1 : 1) again to make 100 mL. Use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography, determine the peak areas of benexate hydrochloride and internal standard in each solution by as directed in the automatic integration method, and then determine the ratio of the peak areas, Q_T and Q_S, of the benexate hydrochloride to that of the internal standard.

$$\text{Amount (mg) of benexate hydrochloride betadex } (C_{23}H_{27}N_3O_4\cdot HCl\cdot C_{42}H_{70}O_{35}) = \text{Amount (mg) of benexate hydrochloride RS, calculated on the anhydrous basis} \times \frac{Q_T}{Q_S} \times \frac{1580.94}{445.95} \times \frac{1}{2}$$

1580.94: Molecular weight of benexate hydrochloride betadex

445.95: Molecular weight of benexate hydrochloride

Internal standard solution—A solution of phenyl benzoate in a mixture of water and acetonitrile (1 : 1) (1 in 400).

Operating conditions

Detector: An ultraviolet-visible spectrometer (wavelength: 290 nm).

Column: A stainless-steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

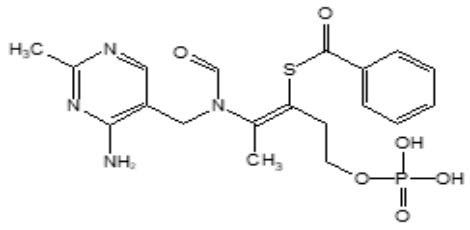
Mobile phase: A mixture of acetonitrile, acetic acid (pH 4.3) and sodium acetate buffer solution (11 : 9).

Flow rate: Adjust the flow rate so that the retention time of the internal standard is about 8 minutes.

Selection of column: Proceed with 10 μL of the standard solution under the above conditions and select the column in which benexate hydrochloride and the internal standard are eluted in this order with the resolution being NLT 3.

Packaging and storage Preserve in tight containers.

Benfotiamine
벤포티아민



$C_{19}H_{23}N_4O_6PS$: 466.45

S-[2-[[(4-Amino-2-methyl-5-pyrimidinyl)methyl]formylamino]-1-[2-(phosphonooxy)ethyl]-1-propen-1-yl] benzenecarbothioic acid ester, [*22457-89-2*]

Benfotiamine, when dried, contains NLT 98.0% and

NMT 102.0% of benfotiamine ($C_{19}H_{23}N_4O_6PS$).

Description Benfotiamine occurs as white crystals or a crystalline powder and is odorless.
It is freely soluble in water or in methanol, slightly soluble in ethanol and practically insoluble in ether or in chloroform.

Melting point—About 200 ℃ (with decomposition).

Identification (1) Dissolve 5 mg of Benfotiamine in 100 mL of acetic acid-sodium acetate buffer solution, pH 4.5. To 1 mL of this solution, add 2 mL of cysteine hydrochloride TS and 1 mL of enzyme TS and warm it at 50 ℃ for 40 minutes. After cooling, add 6 mL of cyanogen bromide TS for thiamine assay, shake to mix for about 30 seconds, add 4 mL of sodium hydroxide solution (3 in 10) and 10 mL of 1-butanol, and shake vigorously to mix. After centrifugation, examine the resulting solution under ultraviolet light; the 1-butanol layer exhibits purplish blue fluorescence. Add more cysteine hydrochloride TS and enzyme TS; the fluorescence disappears.

Cysteine hydrochloride TS—Dissolve 0.7 g of L-cysteine hydrochloride in10 mL of acetic acid-sodium acetate buffer solution, pH 5.0, adjust pH to 5.0, and add acetic acid-sodium acetate buffer solution, pH 5.0 to make 20 mL.

Enzyme TS—Add acetic acid-sodium acetate buffer solution (pH 5.0) to 1 g of the enzyme obtained from *Aspergillus*, which has strong starch saccharifying activity and strong phosphate ester dissociation activity, to make 100 mL. Prepare before use.

(2) To 10 mg of Benfotiamine, add 2 drops of the saturated methanolic solution of hydroxylamine hydrochloride, heat on a steam bath for 3 minutes, allow to stand for 1 minute, add 1 drop of the saturated methanolic solution of potassium hydroxide, and heat the solution until boils. After cooling, add hydrochloric acid (1 in 10) to acidify and add 1 drop of iron(III) chloride TS; the resulting solution exhibits a reddish purple color.

(3) To 50 mg of Benfotiamine, add 1 mL of nitric acid, heat for 1 to 2 minutes, add 5 mL of water and 1 mL of ammonium molybdate TS, and warm again; a yellow precipitate is formed. This precipitate is soluble in ammonia TS.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Benfotiamine in 10 mL of dilute hydrochloric acid; the resulting solution is colorless and clear.

(2) ***Chloride***—Proceed with 0.2 g of Benfotiamine and perform the test. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.053%).

(3) ***Sulfate***—Dissolve 1.5 g of Benfotiamine in 3 mL of dilute hydrochloric acid by warming. After cooling, add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with of 0.35 mL of 0.005 mol/L sulfuric acid, 3 mL of dilute hydrochloric acid and water to make 50 mL (NMT 0.011%).

(4) ***Heavy metals***—Dissolve 1.0 g of Benfotiamine in 5 mL of dilute hydrochloric acid, add 25 mL of water, neutralize with about 3 mL of ammonia TS, and add 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution as follows: dissolve 0.5 g of Benfotiamine in 2.5 mL of dilute hydrochloric acid, add 25 mL of water and about 1.5 mL of ammonia TS to neutralize, and add 2 mL of dilute acetic acid, 1.0 mL of lead standard solution and water to make 50 mL (NMT 20 ppm).

(5) ***Benzoic acid***—Dissolve 1.0 g of Benfotiamine in 15 mL of ether, shake to mix, and filter. Rinse the filter paper with 15 mL of ether, combine the filtrate and the washings, and evaporate it to dryness on a steam bath. To the resulting residue, dissolve in 5 mL of water by warming, and immediately add 3 drops of hydrogen peroxide water (2 in 175), and heat on a steam bath for 5 minutes. After cooling, add 2 drops of iron(III) chloride TS and allow it to stand for 20 minutes; the resulting solution does not exhibit a red color.

(6) ***Thiamine***—Dissolve 50 mg of Benfotiamine in 10 mL of 0.1 mol/L hydrochloric acid by warming and cool it down. To 1 mL of this solution, add 3 mL of cyanogen bromide TS for thiamine assay, shake to mix, add 1 mL of sodium hydroxide solution (3 in 10) and 10 mL of 1-butanol, shake vigorously to mix, and allow it to stand still. Then, filter the 1-butanol layer and examine the filtrate under ultraviolet light (main wavelength: 365 nm); the fluorescence that appears is not more intense than that appears in the solution prepared in the same manner with an aqueous solution containing 5 μg of thiamine hydrochloride per mL (thiamine hydrochloride: NMT 0.1%).

Loss on drying NMT 1.5% (1 g, 105 ℃, 2 hours).

Assay Weigh accurately about 35 mg of Benfotiamine, previously dried, and perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in well-closed containers.

Benfotiamine, Pyridoxine Hydrochloride and Cyanocobalamin capsules
벤포티아민·피리독신염산염·시아노코발라민 캡슐

Benfotiamine, Pyridoxine Hydrochloride and Cyanocobalamin Capsules contain NLT 90.0% and NMT 130.0% of the labeled amount of benfotiamine ($C_{19}H_{23}N_4O_6PS$: 466.45), NLT 90.0% and NMT 150.0% of the labeled amount of pyridoxine hydrochloride

($C_8H_{11}NO_3 \cdot HCl$: 205.64) and cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$: 1355.38).

Method of preparation Prepare as directed under Capsules, with Benfotiamine, Pyridoxine Hydrochloride and Cyanocobalamin.

Identification ***Benfotiamine, pyridoxine hydrochloride and cyanocobalamin***—Perform the test as directed under the Analysis for Vitamins with the contents of Benfotiamine, Pyridoxine Hydrochloride and Cyanocobalamin Capsules.

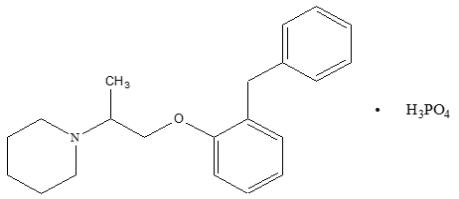
Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Benfotiamine, pyridoxine hydrochloride and cyanocobalamin—Weigh accurately the mass of contents of NLT 20 capsules of Benfotiamine, Pyridoxine Hydrochloride and Cyanocobalamin Capsules and perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in well-closed containers.

Benproperine Phosphate
벤프로페린인산염



$C_{21}H_{27}NO \cdot H_3PO_4$: 407.44

1-[1-Methyl-2-[2-(phenylmethyl) phenoxy]ethyl]piperidine trihydrogen phosphate, [*19428-14-9*]

Benproperine Phosphate contains NLT 98.0% and NMT 101.0% of benproperine phosphate ($C_{21}H_{27}NO \cdot H_3PO_4$), calculated on the anhydrous basis.

Description Benproperine Phosphate occurs as a white crystalline powder and has a characteristic odor.
It is freely soluble in methanol or in acetic acid(100), soluble in water, and insoluble in ethanol(95) or in dichloromethane.
The pH of the aqueous solution of Benproperine Phosphate (1 in 20) is between 4.0 and 6.0.

Identification (1) To 5 mL of the aqueous solution of Benproperine Phosphate (1 in 200), add 1 mL of dilute hydrochloric acid and 5 drops of Reinecke salt TS; a pale red precipitation is formed.

(2) To 25 mL of the aqueous solution of Benproperine Phosphate (1 in 50), add 5 mL of sodium hydroxide TS, and extract three times with 5 mL each of dichloromethane. To the water layer, add 5 mL of dilute nitric acid and 1 mL of ammonium molybdate TS; the resulting solution exhibits a pale yellow color. Heat this solution; a yellow precipitate is formed.

(3) Determine the absorption spectrum of the aqueous solution of Benproperine Phosphate (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 268 nm and 272 nm and between 274 nm and 278 nm.

Melting point Between 149 and 153 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Benproperine Phosphate in 10 mL of water; the resulting solution is colorless and clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Benproperine Phosphate according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Benproperine Phosphate according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Weigh 0.10 g of Benproperine Phosphate, dissolve in methanol to make 10 mL, and use this solution as the test solution. Pipet 1.0 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of isobutanol and ammonia water(28) (3 : 1) to a distance of about 10 cm, and air-dry the plate. Allow the plate to stand in a container filled with iodine vapor; the spots other than the principal spot obtained from the test solution are not more intense than the spots obtained with the standard solution.

Water NMT 1.5% (0.3 g, volumetric titration, direct titration).

Assay Weigh accurately about 0.8 g of Benproperine Phosphate, dissolve in 40 mL of acetic acid(100) for nonaqueous titration, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 40.74 mg of $C_{21}H_{27}NO \cdot H_3PO_4$

Packaging and storage Preserve in tight containers.

Benproperine Phosphate Tablets
벤프로페린인산염 정

Benproperine Phosphate Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of benproperine phosphate ($C_{21}H_{27}NO \cdot H_3PO_4$: 407.44).

Method of preparation Prepare Benproperine Phosphate Tablets as directed under Tablets, with Benproperine Phosphate.

Identification (1) Weigh an amount of Benproperine Phosphate Tablets, equivalent to 40 mg of benproperine, according to the labeled amount, add 20 mL of water, shake to mix, and filter. Add 2 drops of dilute hydrochloric acid to 10 mL of the filtrate, and add 5 drops of ammonium reinecke salt TS; a pink precipitate is formed.

(2) Add dilute nitric acid to a portion of the filtrate in (1) to make it acidic, add ammonium molybdate TS, and warm; Yellow precipitates are formed. These precipitates dissolve when sodium hydroxide solution or ammonia TS is added.

Dissolution Perform the test with 1 tablet of Benproperine Phosphate Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of Solution 2 as the dissolution medium. Take the dissolved solution 45 minutes after starting the Dissolution and filter it. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add the dissolution medium to make exactly *V'* mL so that it contains about 100 μg of benproperine phosphate per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 20 mg of benproperine phosphate RS, and add the dissolution medium to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of benproperine phosphate ($C_{21}H_{27}NO \cdot H_3PO_4$) from each solution. Meets the requirements if the dissolution rate of Benproperine Phosphate Tablets in 45 minutes is NLT 75%.

Dissolution rate (%) according to the labeled amount of benproperine phosphate ($C_{21}H_{27}NO \cdot H_3PO_4$)

$$= W_S \times (V' / V) \times (A_T / A_S) \times (1 / C) \times 90$$

W_S: Amount (mg) of benproperine phosphate RS

C: Labeled amount (mg) of benproperine phosphate ($C_{21}H_{27}NO \cdot H_3PO_4$) in 1 tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of methanol and 0.1 mol/L ammonium acetate solution (pH 3.3) (3 : 1).

Flow rate: 1.0 mL/min

0.1 mol/L ammonium acetate solution (pH 3.3)— Dissolve 7.7 g of ammonium acetate in 800 mL of water, add acetic acid(100) to adjust pH to 3.3, and add water to make 1000 mL.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Benproperine Phosphate Tablets, and powder. Weigh accurately an amount, equivalent to 5 mg of benproperine phosphate ($C_{21}H_{27}NO \cdot H_3PO_4$), add the mobile phase to make exactly 100 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 50 mg of benproperine phosphate RS, and add the mobile phase to make exactly 100 mL. Pipet 10 mL of this solution, add the mobile phase to it make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and determine the peak area, A_T and A_S, of benproperine phosphate in each solution.

Amount (mg) of benproperine phosphate ($C_{21}H_{27}NO \cdot H_3PO_4$)

$$= \text{Amount (mg) of benproperine phosphate RS} \times (A_T / A_S) \times 0.1$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of methanol and 0.1 mol/L ammonium acetate solution (pH 3.3) (3 : 1).

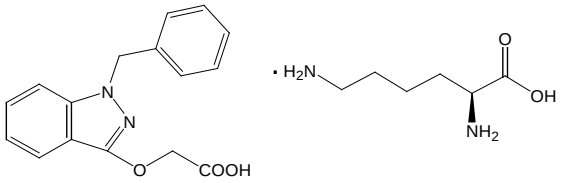
Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area of benproperine phosphate is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Benserazide Hydrochloride
벤세라지드염산염


and enantiomer

$C_{10}H_{15}N_3O_5 \cdot HCl$: 293.70

2-Amino-3-hydroxy-*N′*-[(2,3,4-trihydroxyphenyl)methyl]propanehydrazidehydrochloride [*14919-77-8*]

Benserazide Hydrochloride contains NLT 98.0% and NMT 101.0% of benserazide hydrochloride ($C_{10}H_{15}N_3O_5 \cdot HCl$), calculated on the anhydrous basis.

Description Benserazide Hydrochloride occurs as a white to grayish white crystalline powder.
It is freely soluble in water or formic acid, sparingly soluble in methanol, very slightly soluble in ethanol(95), and practically insoluble in ether.
It is hygroscopic.
It is gradually colored by light.
An aqueous solution of Benserazide Hydrochloride (1 in 100) shows no optical rotation.
Dissolve 1.0 g of Benserazide Hydrochloride in 100 mL of water; the pH of this solution is between 4.0 and 5.0.

Identification (1) Determine the absorption spectra of the solutions of Benserazide Hydrochloride and benserazide hydrochloride RS in 0.1 mol/L hydrochloric acid TS (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Benserazide Hydrochloride and benserazide hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

(3) To 10 mL of an aqueous solution of Benserazide Hydrochloride (1 in 30), add silver nitrate TS; a white precipitate is formed. To a portion of the precipitate, add dilute nitric acid; the precipitate does not dissolve.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Benserazide Hydrochloride in 10 mL of water and perform the test as directed under the Ultraviolet-visible Spectroscopy; the absorbance at the wavelength of 430 nm is NMT 0.10.

(2) ***Heavy metals***—Proceed with 1.0 g of Benserazide Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Perform the test using light-resistant containers. Dissolve 0.25 g of Benserazide Hydrochloride in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL and 3 mL each of this solution, add methanol to make exactly 200 mL, and use these solutions as the standard solution (1) and the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the test solution, the standard solution (1) and the standard solution (2) on the thin-layer chromatographic plate made of cellulose for thin-layer chromatography. Next, develop the plate with a solution of formic acid in sodium chloride TS (1 in 1000) (as the developing solvent) to a distance of about 10 cm, and air-dry the plate. Spray evenly sodium carbonate TS on the plate, air-dry, and spray evenly Folin's TS; the spots other than the principal spot obtained from the test solution are not more intense than the spot obtained from the standard solution (2), and the number of spots which are more intense than the spot obtained from the standard solution (1) is NMT 2.

Water NMT 2.5% (0.5 g, volumetric titration, direct titration). But use a solution of salicylic acid in methanol for water determination (3 in 20) instead of methanol for water determination.

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Benserazide Hydrochloride, dissolve in 5 mL of formic acid, add 50 mL of acetic acid(100), and titrate immediately with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 29.370 mg of $C_{10}H_{15}N_3O_5 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Benzalkonium Chloride
벤잘코늄염화물

Benzalkonium Chloride is presented as $[C_6H_5CH_2N(CH_3)_2R]Cl$, where R ranges from C_8H_{17} to $C_{18}H_{37}$ and mainly consists of $C_{12}H_{25}$ and $C_{14}H_{29}$.

Benzalkonium Chloride contains NLT 95.0% and NMT 105.0% of benzalkonium chloride ($C_{22}H_{40}ClN$: 354.01), calculated on the anhydrous basis.

Description Benzalkonium Chloride occurs as a white to yellowish white power, a colorless to pale yellow gelatin-shaped small piece, jelly-like fluid or a mass.
It has a characteristic odor.
It is very soluble in water or ethanol(95), and practically insoluble in ether.
An aqueous solution of Benzalkonium Chloride foams

heavily when shaken.

Identification (1) Dissolve 0.2 g of Benzalkonium Chloride in 1 mL of sulfuric acid, add 0.1 g of sodium nitrate, and heat on a steam bath for 5 minutes. After cooling, add 10 mL of water and 0.5 g of zinc powder, heat for 5 minutes, cool it down, and filter. The filtrate responds to the Qualitative Analysis for primary aromatic amine. The resulting solution exhibits a red color.

(2) To 2 mL of an aqueous solution of Benzalkonium Chloride (1 in 1000), add a mixture of 0.2 mL of bromophenol blue solution (1 in 2000) and 0.5 mL of sodium hydroxide TS; the resulting solution exhibits a blue color. To the resulting solution, add 4 mL of chloroform and shake well to mix; the blue color is moved to the chloroform layer. Separately, take the chloroform layer, and add dropwise a solution of sodium lauryl sulfate (1 in 1000) while shaking to mix; the chloroform layer becomes colorless.

(3) Determine the absorption spectra of Benzalkonium Chloride and benzalkonium chloride RS in 0.1 mol/L hydrochloric acid TS (1 in 2000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) To 1 mL of an aqueous solution of Benzalkonium Chloride (1 in 100), add 2 mL of ethanol(95) and 0.5 mL of dilute nitric acid and 1 mL of silver nitrate TS; a white precipitate is formed. The precipitate does not dissolve on the addition of dilute nitric acid, but dissolves on the addition of ammonia TS.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Benzalkonium Chloride in 10 mL of water; the resulting solution is clear and colorless to pale yellow.

(2) ***Petroleum ether-soluble substances***—To 3.0 g of Benzalkonium Chloride, add water to make 50 mL, and then add 50 mL of ethanol(99.5). Add 5 mL of 0.5 mol/L sodium hydroxide TS and extract three times with 50-mL portions of petroleum ether. Combine the petroleum ether extracts, wash three times with 50-mL portions of dilute ethanol, add 10 g of anhydrous sodium sulfate, and shake well to mix. Filter through a dried filter paper, wash the paper two times with 10-mL portions of petroleum ether, evaporate petroleum ether on a water bath by heating, and dry the residue at 105 ℃ for 1 hour; the residue is NMT 1.0%.

Water NMT 15.0% (0.2 g, volumetric titration, direct titration).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.15 g of Benzalkonium Chloride, dissolve in 75 mL of water, add dropwise diluted dilute hydrochloric acid (1 in 2) to adjust the pH between 2.6 and 3.4. Add 1 drop of methyl orange TS and titrate with 0.02 mol/L sodium tetraphenylborate VS until the solution exhibits a red color.

Each mL of 0.02 mol/L sodium tetraphenylborate VS
= 7.080 mg of $C_{22}H_{40}ClN$

Packaging and storage Preserve in tight containers.

Benzalkonium Chloride Solution
벤잘코늄염화물 액

Benzalkonium Chloride Solution is an aqueous solution containing NMT 50.0 w/v% of benzalkonium chloride.
Benzalkonium Chloride Solution contains NLT 93.0% and NMT 107.0% of benzalkonium chloride ($C_{22}H_{40}ClN$: 354.01), according to the labeled amount.

Method of preparation Prepare with Benzalkonium Chloride dissolved in Tap Water or Purified Water. Prepare with Benzalkonium Chloride Concentrated Solution 50 diluted in Tap Water or Purified Water.

Description Benzalkonium Chloride Solution occurs as a clear and colorless to pale yellow liquid and has a characteristic odor.
It foams heavily on shaking.

Identification (1) Weigh an amount of Benzalkonium Chloride Solution, equivalent to 0.2 g of Benzalkonium Chloride, according to the labeled amount, evaporate to dryness on a steam bath, and perform the test as directed under the Identification (1) of Benzalkonium Chloride.

(2) Weigh an amount of Benzalkonium Chloride Solution, equivalent to 0.01 g of Benzalkonium Chloride, according to the labeled amount, and add water to make 10 mL. With 2 mL of this solution, perform the test as directed under the Identification (2) of Benzalkonium Chloride.

(3) Weigh an amount of Benzalkonium Chloride Solution, equivalent to 1g of benzalkonium chloride, according to the labeled amount, and if necessary, add water or concentrate on a steam bath to make 10 mL. To 1 mL of this solution, add 0.1 mol/L hydrochloric acid TS to make 200 mL, and perform the test with the resulting solution as directed under the Identification (3) of Benzalkonium Chloride.

(4) Weigh an amount of Benzalkonium Chloride Solution, equivalent to 0.1 g of Benzalkonium Chloride, according to the labeled amount, and if necessary, add water or concentrate on a steam bath to make 10 mL. With 1 mL of this solution, perform the test as directed under the Identification (4) of Benzalkonium Chloride.

Assay Weigh an amount of Benzalkonium Chloride Solution, equivalent to about 0.15 g of benzalkonium chloride ($C_{22}H_{40}ClN$), add water to make 75 mL if necessary, and perform the test as directed under the Assay of Benzalkonium Chloride.

Each mL of 0.02 mol/L sodium tetraphenylborate VS
= 7.080 mg of $C_{22}H_{40}ClN$

Packaging and storage Preserve in tight containers.

Benzalkonium Chloride Concentrated Solution 50
벤잘코늄염화물농축액 50

Benzalkonium Chloride Concentrated Solution 50 is an aqueous solution, presented as $[C_6H_5CH_2N(CH_3)_2R]Cl$, where R ranges from C_8H_{17} to $C_{18}H_{37}$ and mainly consists of $C_{12}H_{25}$ and $C_{14}H_{29}$.

Benzalkonium Chloride Concentrated Solution 50 contains NLT 50.0% and NMT 55.0% of benzalkonium chloride ($C_{22}H_{40}ClN$: 354.01).

Description Benzalkonium Chloride Concentrated Solution 50 occurs as a colorless to pale yellow liquid or jelly-like fluid, and has a characteristic odor.
It is very soluble in water or ethanol(95) and practically insoluble in ether.
A solution prepared by adding water to Benzalkonium Chloride Concentrated Solution 50 foams heavily when shaken.

Identification (1) Dissolve 0.4 g of Benzalkonium Chloride Concentrated Solution 50 in 1 mL of sulfuric acid, add 0.1 g of sodium nitrate, and heat on a steam bath for 5 minutes. After cooling, add 10 mL of water and 0.5 g of zinc powder, heat for 5 minutes, allow to cool, and filter. The filtrate responds to the Qualitative Analysis for primary aromatic amine. The resulting solution exhibits a red color.

(2) To 2 mL of an aqueous solution of Benzalkonium Chloride Concentrated Solution 50 (1 in 500), add a mixture of 0.2 mL of bromophenol blue solution (1 in 2000) and 0.5 mL of sodium hydroxide TS; the resulting solution exhibits a blue color. To this solution, add 4 mL of chloroform and shake well to mix; the blue color is moved to the chloroform layer. Separately, take the chloroform layer, and add dropwise a solution of sodium lauryl sulfate (1 in 1000) while shaking to mix; the chloroform layer becomes colorless.

(3) Determine the absorption spectra of Benzalkonium Chloride Concentrated Solution 50 and benzalkonium chloride RS in 0.1 mol/L hydrochloric acid TS (1 in 1000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) To 1 mL of an aqueous solution of Benzalkonium Chloride Concentrated Solution 50 (1 in 50), add 2 mL of ethanol(95), 0.5 mL of dilute nitric acid and 1 mL of silver nitrate TS; a white precipitate is formed. The precipitate does not dissolve on the addition of dilute nitric acid, but dissolves on the addition of ammonia TS.

Purity (1) ***Clarity and color of solution***—Dissolve 2.0 g of Benzalkonium Chloride Concentrated Solution 50 in 10 mL of water; the resulting solution is clear and colorless to pale yellow.

(2) ***Petroleum ether-soluble substances***—Weigh 6.0 g of Benzalkonium Chloride Concentrated Solution 50, add water to make 50 mL, and add 50 mL of ethanol(99.5). Add 5 mL of 0.5 mol/L sodium hydroxide TS and extract with three 50-mL portions of petroleum ether. Combine the petroleum ether extracts, wash with three 50-mL portions of dilute ethanol, add 10 g of anhydrous sodium sulfate, and shake well to mix. Filter through a dried filter paper, wash the paper with two 10-mL portions of petroleum ether, evaporate petroleum ether by heating on a steam bath, and dry the residue at 105 ℃ for 1 hour; the residue is NMT 1.0%.

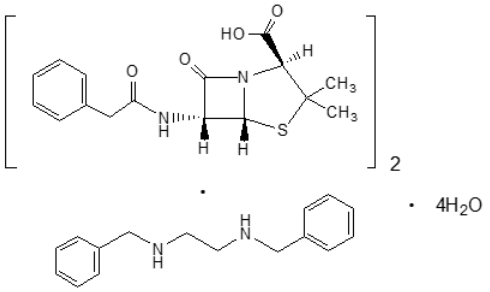
Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.30 g of Benzalkonium Chloride Concentrated Solution 50, dissolve in 75 mL of water, add dropwise diluted dilute hydrochloric acid (1 in 2) to adjust the pH between 2.6 and 3.4. Add 1 drop of methyl orange TS and titrate with 0.02 mol/L sodium tetraphenylborate VS until the solution exhibits a red color.

Each mL of 0.02 mol/L sodium tetraphenylborate VS
= 7.080 mg of $C_{22}H_{40}ClN$

Packaging and storage Preserve in tight containers.

Benzathine Penicillin G Hydrate
벤자틴페니실린G수화물



Benzathine Penicillin G
$(C_{16}H_{18}N_2O_4S)_2 \cdot C_{16}H_{20}N_2 \cdot 4H_2O$: 981.19
(2*S*,5*R*,6*R*)-3,3-Dimethyl-7-oxo-6-(2-phenyl-acetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid compound with *N*,*N*-dibenzylethylenediamine (2 : 1), tetrahydrate [*41372-02-5*]

Benzathine Penicillin G Hydrate is the *N*,*N*-dibenzylethylenediamine salt of a penicillin compound with antibacterial activity produced by the growth of the *Penicillium* genus.

Benzathine Penicillin G Hydrate contains NLT 1213

units (potency) and NMT 1333 unit (potency) of penicillin G sodium ($C_{16}H_{17}N_2O_4S$: 356.37) per mg, calculated on the anhydrous basis. 1 unit is equivalent to 0.6 μg of penicillin G sodium. Benzathine Penicillin G Hydrate contains NLT 24.0% and NMT 27.0% of *N*,*N*-dibenzylethylenediamine ($C_{16}H_{20}N_2$: 240.34), calculated on the anhydrous basis.

Description Benzathine Penicillin G Hydrate occurs as a white crystalline powder.
It is slightly soluble in methanol or ethanol(99.5) and practically insoluble in water.

Identification (1) Determine the absorption spectra of the solutions of Benzathine Penicillin G Hydrate and benzathine penicillin G RS in methanol (1 in 2000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Benzathine Penicillin G Hydrate and benzathine penicillin G RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

Crystallinity Meets the requirements.

Benzathine penicillin G Weigh accurately about 50 mg of Benzathine Penicillin G Hydrate, dissolve in methanol, and make exactly 100 mL. With this solution, determine the absorbance at the wavelength of 263 nm using methanol as the control solution and calculate $E_{1cm}^{1\%}$.

$$\text{Content (\%) of benzathine penicillin G} = E_{1cm}^{1\%} \times \frac{100}{7}$$

Optical rotation $[\alpha]_D^{20}$: Between +217° and +233° (0.1 g, calculated on the anhydrous basis, methanol, 20 mL, 100 mm).

pH The pH of a saturated solution of Benzathine Penicillin G Hydrate is between pH 5.0 and 7.5.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Benzathine Penicillin G Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Benzathine Penicillin G Hydrate according to Method 3 and perform the test (NMT 2 ppm).

(3) ***Related substances***—Dissolve 70 mg of Benzathine Penicillin G Hydrate in 25 mL of methanol, add a solution, prepared by dissolving 1.02 g of anhydrous sodium dihydrogen phosphate and 6.80 g of potassium dihydrogen phosphate in water to make 1000 mL, to make 50 mL, and use this solution as the test solution. Pipet 1.0 mL of the test solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the test solution and the standard solution according to the following conditions as directed under the Liquid Chromatography. Determine the peak area of each of the solutions; the area of the peak with the relative retention time of 2.4 for penicillin G from the test solution is not greater than 2 times the total area of peaks of penicillin G and *N*,*N*-dibenzylethylenediamine from the standard solution. The individual peak area other than the peak with the relative retention time of about 2.4 for penicillin G, *N*,*N*-dibenzylethylenediamine and benzylpenicillin from the test solution is not greater than the total area of peaks of penicillin G and *N*,*N*-dibenzylethylenediamine from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Control the gradient elution by changing the mixing ratio of the mobile phases A and B as directed under the following table.

Mobile phase A: A mixture of water, methanol and 0.25 mol/L potassium dihydrogen phosphate TS (pH 3.5) (6 : 3 : 1).

Mobile phase B: A mixture of methanol, water and 0.25 mol/L potassium dihydrogen phosphate TS (pH 3.5) (6 : 3 : 1).

Time (min)	Mobile Phase A (vol%)	Mobile Phase B (vol%)
0 - 10	75	25
10 - 20	75 → 0	25 → 100
20 - 55	0	100

Flow rate: 1.0 mL/min

System suitability

Test for required detectability: Pipet 1 mL of the standard solution and add the mobile phase A to make exactly 20 mL. Verify that the peak area of penicillin G obtained from 20 μL of this solution is 3.5% - 6.5% of the peak area of penicillin G obtained from the standard solution.

System performance: Proceed with 20 μL of the standard solution according to the above conditions; *N*,*N*-dibenzylethylenediamine and penicillin G are eluted in this order with the resolution being NLT 25.

System repeatability: Repeat the test 3 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of penicillin G is NMT 2.0%.

Time span of measurement: About 3 times the retention time of penicillin G after the solvent peak.

Water Between 5.0% and 8.0% (1 g, volumetric titration, direct titration).

Sterility It meets the requirements when Benzathine Penicillin G Hydrate is used in the manufacturing of sterile preparations. However, it is exempt from the requirements when there is a final sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins Less than 0.01 EU per 100 units (potency) of penicillin G when used in the manufacturing of sterile preparations.

Assay (1) ***Penicillin G***—Weigh accurately an amount of Benzathine Penicillin G Hydrate, equivalent to about 85000 units, and dissolve in 25 mL of methanol. Add a portion of a 1000 mL solution, dissolving 1.02 g of anhydrous sodium dihydrogen phosphate and 6.80 g of potassium dihydrogen phosphate in water, to make exactly 50 mL. Pipet 5mL of this solution, add a mixture of the solution, prepared by dissolving 1.02 g of anhydrous sodium dihydrogen phosphate and 6.80 g of potassium dihydrogen phosphate in water to make 1000 mL, and methanol (1 : 1) to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately an amount of penicillin G potassium RS, equivalent to about 85000 units, and about 25 mg of *N,N*-dibenzylethylenediamine diacetate, dissolve in 25 mL of methanol. Add the solution, prepared by dissolving 1.02 g of anhydrous sodium dihydrogen phosphate and 6.80 g of potassium dihydrogen phosphate in water to make 1000 mL, to make exactly 50 mL. Pipet 5mL of this solution, add 50 mL of the solution, prepared by dissolving 1.02 g of anhydrous sodium dihydrogen phosphate and 6.80 g of potassium dihydrogen phosphate in water to make 1000 mL, and 50 mL of methanol to make exactly 20 mL, and use this solution as the standard solution. Pipet 20 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S of penicillin G, respectively.

$$\text{Amount (unit) of penicillin G sodium} = \text{Potency (unit) of penicillin G potassium RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Water, methanol and 0.25 mol/L potassium dihydrogen phosphate TS (pH 3.5) (11 : 17 : 2)

Flow rate: Adjust the flow rate so that the retention time of penicillin G is about 18 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; *N,N*-dibenzylethylenediamine and penicillin G are eluted in this order with the resolution being NLT 20.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviations of the peak areas of *N,N*-dibenzylethylenediamine and penicillin G are NMT 2.0%, respectively.

(2) ***N,N-Dibenzylethylenediamine***—From the chromatograms of the test solution and the standard solution obtained from (1), calculate the peak areas, A_T and A_S, respectively, equivalent to *N,N*-dibenzylethylenediamine.

$$\text{Content (\%) of } N,N\text{-dibenzylethylenediamine } (C_{16}H_{20}N_2) = \frac{\text{Amount (mg) of } N,N\text{-Dibenzylethylenediamine diacetate taken}}{\text{Amount (mg) of Benzathine Penicillin G Hydrate taken}} \times \frac{A_T}{A_S} \times 100 \times 0.667$$

0.667: Conversion factor from *N,N*-dibenzylethylenediamine diacetate ($C_{16}H_{20}N_2 \cdot 2CH_3COOH$) to *N,N*-dibenzylethylenediamine (benzathine, C_{16202})

Packaging and storage Preserve in light-resistant, tight containers.

Benzathine Penicillin G for Injectable Suspension
현탁주사용 벤자틴페니실린G

Benzathine Penicillin G for Injectable Suspension is an injectable suspension, suspended before use, and contains NLT 90.0% and NMT 120.0% of the labeled amount of benzathine penicillin G hydrate [$(C_{16}H_{18}N_2O_4S)_2 \cdot C_{16}H_{20}N_2 \cdot 4H_2O$: 981.19].

Method of preparation Prepare as directed under Injections, with Benzathine Penicillin G Hydrate.

Description Benzathine Penicillin G for Injectable Suspension occurs as a white to pale yellowish white crystalline powder.

Identification Determine the infrared spectra of Benzathine Penicillin G for Injectable Suspension and benzathine penicillin G hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

pH The pH of a saturated solution of Benzathine Penicillin G for Injectable Suspension is between pH 5.0 and 7.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.01 EU per 100 units (potency) of penicillin G.

Uniformity of dosage units Meets the requirements.

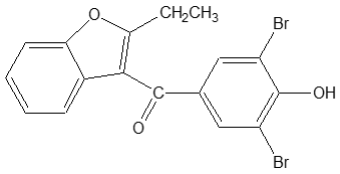
Water NMT 8.0% (0.1 g, volumetric titration, direct titration).

Assay Weigh accurately an appropriate amount of Benzathine Penicillin G for Injectable Suspension, dissolve with 1 mol/L sodium hydroxide TS to obtain a solution with a concentration of 2000 units (potency) per mL, and use this solution as the test solution. Pipet 2 mL of the test solution, place in a flask with a glass stopper, allow to stand for 15 minutes, add exactly 2.0 mL of diluted hydrochloric acid (1 in 10) and 10 mL of 0.01 mol/L iodine solution, and allow to stand for 15 minutes. Add 5 mL of carbon tetrachloride and shake if necessary, and titrate with 0.01 mol/L sodium thiosulfate VS using a micro burette until the solution in the flask turns colorless. In case of adding carbon tetrachloride, titrate until the carbon tetrachloride layer turns colorless. Use between 0.2 mL and 0.5 mL of starch TS as the indicator, if necessary. Separately, weigh accurately an amount of penicillin G sodium hydrate RS, equivalent to the amount of the sample taken, dissolve in 1% phosphate buffer solution, pH 6.0, to prepare a solution containing 2000 units (potency) per mL, and use this solution as the standard solution. Pipet 2 mL of the standard solution, place in a flask with a glass stopper, add 2.0 mL of 1 mol/L sodium hydroxide TS, allow to stand for 15 minutes, and proceed as above. Separately, weigh accurately Benzathine Penicillin G for Injectable Suspension and make a suspension containing 2000 units (potency) per mL by adding 1% phosphate buffer solution, pH 6.0. Place 2.0 mL each of this solution and the standard solution in a flask with a glass stopper, respectively, add exactly 10 mL each of 0.01 mol/L iodine solution, add about 5 mL of carbon tetrachloride and shake, if necessary, titrate with 0.01 mol/L sodium thiosulfate VS using a micro burette, and perform a blank test to make any necessary correction. Denote the volumes (mL) of 0.01 mol/L of iodine solution consumed in the titrations of the test solution and the standard solution as V_T and V_S, respectively.

$$\text{Potency (μg) of penicillin G sodium } (C_{16}H_{17}N_2NaO_4S) = \text{Potency (μg) of penicillin G sodium RS} \times \frac{V_T}{V_S}$$

Packaging and storage Preserve in hermetic containers, in a refrigerator.

Benzbromarone
벤즈브로마론



$C_{17}H_{12}Br_2O_3$: 424.08
(3,5-Dibromo-4-hydroxyphenyl)-(2-ethyl-1-benzofuran-3-yl)methanone [*3562-84-3*]

Benzbromarone, when dried, contains NLT 98.5% and NMT 101.0% of benzbromarone ($C_{17}H_{12}Br_2O_3$).

Description Benzbromarone occurs as a white to pale yellow powder, and is odorless and tasteless.
It is very soluble in *N*,*N*-dimethylformamide, freely soluble in acetone or in chloroform, soluble in ether, sparingly soluble in ethanol(95) and practically insoluble in water.
It is soluble in dilute sodium hydroxide TS.

Identification (1) Determine the absorption spectra of the solutions of Benzbromarone and benzbromarone RS in 0.01 mol/L sodium hydroxide TS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Benzbromarone and benzbromarone RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 149 and 153 ℃.

Purity (1) ***Sulfate***—Dissolve 1.0 g of Benzbromarone in 40 mL of acetone and add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid, 40 mL of acetone, 1 mL of dilute hydrochloric acid and water to make 50 mL (NMT 0.019%).

(2) ***Soluble halide***—Dissolve 0.5 g of Benzbromarone in 40 mL of acetone and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test as directed under the Chloride. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid, 40 mL of acetone, 6 mL of dilute nitric acid and water to make 50 mL.

(3) ***Heavy metals***—Proceed with 2.0 g of Benzbromarone according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Iron***—Prepare the test solution with 1.0 g of Benzbromarone according to Method 3 and perform the test according to Method A. Prepare the control solution with 2.0 mL of iron standard solution (NMT 20 ppm).

(5) ***Related substances***—Dissolve 0.10 g of Benzbromarone in 10 mL of acetone, and use this solution as the test solution. Pipet 1 mL of this solution, add acetone to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (fluorescent indicator added). Next, develop the plate with a mixture of cyclohexane, 4-methyl-2-pentanol, ethanol(99.5) and acetic acid(100) (100 : 20 : 2 : 1) (as the developing solvent) to a distance of about 15 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots obtained from the standard solution.

Loss on drying NMT 0.5% (1 g, NMT 0.67 kPa, phosphorus pentoxide, 50 ℃, 4 hours).

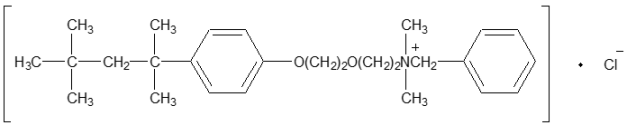
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.6 g of Benzbromarone, previously dried, dissolve in 30 mL of *N,N*-dimethylformamide, and titrate with 0.1 mol/L tetramethylammonium hydroxide VS (indicator: 5 drops of thymol blue-dimethylformamide TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L tetramethylammonium hydroxide VS
= 42.41 mg of $C_{17}H_{12}Br_2O_3$

Packaging and storage Preserve in light-resistant, tight containers.

Benzethonium Chloride
벤제토늄염화물



$C_{27}H_{42}ClNO_2$: 448.08

Benzyl-dimethyl-[2-[2-[4-(2,4,4-trimethylpentan-2-yl)phenoxy]ethoxy]ethyl]azanium chloride [*121-54-0*]

Benzethonium Chloride, when dried, contains NLT 97.0% and NMT 101.0% of benzethonium chloride ($C_{27}H_{42}ClNO_2$).

Description Benzethonium Chloride occurs as clear and colorless crystals and is odorless.
It is very soluble in ethanol(95), freely soluble in water, and practically insoluble in ether.
An aqueous solution of Benzethonium Chloride foams heavily when shaken.

Identification (1) Dissolve 0.2 g of Benzethonium Chloride in 1 mL of sulfuric acid, add 0.1 g of sodium nitrate, and heat on a steam bath for 5 minutes. After cooling, add 10 mL of water and 0.5 g of zinc powder, heat for 5 minutes, cool it down, and filter. The filtrate responds to the Qualitative Analysis for primary aromatic amine. The resulting solution exhibits a red color.

(2) To 2 mL of an aqueous solution of Benzethonium Chloride (1 in 1000), add a mixture of 0.2 mL of bromophenol blue solution (1 in 2000) and 0.5 mL of sodium hydroxide TS; the resulting solution exhibits a blue color. To this solution, add 4 mL of chloroform and shake well to mix; the blue color is moved to the chloroform layer. Separately, take the chloroform layer, and add dropwise sodium lauryl sulfate (1 in 1000) while shaking to mix; the chloroform layer becomes colorless.

(3) Determine the absorption spectra of Benzethonium Chloride and benzethonium chloride RS in 0.1 mol/L hydrochloric acid TS (1 in 5000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) To 1 mL of an aqueous solution of Benzethonium Chloride (1 in 100), add 2 mL of ethanol(95) and 0.5 mL of dilute nitric acid and 1 mL of silver nitrate TS; a white precipitate is formed. The precipitate does not dissolve on the addition of dilute nitric acid, but it dissolves on the addition of ammonia TS.

Melting point Between 158 and 164 ℃ (after drying).

Purity ***Ammonium***—Dissolve 0.1 g of Benzethonium Chloride in 5 mL of water, add 3 mL of sodium hydroxide TS, and boil; the resulting gas does not change wet red litmus paper into a blue color.

Loss on drying NMT 5.0% (1 g, 105 °C, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Benzethonium Chloride, previously dried, dissolve in 75 mL of water, add dropwise diluted dilute hydrochloric acid (1 in 2) to adjust the pH between 2.6 and 3.4. Add 1 drop of methyl orange TS and titrate with 0.02 mol/L sodium tetraphenylborate VS until the solution exhibits a red color.

Each mL of 0.02 mol/L sodium tetraphenylborate VS
= 8.962 mg of $C_{27}H_{42}ClNO_2$

Packaging and storage Preserve in light-resistant, tight containers.

Benzethonium Chloride Solution
벤제토늄염화물 액

Benzethonium Chloride Solution contains NLT 93.0% and NMT 107.0% of benzethonium chloride ($C_{27}H_{42}ClNO_2$: 448.08).

Method of preparation Prepare with Benzethonium Chloride dissolved in Tap Water or Purified Water.

Description Benzethonium Chloride Solution occurs as a clear and colorless liquid and is odorless.
It foams heavily when shaken.

Identification (1) Weigh an amount of Benzethonium Chloride Solution, equivalent to 0.2 g of Benzethonium Chloride, according to the labeled amount, and evaporate to dryness on a steam bath. With the residue, perform the test as directed under the Identification (1) of Benzethonium Chloride.

(2) Weigh an amount of Benzethonium Chloride Solution, equivalent to 10 mg of Benzethonium Chloride, according to the labeled amount, and add water to make 10 mL. With 2 mL of this solution, perform the test as directed under the Identification (2) of Benzethonium Chloride.

(3) Weigh an amount of Benzethonium Chloride Solution, equivalent to 1g of Benzethonium Chloride, according to the labeled amount, and if necessary, add water or concentrate on a steam bath to make 10 mL. To 1 mL of this solution, add 0.1 mol/L hydrochloric acid TS to make 500 mL, and determine the absorption spectrum of the resulting solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 262 nm and 264 nm, 268 nm and 270 nm, and 274 nm and 276 nm.

(4) Weigh an amount of Benzethonium Chloride Solution, equivalent to 0.1 g of Benzethonium Chloride, according to the labeled amount, and if necessary, add water or concentrate on a steam bath to make 10 mL. With 1 mL of this solution, perform the test as directed under the Identification (4) of Benzethonium Chloride.

Purity (1) ***Nitrite***—Add 1.0 mL of Benzethonium Chloride Solution in a mixture of 1 mL of glycine solution (1 in 10) and 0.5 mL of acetic anhydride; no gas is generated.

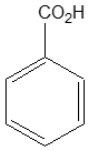
(2) ***Oxidizing material*—**To 5 mL of Benzethonium Chloride Solution, add 0.5 mL of potassium iodide TS and 2 to 3 drops of dilute hydrochloric acid; the resulting solution does not exhibit a yellow color.

Assay Weigh accurately an amount of Benzethonium Chloride Solution, equivalent to about 0.2 g of benzethonium chloride ($C_{27}H_{42}ClNO_2$), add water to make 75 mL if necessary, and perform the test as directed under the Assay of Benzethonium Chloride.

Each mL of 0.02 mol/L sodium tetraphenylborate VS
= 8.962 mg of $C_{27}H_{42}ClNO_2$

Packaging and storage Preserve in light-resistant, tight containers.

Benzoic Acid
벤조산



$C_7H_6O_2$: 122.12

Benzoic acid [*65-85-0*]

Benzoic Acid, when dried, contains NLT 99.5% and NMT 101.0% of benzoic acid ($C_7H_6O_2$).

Description Benzoic Acid occurs as white crystals or a crystalline powder.
It is odorless or has a slightly benzaldehyde-like odor.
It is freely soluble in ethanol(95), acetone, or ether, soluble in hot water, and slightly soluble in water.

Identification Dissolve 1 g of Benzoic Acid in 8 mL of sodium hydroxide TS and add water to make 100 mL; the resulting solution responds to the Qualitative Analysis (2) for benzoate.

Melting point Between 121 and 124 ℃.

Purity (1) ***Heavy metals***—Dissolve 1.0 g of Benzoic Acid in 25 mL of acetone and add 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 2 mL of dilute acetic acid, 25 mL of acetone and water to 1.0 mL of the lead standard solution to make 50 mL (NMT 10 ppm).

(2) ***Chlorine compound***—Transfer 0.5 g of Benzoic Acid and 0.7 g of calcium carbonate to a crucible, add a small amount of water, mix, and dry. Ignite it at about 600 ℃, dissolve in 20 mL of dilute nitric acid, and filter. Wash the residue with 15 mL of water, combine the washing and the filtrate, and add water to make 50 mL. To this solution, add 0.5 mL of silver nitrate TS; the turbidity of this solution is not more intense than the control solution.

Control solution—Dissolve 0.7 g of calcium carbonate in 20 mL of dilute nitric acid and filter. Wash the residue with 15 mL of water, combine the washing and the filtrate, add 1.2 mL of 0.01 mol/L hydrochloric acid and water to make 50 mL, and add 0.5 mL of silver nitrate TS.

(3) ***Potassium permanganate reducing substances***—Add 1.5 mL of sulfuric acid in 100 mL of water while boiling, add dropwise 0.02 mol/L potassium permanganate solution until the red color of the solution persists for 30 seconds, dissolve 1.0 g of Benzoic Acid in this hot solution, and add 0.50 mL of 0.02 mol/L potassium permanganate solution; the red color of the solution does not disappear within 15 seconds.

(4) ***Phthalic acid***—Weigh accurately about 100 mg of Benzoic Acid, dissolve in 1 mL of water, add 1 mL of resorcinol-sulfuric acid TS, evaporate the water by heating in an oil bath at between 120 and 125 ℃, and heat again for 90 minutes. After cooling, dissolve the resulting residue in 5 mL of water. Take 1 mL of this solution, add 10 mL of sodium hydroxide (43 in 500), and use this solution as the test solution. Separately, take exactly 61 mg of potassium hydrogen phthalate and dissolve in 1000 mL of water. Take 1 mL of this solution and proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbances of these solutions at the wavelength of 495 nm; the absorbance of the test solution is NMT that of the standard solution.

(5) ***Readily carbonizable substances***—Perform the test with 0.5 g of Benzoic Acid. The color of the solution is not more intense than matching fluids for color Q.

Loss on drying NMT 0.5% (1 g, silica gel, 3 hours).

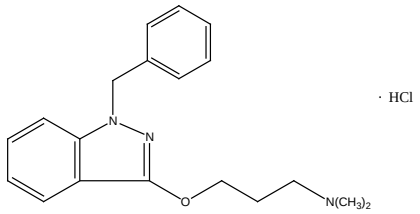
Residue on ignition NMT 0.05% (1 g).

Assay Weigh accurately about 0.5 g of Benzoic Acid, previously dried, dissolve in 25 mL of neutralized ethanol and 25 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (Indicator: 3 drops of phenolphthalein TS).

Each mL of 0.1 mol/L sodium hydroxide VS
= 12.212 mg of $C_7H_6O_2$

Packaging and storage Preserve in well-closed containers.

Benzydamine Hydrochloride
벤지다민염산염



$C_{19}H_{23}N_3O \cdot HCl$: 345.87
3-(1-Benzylindazol-3-yl)oxy-*N*,*N*-dimethylpropan-1-amine hydrochloride [*132-69-4*]

Benzydamine Hydrochloride contains NLT 99.0% and NMT 101.0% of benzydamine hydrochloride ($C_{19}H_{23}N_3O \cdot HCl$), calculated on the dried basis.

Description Benzydamine Hydrochloride occurs as a white crystalline powder.
It is very soluble in water, freely soluble in ethanol(95) or in chloroform and practically insoluble in ether.

Identification (1) Determine the infrared spectra of Benzydamine Hydrochloride and benzydamine hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Benzydamine Hydrochloride (1 in 50) responds to the Qualitative Analysis for chloride.

pH Dissolve 1.0 g of Benzydamine Hydrochloride in 10 mL of water; the pH of this solution is between 4.0 and 5.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Benzydamine Hydrochloride in 10 mL of water; the resulting solution is clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Benzydamine Hydrochloride according to Method 1 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Primary amines***—Dissolve 50 mg of Benzydamine Hydrochloride in 10 mL of ethanol(95) and add 0.1 mL of hydrochloric acid and 2 mL of the solution of 4-dimethylaminobenzaldehyde in ethanol(95) (1 in 20); the resulting yellow color obtained is not more intense than that obtained with 10 mL of the solution of 2-aminobenzoic acid in ethanol(95) (0.5 μg/mL) prepared in the same manner as in the preparation of the test solution.

(4) ***Related substances***—Dissolve 25 mg of Benzydamine Hydrochloride in a mixture of methanol and water (1 : 1) to make exactly 10 mL, and use this solution as the test solution. Dissolve 5 mg of benzydamine hydrochloride related substance I RS (3-dimethylaminopropyl

2-benzylaminobenzoate hydrochloride) and 12.5 mg of benzydamine hydrochloride related substance II RS [3-(1,5-dibenzyl-1*H*-indazol-3-yl)oxypropyldimethylamine hydrochloride] in a mixture of methanol and water (1 : 1) to make exactly 100 mL. To 1.0 mL of this solution, add a mixture of methanol and water (1 : 1) to make exactly 10 mL and use this solution as the standard solution (1). Dissolve 2.5 mg of benzydamine hydrochloride related substance III RS (1-benzyl-1*H*-indazol-3-ol) in a mixture of methanol and water (1 : 1) to make exactly 100 mL. To 1.0 mL of this solution, add a mixture of methanol and water (1 : 1) to make exactly 10 mL and use this solution as the standard solution (2). To 1.0 mL of the test solution, add a mixture of methanol and water (1 : 1) to make exactly 100 mL and use this solution as the standard solution (3). Mix exactly 1.0 mL each of the test solution and the standard solutions (1) and (2) and use the resulting solution as the standard solution (4). Perform the test with 20 μL each of the test solution and the standard solutions as directed under the Liquid Chromatography and determine the area of each peak obtained from each solution by the automatic integration method. The area of any peak of the related substance I or the related substance II obtained from the test solution is not greater than the area of the corresponding peak obtained from the standard solution (1) (NMT 0.2% for the related substance I and NMT 0.5% for the related substance II); the area of any peak of the related substance III is not greater than the area of the corresponding peak obtained from the standard solution (2) (0.1%); the area of any other secondary peak is not greater than the area of the corresponding peak obtained from the standard solution (3) (0.1%), and the sum of the areas of any such peaks is not greater than 1%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 320 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: Use the mobile phases A and B to control stepwise or based on the gradient elution as follows.

Mobile phase A: Add phosphoric acid to a solution containing 0.01 mol/L potassium dihydrogen phosphate and 0.005 mol/L sodium octyl sulphate to adjust pH to 3.0 ± 0.1.

Mobile phase B: Methanol

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0	50	50
0 - 20	50 → 30	50 → 70
20 - 22	30 → 50	70 → 50
22 - 30	50	50

Flow rate: 1.5 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution (4) according to the above conditions and adjust to make the retention time of benzydamine to about 10 minutes; the resolution between the two peaks adjacent to benzydamine is NLT 2.5.

Loss on drying NMT 0.5% (1 g, 0.67 kPa, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Benzydamine Hydrochloride, dissolve in 100 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 34.59 mg of $C_{19}H_{23}N_3O \cdot HCl$

Containers and storage Preserve in well-closed containers.

Benzydamine Hydrochloride Tablets
벤지다민염산염 정

Benzydamine Hydrochloride Tablets contain NMT 95.0% and NLT 105.0% of the labeled amount of benzydamine hydrochloride ($C_{19}H_{23}N_3O \cdot HCl$: 345.87).

Method of preparation Prepare Benzydamine Hydrochloride Tablets as directed under Tablets, with Benzydamine Hydrochloride.

Identification (1) Weigh an amount of Benzydamine Hydrochloride Tablets, equivalent to 70 mg of benzydamine hydrochloride, according to the labeled amount, extract with 20 mL of chloroform, filter, and concentrate the filtrate by evaporation on a steam bath. Dissolve in 1 mL of sulfuric acid; the solution exhibits pale yellow. Add 3 drops of formaldehyde solution, allow to stand for a long time (heat, if necessary); the solution exhibits reddish brown.

(2) Weigh an amount of Benzydamine Hydrochloride Tablets, equivalent to 50 mg of benzydamine hydrochloride, according to the labeled amount. Extract with 20 mL of water, filter, pipet 1 mL of the filtrate into a test tube, and add 0.5 mL of nitric acid and 1 mL of silver nitrate TS; white precipitates are formed. The precipitates do not dissolve in dilute nitric acid, but dissolve in an excessive amount of ammonia TS.

(3) Weigh an amount of Benzydamine Hydrochlo-

ride Tablets, equivalent to 50 mg of benzydamine hydrochloride, according to the labeled amount, and dissolve in water to make 100 mL. Filter this solution, and use the filtrate as the test solution. Separately, dissolve 50 mg of benzydamine hydrochloride RS in water to make 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ammonia water(28) and methanol (1.5 : 1) as the developing solvent, and air-dry the plate. Spray evenly hexachloroplatinic(IV) acid-potassium iodide TS on the plate; the R_f value and the color of the spots obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

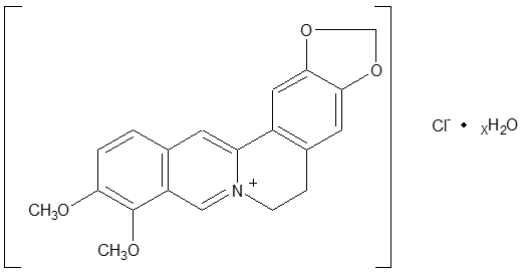
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Benzydamine Hydrochloride Tablets, and power. Then, weigh accurately an amount, equivalent to 25 mg of benzydamine hydrochloride ($C_{19}H_{23}N_3O \cdot HCl$). Dissolve in 20 mL of 1 mol/L hydrochloric acid TS, add water to make exactly 500 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 25 mg of benzydamine hydrochloride RS, add water to make exactly 500 mL, and use this solution as the standard solution. Pipet 2 mL each of the test solution and the standard solution, add acetate buffer solution, pH 5.0 to make exactly 100 mL, and perform the test as directed under the Fluorescence Spectroscopy. Determine the fluorescence intensity, F_T and F_S, at the excitation wavelength of 311 nm and the emission wavelength of 375 nm.

Amount (mg) of benzydamine hydrochloride ($C_{19}H_{23}N_3O \cdot HCl$)
= Amount (mg) of benzydamine hydrochloride RS × (F_T / F_S)

Packaging and storage Preserve in tight containers.

Berberine Chloride Hydrate
베르베린염화물수화물



Berberine Chloride $C_{20}H_{18}ClNO_4 \cdot \chi H_2O$
9,10-Dimethoxy-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinolino[3,2-a]isoquinolin-7-ium chloride hydrate [*141433-60-5*]

Berberine Chloride Hydrate contains NLT 97.0% and NMT 102.0% of berberine chloride ($C_{20}H_{18}ClNO_4$: 371.81), calculated on the anhydrous basis.

Description Berberine Chloride Hydrate occurs as yellow crystals or a crystalline powder and has a slight and characteristic odor and a very bitter taste.
It is sparingly soluble in methanol, slightly soluble in ethanol(95), and very slightly soluble in water.

Identification (1) Determine the absorption spectra as directed under the Ultraviolet-visible Spectroscopy with the solutions of Berberine Chloride Hydrate and berberine chloride hydrate RS (1 in 100000); both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Berberine Chloride Hydrate and berberine chloride hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Add 20 mL of water to 0.1 g of Berberine Chloride Hydrate, dissolve by warming, and add 0.5 mL of nitric acid. After cooling, allow the solution to stand for 10 minutes and filter. Add 1 mL of silver nitrate TS to 3 mL of the filtrate and filter the resulting precipitate to collect; the precipitate does not dissolve in dilute nitric acid, but it dissolves in an excess amount of ammonia TS.

Purity (1) ***Acid***—Add 30 mL of water to 0.1 g of Berberine Chloride Hydrate, shake well to mix, and filter. To the filtrate, add 2 drops of phenolphthalein TS and 0.10 mL of 0.1 mol/L sodium hydroxide; the yellow solution turns orange and red.

(2) ***Sulfate***—Add 48 mL of water and 2 mL of dilute hydrochloric acid to 1.0 g of Berberine Chloride Hydrate, shake to mix for 1 minute, and filter. Discard the first 5 mL of the filtrate, take 25 mL of the subsequent filtrate, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 1 mL of dilute hydrochloric acid,

5 to 10 drops of bromophenol blue TS and water to 0.50 mL of 0.005 mol/L sulfuric acid to make 50 mL (NMT 0.048%).

(3) ***Heavy metals***—Proceed with 1.0 g of Berberine Chloride Hydrate as directed under Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(4) ***Related substances***—Dissolve 10 mg of Berberine Chloride Hydrate in 100 mL of the mobile phase and use this solution as the test solution. Pipet 4 mL of the test solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas in each solution as directed in the automatic integration method; the sum of peak areas other than the major peak from the test solution is not greater than the major peak area from the standard solution.

Operating conditions

For detector, column, column temperature, mobile phase, flow rate, and system performance, proceed as directed in the operating conditions under the Assay.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of berberine obtained from 10 μL of the standard solution is about 10% of the full scale.

Time span of measurement: About 2 times the retention time of berberine after the solvent peak.

Water Between 8% and 12% (0.1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 10 mg of Berberine Chloride Hydrate, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of berberine chloride hydrate RS (previously measure the water content), dissolve in the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 mL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas, A_T and A_S, of berberine in each solution.

Amount (mg) of berberine chloride ($C_{20}H_{18}ClNO_4$)
= Amount (mg) of berberine chloride RS, calculated on the anhydrous basis $\times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 345nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 3.4 g of potassium dihydrogen phosphate and 1.7 g of sodium lauryl sulfate in 1000 mL of a mixture of water and acetonitrile (1 : 1).

Flow rate: Adjust the flow rate so that the retention time of berberine is about 10 minutes.

System suitability

System performance: Dissolve 1 mg each of berberine chloride and palmatine chloride in the mobile phase to make 10 mL. Proceed with 10 μL of this solution according to the above conditions; palmatine and berberine are eluted in this order with the resolution being NLT 1.5.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above conditions; the relative standard deviation of the peak areas of berberine is NMT 1.5%.

Packaging and storage Preserve in light-resistant, tight containers.

Berberine Tannate
베르베린탄닌산염

Berberine Tannate is a compound of berberine and tannic acid. It contains NLT 27.0% and NMT 33.0% of berberine ($C_{20}H_{19}NO_5$: 353.37), calculated on the anhydrous basis.

Description Berberine Tannate occurs as a yellow to pale yellowish brown powder.
It is odorless or has a slightly characteristic odor, and is tasteless.
It is practically insoluble in water, methanol, ethanol(95) or acetonitrile.

Identification (1) Add 10 mL of ethanol(95) to 0.1 g of Berberine Tannate, and heat on a steam bath for 3 minutes with shaking. After cooling, filter the solution and add 1 drop of iron(III) chloride TS to 5 mL of the filtrate; the solution exhibits a bluish green color, and a bluish black precipitate is formed when allowed to stand.

(2) Dissolve 10 mg each of Berberine Tannate and berberine tannate RS in 10 mL of methanol and 0.4 mL of 1 mol/L hydrochloric acid TS and add water to make 200 mL. To 8 mL each of these solutions, add water to make 25 mL. Determine the absorption spectra of the solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Berberine Tannate and berberine tannate RS, previously dried, as directly in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Acid***—Add 30 mL of water to 0.10 g of Berberine Tannate, shake well to mix, and filter. Add 2 drops of phenolphthalein TS and 0.10 mL of 0.1 mol/L sodium hydroxide to the filtrate; the yellow color of the solution turns orange to red.

(2) ***Chloride***—Add 38 mL of water and 12 mL of dilute nitric acid to 1.0 g of Berberine Tannate, shake to mix for 5 minutes, and filter. Discard the first 5 mL of the filtrate, take 25 mL of the subsequent filtrate, and add water to make 50 mL. Use this solution as the test solution. Prepare the control solution as follow; to 0.50 mL of 0.01 mol/L hydrochloric acid, add 6 mL of dilute nitric acid, 10 to 15 drops of bromophenol blue TS and water to make 50 mL (NMT 0.035%).

(3) ***Sulfate***—Add 48 mL of water and 2 mL of dilute hydrochloric acid to 1.0 g of Berberine Tannate, shake to mix for 1 minute, and filter. Discard the first 5 mL of the filtrate, take 25 mL of the subsequent filtrate, add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution as follow; to 0.50 mL of 0.005 mol/L sulfuric acid, add 1 mL of dilute hydrochloric acid, 5 to 10 drops of bromophenol blue TS and water to make 50 mL (NMT 0.048%).

(4) ***Heavy metals***—Proceed with 1.0 g of Berberine Tannate as directed under Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(5) ***Related substances***—Dissolve 10 mg of Berberine Tannate in 100 mL of the mobile phase and use this solution as the test solution. Pipet 4 mL of the test solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas of each solution as directed in the automatic integration method; the sum of peak areas other than the major peak from the test solution is not greater than the major peak area from the standard solution.

Operating conditions

For detector, column, column temperature, mobile phase, flow rate and system performance, proceed as directed in the operating conditions under the Assay.

Test for required detectability: Pipet 2 mL of the standard solution and add the mobile phase to make exactly 20 mL. Confirm that the peak area of berberine from 10 μL of this solution is equivalent to 7% to 13% of the peak area of berberine from the standard solution.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of berberine obtained from 10 μL of the standard solution is about 10% of the full scale.

Time span of measurement: About 2 times the retention time of berberine after the solvent peak.

Water NMT 6.0% (0.7 g, volumetric titration, direct titration).

Residue on ignition NMT 1.0% (1 g).

Assay Weigh accurately about 30 mg of Berberine Tannate, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of berberine chloride RS (previously measure the water content), dissolve in the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of berberine in each solution.

Amount (mg) of berberine chloride ($C_{20}H_{19}NO_5$)
= Amount (mg) of berberine chloride RS, calculated on the anhydrous basis $\times \frac{A_T}{A_S} \times 0.9504$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 345 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: Dissolve 3.4 g of potassium dihydrogen phosphate and 1.7 g of sodium lauryl sulfate in 1000 mL of a mixture of water and acetonitrile (1 : 1).

Flow rate: Adjust the flow rate so that the retention time of berberine is about 10 minutes.

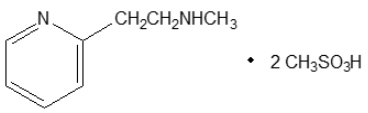
System suitability

System performance: Dissolve 1 mg each of berberine chloride and palmatine chloride in the mobile phase to make 10 mL. Proceed with 10 μL of this solution according to the above conditions; palmatine and berberine are eluted in this order with the resolution being NLT 1.5.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above conditions; the relative standard deviation of the peak areas of berberine is NMT 1.5%.

Packaging and storage Preserve in light-resistant, tight containers.

Betahistine Mesilate
베타히스틴메실산염



$C_8H_{12}N_2 \cdot 2CH_4O_3S$: 328.41

Methanesulfonic acid; *N*-methyl-2-pyridin-2-yl-ethanamine [*5638-76-6*]

Betahistine Mesilate, when dried, contains NLT 98.0% and NMT 101.0% of betahistine mesilate ($C_8H_{12}N_2 \cdot 2CH_4O_3S$).

Method of preparation If there is any possibility of alkyl (methyl, ethyl, isopropyl, etc.) methanesulfonate esters to be inserted as the potential impurities by the manufacturing process of Betahistine Mesilate, take caution with starting material, manufacturing process, and intermediate material control to minimize the residue of impurities in consideration of risk assessment results. If needed, the manufacturing process can be justified by the test data proving that there is no quality risk in the final drug substances.

Description Betahistine Mesilate occurs as white crystals or a crystalline powder.
It is very soluble in water, freely soluble in acetic acid(100), and sparingly soluble in ethanol(99.5).
It is soluble in dilute hydrochloric acid.
It is hygroscopic.

Identification (1) Determine the absorption spectra of the solutions of Betahistine Mesilate and betahistine mesilate RS in 0.1 mol/L hydrochloric acid TS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Betahistine Mesilate and betahistine mesilate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Betahistine Mesilate responds to the Qualitative Analysis (2) for mesylate.

Melting point Between 110 and 114 ℃ (after drying).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Betahistine Mesilate according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 50 mg of Betahistine Mesilate in 10 mL of a mixture of water and acetonitrile (63 : 37), and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of water and acetonitrile (63 : 37) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the peak area other than betahistine obtained from the test solution is not greater than 1/10 the peak area of betahistine from the standard solution. The total area of the peaks other than betahistine from the test solution is not greater than 1/ 2 the peak area of betahistine from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 261 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: Add water to 5 mL of diethylamine and 20 mL of acetic acid(100) to make 1000 mL. In 630 mL of this solution, dissolve 2.3 g of sodium lauryl sulfate, and add 370 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of betahistine is about 5 minutes.

System suitability

Test for required detectability: Pipet 5 mL of the standard solution, and add a mixture of water and acetonitrile (63 : 37) to make exactly 50 mL. Verify that the peak area of betahistine obtained from 20 μL of this solution corresponds to 7% to 13% of the peak area of betahistine obtained from the standard solution.

System performance: Dissolve 10 mg of betahistine mesilate and 10 mg of 2-vinylpyridine in 50 mL of a mixture of water and acetonitrile (63 : 37). Pipet 2 mL of this solution and add a mixture of water and acetonitrile (63 : 37) to make 50 mL. Proceed with 20 μL of this solution according to the above conditions; 2-vinylpyridine and betahistine are eluted in this order with the resolution between these peaks being NLT 5.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of betahistine is NMT 1.0%.

Time span of measurement: About 3 times the retention time of betahistine after the solvent peak.

Loss on drying NMT 1.0% (1 g, phosphorus pentoxide, in vacuum, 70 ℃, 24 hours).

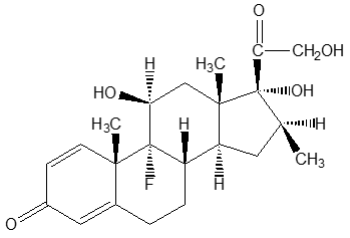
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Betahistine Mesilate, previously dried, and dissolve in 1 mL of acetic acid(100), add 50 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 16.420 mg of $C_8H_{12}N_2 \cdot 2CH_4O_3S$

Packaging and storage Preserve in tight containers.

Betamethasone
베타메타손



$C_{22}H_{29}FO_5$: 392.46

(8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*S*,17*R*)-9-Fluoro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-3-one [*378-44-9*]

Betamethasone, when dried, contains NLT 96.0% and NMT 103.0% of betamethasone ($C_{22}H_{29}FO_5$).

Description Betamethasone occurs as a white to pale yellowish white crystalline powder and is odorless.
It is sparingly soluble in methanol, ethanol(95), acetone or 1,4-dioxane, very slightly soluble in chloroform or ether, and practically insoluble in water.

Melting point—About 240 °C (with decomposition).

Identification (1) Weigh 10 mg of Betamethasone and use a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as the absorbent. Prepare the test solution, as directed under the Oxygen Flask Combustion; the test solution responds to the Qualitative Analysis for fluoride.

(2) Dissolve 1.0 mg each of Betamethasone and betamethasone RS in 10 mL of ethanol(95). Add 10 mL of phenylhydrazinium hydrochloride TS to 2.0 mL of this solution, shake to mix, and heat on a steam bath at 60 °C for 20 minutes. After cooling, determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy, using a solution prepared with 2.0 mL of ethanol(95) in the same manner, as a control solution; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the absorption spectra of Betamethasone and betamethasone RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the spectra, dissolve Betamethasone and betamethasone RS in acetone, respectively, evaporate to dryness and repeat the test on the residues.

Optical rotation $[\alpha]_D^{20}$: Between + 118° and + 126° (0.1 g, previously dried, methanol, 20 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 0.5 g of Betamethasone according to Method 2 and perform the test. Prepare the control solution with 1.5 mL of lead standard solution (NMT 30 ppm).

(2) ***Related substances***—Dissolve 10 mg of Betamethasone in 5 mL of a mixture of chloroform and methanol (9:1) and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of chloroform and methanol (9:1) to make exactly 100 mL and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of dichloromethane, ether, methanol and water (385:75:40:6) (as the developing solvent) to a distance of about 12 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (0.5 g, in vacuum, phosphorous(V) oxide, 4 hours).

Residue on ignition NMT 0.5% (0.1 g, platinum crucible).

Assay Weigh accurately about 20 mg of Betamethasone and betamethasone RS, previously dried, and dissolve each in methanol to make exactly 50 mL. Pipet 5 mL each of these solutions, add 5 mL each of the internal standard solution, and add methanol to make exactly 50 mL, and then use this solution as the test solution and the standard solution. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios of betamethasone to the internal standard for the test solution and the standard solution, Q_T and Q_S, respectively.

$$\text{Amount (mg) of betamethasone } (C_{22}H_{29}FO_5) = \text{Amount (mg) of betamethasone RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of butyl *p*-hydroxybenzoate in methanol (1 in 1750).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm to 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of water and acetonitrile (3:2).

Flow rate: Adjust the flow rate so that the retention time of Betamethasone is about 4 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; be-

tamethasone and the internal standard are eluted in this order with the resolution between these peaks being NLT 10.

System repeatability: Perform the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratios of Betamethasone to the internal standard is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Betamethasone Tablets
베타메타손 정

Betamethasone Tablets contain NLT 90.0% and NMT 107.0% of the labeled amount of betamethasone ($C_{22}H_{29}FO_5$: 392.46).

Method of preparation Prepare Betamethasone Tablets as directed under Tablets, with Betamethasone.

Identification Pulverize Betamethasone Tablets, weigh an amount, equivalent to 2 mg of betamethasone according to the labeled amount, add 20 mL of methanol, shake to mix for 5 minutes, and then filter. Evaporate the filtrate to dryness on a steam bath, and cool. Dissolve the residue in 2 mL of methanol and filter if necessary, use this solution as the test solution Separately, dissolve 2 mg of betamethasone RS in 2 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Next, develop the plate with a mixture of 1-butanol, water and acetic acid(100) (3 : 1 : 1) (as the developing solvent) to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f value of the principal spot obtained from the test solution is the same as that obtained from the standard solution.

Dissolution Perform the test with 1 tablet of Betamethasone Tablets at 50 revolutions per minute according to Method 2 under the Dissolution using a solution prepared by adding 1.0 mL of internal standard solution to 900 mL of water as the dissolution medium. Take NLT 20 mL of the dissolved solution 30 minutes after starting the Dissolution, and filter according to the membrane filtration method. Discard the first 10 mL of the filtrate, take exactly V mL of the subsequent filtrate, add water according to the labeled amount to contain about 0.56 μg of betamethasone per mL to make exactly V' mL, and use this solution as the test solution. Separately, weigh accurately about 28 mg of betamethasone RS, previously dried in a desiccator (in vacuum, phosphorus pentoxide) for 4 hours, and dissolve in methanol to make exactly 100 mL. Pipet 5 mL of this solution and add water to make exactly 100 mL. Pipet 4 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 100 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions. Determine the peak areas, A_T and A_S, of betamethasone for the test solution and the standard solution, respectively.
Meets the requirements if the dissolution rate of Betamethasone Tablets in 30 minutes is NLT 85%.

Dissolution rate (%) of the labeled amount of betamethasone ($C_{22}H_{29}FO_5$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times \frac{9}{5}$$

W_S: Amount (mg) of betamethasone RS

C: Labeled amount (mg) of betamethasone ($C_{22}H_{29}FO_5$) per tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 241 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of methanol and water (3 : 2).

Flow rate: Adjust the flow rate so that the retention time of betamethasone is about 7 minutes.

System suitability

System performance: Proceed with 100 μL of the standard solution under the above conditions; the number of theoretical plates of betamethasone is NLT 3000 plates and the symmetry factor is NMT 2.0.

System repeatability: Repeat the test 6 times with 30 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak area ration of betamethasone to that of the internal standard is NMT 1.0%.

Uniformity of dosage units Meets the requirements. Take 1 tablet of Betamethasone Tablets, and add V mL of water to contain about 50 μg of betamethasone per mL according to the labeled amount. Add exactly 2 mL of internal standard solution per 50 μg of betamethasone in this solution, shake to mix for 10 minutes, centrifuge, and use the clear supernatant as the test solution. Separately, weigh accurately about 20 mg of betamethasone RS, previously dried in a desiccator (in vacuum, phosphorus pentoxide) for 4 hours, and dissolve in acetonitrile to make exactly 200 mL. Pipet 5 mL of this solution, add exactly 5 mL of water and 20 mL of internal standard solution, and use this solution as the standard solution.

Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and determine the peak area ratio, Q_T and Q_S, of betamethasone to that of the internal standard for each solution, respectively.

$$\text{Amount (mg) of betamethasone } (C_{22}H_{29}FO_5) = \text{Amount (mg) of betamethasone RS} \times \frac{Q_T}{Q_S} \times \frac{V}{400}$$

Internal standard solution—A solution of butyl p-hydroxybenzoate in acetonitrile (1 in 40000).

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

System performance: Proceed with 50 μL of the standard solution under the above operating conditions; betamethasone and the internal standard solution are eluted in this order with the resolution being NLT 10.

System repeatability: Repeat the test 6 times with 50 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak area ratio of betamethasone to that of the internal standard is NMT 1.0%.

Assay Weigh accurately the mass of NLT 20 tables of Betamethasone Tablets, and powder. Weigh accurately an amount, equivalent to about 5 mg of betamethasone ($C_{22}H_{29}FO_5$), add 25 mL of water, add exactly 50 mL of the internal standard solution, and shake vigorously for 10 minutes to mix. Filter the solution through a membrane filter with a pore size of NMT 0.5 μm, discard the first 5 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately about 20 mg of betamethasone RS, previously dried in a desiccator (in vacuum, phosphorus pentoxide) for 4 hours, and dissolve in acetonitrile to make exactly 50 mL. Pipet 5 mL of this solution, add exactly 20 mL of the internal standard solution, add 5 mL of water, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and measure the peak area ratio, Q_T and Q_S, of betamethasone to that of the internal standard for each solution, respectively.

$$\text{Amount (mg) of betamethasone } (C_{22}H_{29}FO_5) = \text{Amount (mg) of betamethasone RS} \times \frac{Q_T}{Q_S} \times \frac{1}{4}$$

Internal standard solution—A solution of butyl p-hydroxybenzoate in acetonitrile (1 in 10000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of water and acetonitrile (3 : 2).

Flow rate: Adjust the flow rate so that the retention time of betamethasone is about 4 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution under the above operating conditions; betamethasone and the internal standard solution are eluted in this order with the resolution being NLT 10.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak area ratio of betamethasone to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Betamethasone and d-Chlorpheniramine Maleate Tablets
베타메타손·d-클로르페니라민말레산염 정

Betamethasone and *d*-Chlorpheniramine Maleate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of betamethasone ($C_{22}H_{29}FO_5$: 392.47) and *d*-chlorpheniramine maleate ($C_{16}H_{19}ClN_2C_4H_4O_4$: 390.87).

Method of preparation Prepare Betamethasone and *d*-Chlorpheniramine Maleate Tablets as directed under Tablets, with Betamethasone and *d*-Chlorpheniramine Maleate.

Identification (1) ***Betamethasone***—The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay. (2) *d-Chlorpheniramine Maleate*—Powder 5 tablets of Betamethasone and *d*-Chlorpheniramine Maleate Tablets, add ethanol to contain 2 mg per mL, and filter. Use the filtrate as the test solution. Separately, dissolve 10 mg of *d*-chlorpheniramine maleate RS in 5 mL of ethanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Next, develop the plate with a mixture of methanol and ammonia water(28) (100 : 1.5) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet rays (major wavelength: 254 nm) or spray evenly hexachloroplatinic(IV) acid-potassium io-

dide TS on the plate; the spot of the test solution exhibits color and an Rf value corresponding to that of the standard solution.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Betamethasone and *d*-Chlorpheniramine Maleate Tablets, and powder. Weigh accurately an amount equivalent to about 0.75 mg of betamethasone ($C_{22}H_{29}FO_5$) and 6 mg of *d*-chlorpheniramine maleate ($C_{16}H_{19}ClN_2C_4H_4O_4$), add the mobile phase to make exactly 50 mL, and filter. Use this solution as the test solution. Separately, dissolve betamethasone RS and *d*-chlorpheniramine maleate RS in the methanol to obtain a concentration of 0.0375 mg/mL and 0.3 mg/mL, respectively. Pipet 20 mL of this solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions. Determine the peak areas, A_{T1}, A_{T2}, A_{S1} and A_{S2}, of betamethasone and *d*-chlorpheniramine maleate for each solution.

Amount (mg) of betamethasone ($C_{22}H_{29}FO_5$)
$= 0.0375\ (mg/mL) \times (A_{T1} / A_{S2}) \times 20$

Amount (mg) of *d*-chlorpheniramine maleate ($C_{16}H_{19}ClN_2C_4H_4O_4$)
$= 0.3\ (mg/mL) \times (A_{T1} / A_{S2}) \times 20$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

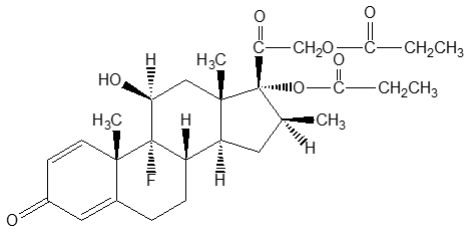
Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 1.01 g of sodium 1-heptanesulfonate in 1000 mL of dilute phosphoric acid (1 in 100). To 700 mL of this solution, add 300 mL of acetonitrile.

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Betamethasone Dipropionate
베타메타손디프로피오네이트



$C_{28}H_{37}FO_7$: 504.59

[2-[(8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*S*,17*R*)-9-Fluoro-11-hydroxy-10,13,16-trimethyl-3-oxo-17-propanoyloxy-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-17-yl]-2-oxoethyl] propanoate [*5593-20-4*]

Betamethasone Dipropionate, when dried, contains NLT 97.0% and NMT 103.0% of betamethasone dipropionate ($C_{28}H_{37}FO_7$) and it contains NLT 3.4% and NMT 4.1% of fluorine (F: 19.00).

Description Betamethasone Dipropionate occurs as a white to pale yellowish white crystalline powder and is odorless.

It is freely soluble in acetone, 1,4-dioxane or chloroform, soluble in methanol, sparingly soluble in ethanol(95), slightly soluble in ether, and practically insoluble in water or hexane.

It is gradually colored by light.

Identification (1) Add 4 mL of isoniazid TS to 1 mL of Betamethasone Dipropionate in methanol (1 in 10000), and heat on a steam bath for 2 minutes; the solution exhibits a yellow color.

(2) Weigh 10 mg of Betamethasone Dipropionate and use a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as the absorbent. Prepare the test solution, as directed under the Oxygen Flask Combustion; the test solution responds to the Qualitative Analysis for fluoride.

(3) Determine the absorption spectra of solutions of Betamethasone Dipropionate and betamethasone dipropionate RS in methanol (3 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared spectra of Betamethasone Dipropionate and betamethasone dipropionate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between + 77° and + 84° (50 mg, previously dried, acetone, 10 mL, 100 mm).

Melting point Between 176 and 180 ℃.

Purity (1) ***Fluoride***—Prepare 0.10 g of betamethasone dipropionate, add 10.0 mL of diluted 0.01 mol/L sodium hydroxide TS (1 in 20), shake for 10 minutes, and filter through a membrane filter with a pore size of 0.4 μm.

Transfer 5.0 mL of the filtrate into a 20-mL volumetric flask, add 10 mL of a mixture of alizarin complexone TS, acetic acid-potassium acetate buffer solution, pH 4.3 and cerium(III) nitrate TS (1:1:1), add water again to make 20 mL, and allow it to stand for 1 hour. Use it as the test solution. Separately, transfer 1.0 mL of standard fluorine solution into a 20-mL volumetric flask, add 5.0 mL of diluted 0.01 mol/L of sodium hydroxide TS (1 in 20) and 10 mL of a mixture of alizarin complexone TS, acetic acid-potassium acetate buffer solution, pH 4.3 and cerium(III) nitrate TS (1 : 1 : 1), and use this solution as the standard solution. Use 5.0 mL of diluted 0.01 mol/L sodium hydroxide TS (1 in 20) with these solutions and use it as the control solution. Determine the absorbance as directed under the Ultraviolet-visible Spectroscopy; the absorbance of the test solution at 600 nm is not greater than that of the standard solution (NMT 0.012%).

(2) ***Heavy metals***—Proceed with 1.0 g of Betamethasone Dipropionate as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Perform the test without exposure to daylight, using light-resistant vessels. Dissolve 10 mg of Betamethasone Dipropionate in 10 mL of chloroform, and use this solution as the test solution. Pipet 3 mL of this solution, add chloroform to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin-layer chromatography. Spot 20 μL each of the test solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Then, develop the plate with a mixture of chloroform and acetone (7 : 1) (as the developing solvent) to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 1.0% (0.5 g, 105 °C, 3 hours).

Residue on ignition NMT 0.2% (0.5 g, platinum crucible).

Assay (1) ***Betamethasone Dipropionate***—Weigh accurately about 15 mg of Betamethasone Dipropionate, previously dried, and dissolve in methanol to make exactly 100 mL. Pipet 5 mL of Betamethasone Dipropionate and add methanol to make exactly 50 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance A, at the absorbance maximum wavelength at about 239 nm.

$$\text{Amount (mg) of betamethasone dipropionate } (C_{28}H_{37}FO_7) = \frac{A}{312} \times 10000$$

(2) ***Fluorine***—Weigh accurately about 10 mg of Betamethasone Dipropionate, previously dried, and perform the test as directed under the Assay of fluorine under the Oxygen Flask Combustion, using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as an absorbent.

Packaging and storage Preserve in light-resistant, tight containers.

Betamethasone Dipropionate and Gentamicin Sulfate Cream
베타메타손디프로피오네이트·겐타마이신황산염 크림

Betamethasone Dipropionate and Gentamicin Sulfate Cream contains NLT 90.0% and NMT 110.0% of the labeled mount of betametasone dipropionate ($C_{28}H_{37}FO_7$: 504.59) and NLT 90.0% and NMT 120.0% of the labeled amount of gentamicin sulfate.

Method of preparation Prepare as directed under Creams, with Betametasone Dipropionate and Gentamicin Sulfate.

Identification (1) ***Betametasone dipropionate***—The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

(2) ***Gentamicin sulfate***—Extract an amount equivalent to 7.5 mg of Betamethasone Dipropionate and Gentamicin Sulfate Cream with 20 mL of ethyl acetate and 10 mL of water, and use the water layer as the test solution. Separately, dissolve gentamicin RS in water to make 0.075%(w/v), and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 50 μL each of the test solution and the standard solution onto a thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of 13.5 M ammonia water, ethyl acetate and methanol (1 : 2 : 1) as the developing solvent, and air-dry the plate. Place the plate in a suitable container containing between 2 g and 4 g of iodine crystal, cover with a lid, and allow to stand for 3 to 5 minutes; the test solution and the standard solution show the same color spots at the same R_f value.

Assay (1) ***Betametasone dipropionate***—Weigh an amount of Betamethasone Dipropionate and Gentamicin Sulfate Cream, equivalent to 1.0 mg of betametasone dipropionate ($C_{28}H_{37}FO_7$), add 30 mL of methanol, shake to mix, add methanol to make 50 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 20 mg of betametasone dipropionate RS and dissolve in methanol to make 100 mL. Take 10.0 mL of this solution, add methanol to make 50 mL, and use this solu-

tion as the standard solution. Perform the test with 15 μL each of the test solution and the standard solution according to the following conditions as directed under the Liquid Chromatography, and determine the peak areas, A_T and A_S of each solution.

Amount (mg) of betamethasone dipropionate ($C_{28}H_{37}FO_7$)
= Amount (mg) of betametasone dipropionate RS $\times \frac{A_T}{A_S} \times \frac{1}{20}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and water (45 : 55).

Flow rate: 1.5 mL/min

(2) ***Gentamicin sulfate***—Cylinder plate method Perform test according to (1) and (2) of the Assay for Gentamicin sulfate. However, prepare the test solution as the following method.

Method 1 Weigh accurately an amount of Betamethasone Dipropionate and Gentamicin Sulfate Cream, equivalent to about 1.0 mg (potency) according to the labeled potency, place in a blender, add 80 mL of 0.1 mol/L phosphate buffer solution (pH 8.0), warmed previously to 70 to 85 ℃, grind at high speed for 3 to 5 minutes, cool, then add the above buffer solution to make 100.0 mL of solution.

Method 2 Weigh accurately an amount of Betamethasone Dipropionate and Gentamicin Sulfate Cream, equivalent to 1.0 mg (potency) according to the labeled potency, place in a separatory funnel, add 50 mL of ether, shake to mix until uniform, extract three times with 25 mL of 0.1 mol/L phosphate buffer solution, pH 8.0, combine the extracts, and add the above buffer solution to make 100 mL of solution.

Pipet appropriate amounts of the solutions from Method 1 or Method 2, dilute with 0.1 mol/L phosphate buffer solution, pH 8.0, to the concentrations of (1) ③ and (2) ③, respectively, and use these as the test solutions.

Packaging and storage Preserve in tight containers.

Betamethasone Dipropionate, Clotrimazole and Gentamicin Sulfate Cream
베타메타손디프로피오네이트·클로트리마졸·겐타마이신황산염 크림

Betamethasone Dipropionate, Clotrimazole and Gentamicin Sulfate Cream contains NLT 90.0% and NMT 110.0% of the labeled amounts of betametasone diproprionate ($C_{28}H_{37}FO_7$: 504.59) and clotrimazole ($C_{22}H_{17}ClN_2$: 344.84), and NLT 90.0% and NMT 120.0% of the labeled amount of gentamicin sulfate.

Method of preparation Prepare as directed under Creams, with Betametasone Dipropionate, Clotrimazole and Gentamicin Sulfate.

Identification (1) ***Betametasone proprionate and clotrimazole***—The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

(2) ***Gentamicin sulfate***—Extract an amount equivalent to 7.5 mg of Betamethasone Dipropionate, Clotrimazole and Gentamicin Sulfate Cream with 20 mL of ethyl acetate and 10 mL of water, and use the water layer as the test solution. Separately, dissolve gentamicin RS in water to make 0.075%(w/v), and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 50 μL each of the test solution and the standard solution onto a thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of 13.5M ammonia water, ethyl acetate and methanol (1 :2 : 1) as the developing solvent, and air-dry the plate. Place the plate in a suitable container containing between 2 g and 4 g of iodine crystal, cover with a lid, and allow to stand for 3 to 5 minutes; the test solution and the standard solution show the same color spots at the same R_f value.

Assay (1) ***Betametasone propionate and clotrimazole***—Weigh accurately about 1 g of Betamethasone Dipropionate, Clotrimazole and Gentamicin Sulfate Cream, add 2.0 mL of the internal standard solution and 4.0 mL of ethanol, warm for about 10 minutes on a steam bath at 60 ℃, and shake to mix for 3 minutes. Repeat this procedure 3 times, cool for about 20 minutes in iced water, centrifuge, and use the clear supernatant as the test solution. Separately, weigh about 32.0 mg of betametasone dipropionate RS, previously dried, and add ethanol to make 100 mL. Weigh about 50.0 mg of clotrimazole RS, previously dried, and add ethanol to make 10.0 mL. Take 2.0 mL each of these solutions, evaporate to dryness, proceed in the same manner as the test solution, and use the resulting solutions as the standard solutions. Perform the test with 10 μL each of the test solution and the standard solutions as directed under the Liquid Chromatography according to the following conditions and de-

termine the peak area ratios of betametasone dipropionate and clotrimazole with respect to the peak area of the internal standard, Q_{T1}, Q_{T2}, Q_{S1} and Q_{S2}, for each solution.

$$\text{Amount (mg) of betamethasone dipropionate } (C_{28}H_{37}FO_7) = \text{Amount (mg) of betametasone dipropionate RS} \times \frac{Q_T}{Q_S} \times \frac{1}{10}$$

$$\text{Amount (mg) of clotrimazole } (C_{22}H_{17}ClN_2) = \text{Amount (mg) of clotrimazole RS} \times \frac{Q_{T2}}{Q_{S2}} \times \frac{1}{5}$$

Internal standard solution—Weigh about 15 mg of progesterone RS and add ethanol to make 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column, about 3.9 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography.

Mobile phase: A mixture of acetonitrile and 0.05 mol/L dibasic ammonium phosphate (65 : 35).

Flow rate: 0.65 mL/min

(2) ***Gentamicin sulfate***—Cylinder plate method Perform test according to (1) and (2) of the Assay for gentamicin sulfate. However, prepare the test solution as following methods.

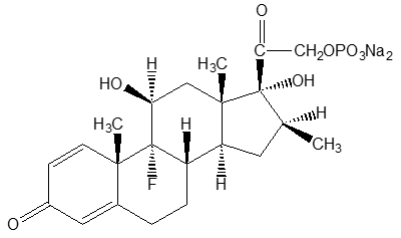
Method 1 Weigh accurately an amount of Betamethasone Dipropionate, Clotrimazole and Gentamicin Sulfate Cream, equivalent to about 1.0 mg (potency) according to the labeled potency, place in a blender, add 80 mL of 0.1 mol/L phosphate buffer solution (pH 8.0), warmed previously to 70 ℃ to 85 ℃, mix at high speed for 3 to 5 minutes, cool, then add the above buffer solution to make 100.0 mL of solution.

Method 2 Weigh accurately an amount of Betamethasone Dipropionate, Clotrimazole and Gentamicin Sulfate Cream, equivalent to about 1.0 mg (potency) according to the labeled potency, place in a separatory funnel, add 50 mL of ether, and shake to mix until homogeneous. Extract 3 times with 25 mL each of 0.1 mol/L phosphate buffer solution, pH 8.0, combine the extracts, and add the above buffer solution to make 100 mL of solution.

Pipet appropriate amounts of the solutions from Method 1 and Method 2 and dilute with 0.1 mol/L phosphate buffer solution, pH 8.0, to the concentrations of (1) ④ and (2) ③, and use these solutions as the test solutions.

Packaging and storage Preserve in tight containers.

Betamethasone Sodium Phosphate
베타메타손포스페이트나트륨



$C_{22}H_{28}FNa_2O_8P$: 516.41

Disodium [2-[(8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*S*,17*R*)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-17-yl]-2-oxoethyl] phosphate [*151-73-5*]

Betamethasone Sodium Phosphate contains NLT 97.0% and NMT 103.0% of betamethasone sodium phosphate ($C_{22}H_{28}FNa_2O_8P$), calculated on the anhydrous basis.

Description Betamethasone Sodium Phosphate occurs as a white to pale yellowish white crystalline powder or a mass and is odorless.

It is freely soluble in water, sparingly soluble in methanol, slightly soluble in ethanol(95), and practically insoluble in ether.

It is hygroscopic.

Melting point—About 213 °C (with decomposition).

Identification (1) Dissolve 2 mg of Betamethasone Sodium Phosphate in 2 mL of sulfuric acid; the resulting solution exhibits a brown color, changing slowly to blackish brown.

(2) Weigh 10 mg of Betamethasone Sodium Phosphate and use a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as the absorbent. Prepared the test solution, as directed under the Oxygen Flask Combustion; the test solution responds to the Qualitative Analysis (2) for fluoride.

(3) Transfer 40 mg of Betamethasone Sodium Phosphate to a platinum crucible and carbonize by heating. After cooling, add 5 drops of nitric acid and incinerate by ignition. To the residue, add 10 mL of diluted nitric acid (1 in 50), and boil for several minutes. After cooling, the solution responds to the Qualitative Analysis (2) for phosphate. Neutralize the test solution by adding ammonia TS; the resulting solution responds to the Qualitative Analysis for sodium salt and Qualitative Analysis (1) or (3) for phosphate.

(4) Determine the infrared spectra of Betamethasone Sodium Phosphate and betamethasone sodium phosphate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between + 99° and + 105° (0.1 g, calculated on the anhydrous basis, water, 10 mL, 100 mm).

pH Dissolve 0.10 g of Betamethasone Sodium Phosphate in 20 mL of water; the pH of the solution is between 7.5 and 9.0.

Purity (1) ***Clarity and color of solution***—Dissolve 0.25 g of Betamethasone Sodium Phosphate in 10 mL of water; the resulting solution is clear and colorless.

(2) ***Free phosphoric acid***—Weigh accurately about 20 mg of Betamethasone Sodium Phosphate, dissolve in 20 mL of water, and use this solution as the test solution. Separately, pipet 4 mL of phosphoric acid RS, add 20 mL of water, and use this solution as the standard solution. To the test solution and the standard solution, add exactly 7 mL of dilute sulfuric acid, 2 mL of ammonium molybdate-sulfuric acid TS and 2 mL of *p*-aminophenol sulfate TS, shake well to mix, allow to stand at 20 ± 1 ℃ for 15 minutes, and add water to make exactly 50 mL, respectively. Allow to stand at 20 ± 1 ℃ for 15 minutes. Prepare the control solution as using the solution prepared in the same manner with 20 mL of water. Perform the test with these solutions as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbances, A_T and A_S, at the wavelength of 730 nm; the amount of free phosphoric acid is NMT 0.5%.

$$\text{Content (\%) of free phosphoric acid } (H_3PO_4) = \frac{A_T}{A_S} \times \frac{1}{W} \times 10.32$$

W: Amount (mg) of Betamethasone Sodium Phosphate, calculated on the anhydrous basis.

(3) ***Betamethasone***—Dissolve 20 mg of Betamethasone Sodium Phosphate in exactly 2 mL of methanol, and use this solution as the test solution. Separately, weigh 20 mg of betamethasone RS, and dissolve in exactly 10 mL of methanol. Pipet 1 mL of this solution, add methanol to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a freshly prepared mixture of *1*-butanol, water and acetic anhydride (3 : 1 : 1) (as the developing solvent) to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the spot from the test solution corresponding to the spot from the standard solution is not more intense than the spot from the standard solution.

Water NMT 10.0% (0.2 g, volumetric titration, back titration).

Assay Weigh accurately 20 mg each of Betamethasone Sodium Phosphate and betamethasone sodium phosphate RS (water previously determined), and dissolve each in methanol to make exactly 20 mL. Pipet 5 mL each of these solutions, add exactly 5 mL of the internal standard solution, add methanol to make 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios of betamethasone phosphate to that of the internal standard, Q_T and Q_S, respectively.

$$\text{Amount (mg) of betamethasone sodium phosphate } (C_{22}H_{28}FNa_2O_8P) = \text{Amount (mg) of betamethasone sodium phosphate RS, calculated on the anhydrous basis} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of butyl *p*-hydroxybenzoate in methanol (1 in 5000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (7 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 1.6 g of tetra *n*-butylammonium bromide, 3.2 g of sodium monohydrogen phosphate and 6.9 g of potassium dihydrogen phosphate in 1000 mL of water, and add 1500 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of betamethasone phosphate is about 5 minutes.

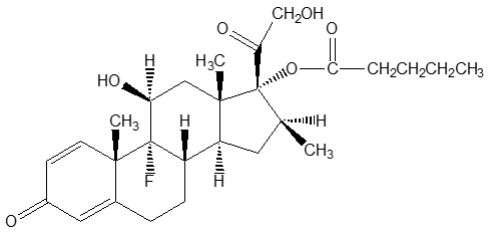
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; betamethasone phosphate and the internal standard are eluted in this order with the resolution between these peaks being NLT 10.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratios of betamethasone phosphate to the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Betamethasone Valerate
베타메타손발레레이트



$C_{27}H_{37}FO_6$: 476.58

[(8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*S*,17*R*)-9-Fluoro-11-hydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-17-yl] pentanoate [*2152-44-5*]

Betamethasone Valerate, when dried, contains NLT 97.0% and NMT 103.0% of betamethasone valerate ($C_{27}H_{37}FO_6$).

Description Betamethasone Valerate occurs as a white crystalline powder and it is odorless.
It is freely soluble in chloroform, soluble in ethanol(95), sparingly soluble in methanol, slightly soluble in ether, and practically insoluble in water.

Melting point—About 190 °C (with decomposition).

Identification (1) Weigh 10 mg of Betamethasone Valerate and use a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as the absorbent. Prepare the test solution, as directed under the Oxygen Flask Combustion,; the test solution responds to the Qualitative Analysis for fluoride.

(2) Determine the infrared spectra of Betamethasone Valerate and betamethasone valerate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between + 77° and + 83° (0.10 g, previously dried, methanol, 20 mL, 100 mm).

Purity (1) ***Related substances***—Perform the test without exposure to light. Dissolve 20 mg of Betamethasone Valerate in 5 mL of a mixture of chloroform and methanol (9 : 1) and use this solution as the test solution. Pipet 1.0 mL of the test solution, add a mixture of chloroform and methanol (9 : 1) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of chloroform and methanol (9 : 1) (as the developing solvent) to a distance of about 12 cm, and air-dry the plate. Spray evenly alkaline blue tetrazolium TS on the plate; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 °C, 3 hours).

Residue on ignition NMT 0.2% (0.5 g, platinum crucible).

Assay Weigh accurately about 10 mg each of Betamethasone Valerate and betamethasone valerate RS, previously dried, and dissolve each in methanol to make exactly 100 mL. Pipet 10.0 mL each of these solutions, add exactly 10 mL each of the internal standard solution, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios of betamethasone valerate to the internal standard for the test solution and the standard solution, Q_T and Q_S, respectively.

$$\text{Amount (mg) of betamethasone valerate } (C_{27}H_{37}FO_6) = \text{Amount (mg) of betamethasone valerate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of isoamyl benzoate in methanol (1 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 20 cm to 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (7 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

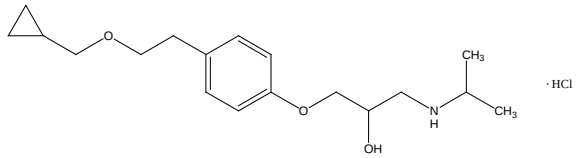
Mobile phase: A mixture of methanol and water (7 : 3).

Flow Rate: Adjust the flow rate so that the retention time of betamethasone valerate is about 10 minutes.

Selection of column: Proceed with 10 μL of the standard solution according to the above conditions; betamethasone valerate and the internal standard are eluted in this order with the resolution between these peaks being NLT 5.

Packaging and storage Preserve in light-resistant, tight containers.

Betaxolol Hydrochloride
베탁솔롤염산염



$C_{18}H_{29}NO_3 \cdot HCl$: 343.89
1-[4-[2-(Cyclopropylmethoxy)ethyl]phenoxy]-3-(propan-2-ylamino)propan-2-ol hydrochloride [*63659-19-8*]

Betaxolol Hydrochloride contains NLT 99.0% and NMT 101.0% of betaxolol hydrochloride ($C_{18}H_{29}NO_3 \cdot HCl$), calculated on the dried basis.

Description Betaxolol Hydrochloride occurs as a white crystalline powder.
It is very soluble in water, and freely soluble in methanol, ethanol(95), or acetic acid(100).
An aqueous solution of Betaxolol Hydrochloride (1 in 100) shows no optical rotation.

Identification (1) Determine the absorption spectra of solutions of Betaxolol Hydrochloride and betaxolol hydrochloride RS in ethanol(95) (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Betaxolol Hydrochloride and betaxolol hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Betaxolol Hydrochloride (1 in 10) responds to the Qualitative Analysis for chloride.

Melting point Between 114 and 117 ℃.

pH Dissolve 1 g of Betaxolol Hydrochloride in 50 mL of water; the pH of this solution is between 4.5 and 6.5.

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Betaxolol Hydrochloride in 10 mL of water; the resulting solution is clear and colorless.

(2) ***Heavy metals*—**Proceed with 2.0 g of Betaxolol Hydrochloride according to Method 4 under the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Prepare the test solution with 2.0 g of Betaxolol Hydrochloride according to Method 3 and perform the test (NMT 1 ppm).

(4) ***Related substance I*—**Dissolve 0.10 g of Betaxolol Hydrochloride in 10 mL of methanol and use this solution as the test solution. Pipet 3 mL of this solution and add methanol to make exactly 50 mL. Pipet 1 mL of this solution, add methanol to make exactly 20 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of ethyl acetate, water and acetic acid(100) (10 : 3 : 3) (as the developing solvent) to a distance of about 10 cm, and air-dry the plate. Allow the plate to stand in iodine vapor for 1 hour; the spots other than the principal spot obtained from the test solution are NMT 3 and not more intense than the spots obtained from the standard solution.

(5) ***Related substance II*—**Dissolve 0.10 g of Betaxolol Hydrochloride in 50 mL of the mobile phase, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to it make exactly 200 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine peak area in each solution by the automatic integration method; individual peak area other than betaxolol from the test solution is not greater than the peak area of betaxolol from the standard solution. The total peak area other than betaxolol from the test solution is not greater than 2 times the peak area of betaxolol from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 273 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of diluted 0.05 mol/L potassium dihydrogen phosphate (1 in 2) adjusted to pH 3.0 by adding 1 mol/L hydrochloric acid TS, acetonitrile and methanol (26 : 7 : 7).

Flow rate: Adjust the flow rate so that the retention time of betaxolol is about 9 minutes.

System suitability

Test for required detectability: Pipet 4 mL of the standard solution and add the mobile phase to make exactly 20 mL. Verify that the peak area of betaxolol obtained from 10 μL of this solution corresponds to 14% to 26% of the peak area of betaxolol obtained from the standard solution.

System performance: Dissolve 50 mg of Betaxolol Hydrochloride and 5 mg of 2-naphtol in 200 mL of the mobile phase. Proceed with 10 μL of this solution according to the above conditions; betaxolol and 2-naphtol are eluted in this order with the resolution being NLT 10.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the

above conditions; the relative standard deviation of the peak area of betaxolol is NMT 2.0%.

Time span of measurement: About 2 times the retention time of betaxolol after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 °C, 4 hours).

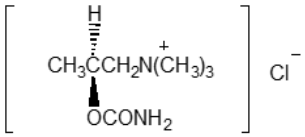
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Betaxolol Hydrochloride, dissolve in 50 mL of acetic acid(100), add 7 mL of mercury acetate TS, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 34.39 mg of $C_{18}H_{29}NO_3 \cdot HCl$

Packaging and storage Preserve in tight containers.

Bethanechol Chloride
베타네콜염화물



and enantiomer

$C_7H_{17}ClN_2O_2$: 196.68
2-Carbamoyloxypropyl(trimethyl)azanium chloride [*590-63-6*]

Bethanechol Chloride, when dried, contains NLT 98.0% and NMT 101.0% of bethanechol chloride ($C_7H_{17}ClN_2O_2$).

Description Bethanechol Chloride occurs as colorless or white crystals or a crystalline powder.
It is very soluble in water, freely soluble in acetic acid(100), and sparingly soluble in ethanol(99.5).
It is hygroscopic.
An aqueous solution of Bethanechol Chloride (1 in 10) shows no optical rotation.

Identification (1) To 2 mL of an aqueous solution of Bethanechol Chloride (1 in 40), add 0.1 mL of cobalt(II) chloride hexahydrate solution (1 in 100), and add 0.1 mL of potassium hexacyanoferrate(II) TS; the solution exhibits a green color, and the color almost entirely fades within 10 minutes.

(2) Add 0.1 mL of iodine TS to 1 mL of an aqueous solution of bethanechol chloride (1 in 100); the solution exhibits a greenish brown color.

(3) Determine the infrared spectra of Bethanechol Chloride and bethanechol chloride RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) An aqueous solution of Bethanechol Chloride (1 in 100) responds to the Qualitative Analysis for chloride.

Melting point Between 217 and 221 °C (after drying).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Bethanechol Chloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 0.1 g of Bethanechol Chloride in 2.5 mL of water, and use this solution as the test solution. Pipet 1 mL of the test solution, add water to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 1 μL each of the test solution and the standard solution on a plate of cellulose for thin-layer chromatography. Develop the plate with a mixture of a solution of ammonium chloride acetate (1 in 100), acetone, *1*-butanol and formic acid (20 : 20 : 20 : 1) (as the developing solvent) to a distance of about 10 cm, and dry the plate at 105 °C for 15 minutes. Spray evenly hexachloroplatinic(IV) acid-potassium iodide TS on the plate, and allow to stand for 30 minutes; the spots other than the principal spot from the test solution are not more intense than those from the standard solution.

Loss on drying NMT 1.0% (1 g, 105 °C, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Chloride content Weigh accurately 0.4 g of Bethanechol Chloride, previously dried, and dissolve in 30 mL of water. Add 40.0 mL of 0.1 mol/L silver nitrate TS, then add 3 mL of nitric acid and 5 mL of nitrobenzene, and shake to mix for a few minutes. Add 2 mL of ammonium iron(III) sulfate TS and titrate the excess silver nitrate with 0.1 mol/L ammonium thiocyanate VS. The content of chloride is between 17.7% and 18.3%.

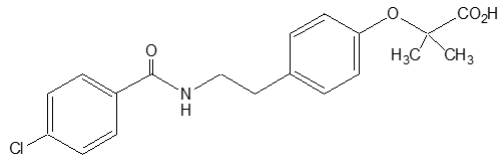
Each mL of 0.1 mol/L silver nitrate TS
= 3.545 mg of Cl

Assay Weigh accurately 0.4 g of Bethanechol Chloride, previously dried, dissolve in 2 mL of acetic acid(100), add 40 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 19.668 mg of $C_7H_{17}ClN_2O_2$

Packaging and storage Preserve in tight containers.

Bezafibrate
베자피브레이트



$C_{19}H_{20}ClNO_4$: 361.82
2-[4-[2-[(4-Chlorobenzoyl)amino]ethyl]phenoxy]-2-methylpropanoic acid [*41859-67-0*]

Bezafibrate, when dried, contains NLT 98.5% and NMT 101.0% of bezafibrate ($C_{19}H_{20}ClNO_4$).

Description Bezafibrate occurs as a white crystalline powder.
It is freely soluble in *N*,*N*-dimethylformamide, soluble in methanol, slightly soluble in ethanol(99.5), and practically insoluble in water.

Identification (1) Determine the absorption spectra of the solutions of Bezafibrate and bezafibrate RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Bezafibrate and bezafibrate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Perform the test as directed under the Flame Coloration (2) with Bezafibrate; it exhibits a green color.

Melting point Between 181 and 186 ℃.

Purity (1) ***Chloride*—**Weigh 3.0 g of Bezafibrate, dissolve in 15 mL of *N*,*N*-dimethylformamide, add water to make 60 mL, and shake well. Allow the solution to stand for at least 12 hours and filter. To 40 mL of the filtrate, add 6 mL of dilute nitric acid and water to make 50 mL, and use this solution as the test solution. Prepare the control solution by adding 0.70 mL of 0.01 mol/L hydrochloric acid, 10 mL of *N*,*N*-dimethylformamide, 6 mL of dilute nitric acid and water to make 50 mL (NMT 0.012%).

(2) ***Heavy metals***—Proceed with 2.0 g of Bezafibrate as directed under Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 0.10 g of Bezafibrate in 35 mL of methanol, add diluted 0.5 mol/L ammonium acetate TS (1 in 50) again to make 50 mL, and use this solution as the test solution. Pipet 1.0 mL of the test solution, add 70 mL of methanol and diluted 0.5 mol/L ammonium acetate TS (1 in 50) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas by the automatic integration method; the peak areas of with the relative retention time of about 0.65 and 1.86 of bezafibrate from the test solution are not greater than 0.5 times that the peak area of bezafibrate from each standard solution. the peak areas of other than the bezafibrate from the test solution are not greater than 0.2 times the peak area of bezafibrate from the standard solution. Also, the sum of peak area other than the bezafibrate from the test solution is not greater than 0.75 times the peak area of bezafibrate from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: A mixture of methanol and diluted acetic acid(100) (1 in 100) (9 : 4).

Flow rate: Adjust the flow rate so that the retention time of bezafibrate is about 6 minutes.

System suitability

Test for required detectability: Pipet 5 mL of the standard solution and add a mixture of methanol and diluted 0.5 mol/L ammonium acetate TS (1 in 50) (7 : 3) to make exactly 50 mL. Confirm that the peak area of bezafibrate from 5 μL of this solution is equivalent to 7% to 13% of the peak area of bezafibrate from the standard solution.

System performance: Dissolve 20 mg of Bezafibrate and 10 mg of 4-chlorobenzoate in 70 mL of methanol and add diluted 0.5 mol/L ammonium acetate TS (1 in 50) to make 100 mL. Proceed with 5 μL of this solution under the above operating conditions; 4-chlorobenzoate and bezafibrate are eluted in this order with the resolution between these peaks being NLT 3.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak area of bezafibrate is NMT 2.0%.

Time span of measurement: About 2.5 times the retention time of bezafibrate after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.7 g of Bezafibrate, previously dried, dissolve it in 50 mL of ethanol(99.5), and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of phenolphthalein TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 36.183 mg of $C_{19}H_{20}ClNO_4$

Packaging and storage Preserve in tight containers.

Bezafibrate Tablets
베자피브레이트 정

Bezafibrate Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of bezafibrate ($C_{19}H_{20}ClNO_4$: 361.82).

Method of preparation Prepare as directed under Tablets, with Bezafibrate.

Identification Weigh accurately an amount of Bezafibrate Tablets, equivalent to 0.4 g of bezafibrate according to the labeled amount, add 40 mL of methanol, shake well to mix, centrifuge, and use the clear supernatant as the test solution. Separately, weigh 25 mg of bezafibrate RS, dissolve with 2.5 mL of methanol, and use this solution as the standard solution A. Separately, weigh 10 mg of *N*-(4-chlorobenzoyl)-tyramine RS, dissolve in 5 mL of methanol. Take 1 mL of this solution, add methanol to make 100 mL, and use this solution as the standard solution B. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solutions on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Next, develop the plate with a mixture of xylene, methyl ethyl ketone, and acetic acid(100) (60 : 30 : 2.7) (as the developing solvent) to a distance of about 10 cm, and dry at about 105 °C. Examine under ultraviolet light (main wavelength: 254 nm);. the spot of the test solution exhibits its color and an R_f value corresponding to that of the standard solution A.

Purity Proceed as directed under the Identification; the spot corresponding to *N*-(4-chlorobenzoyl)-tyramine from the test solution is not more intense than that from the standard solution B.

Disintegration Meets the requirements.

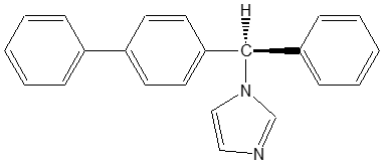
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Bezafibrate Tablets, and powder. Weigh accurately amount, equivalent to about 0.1 g of bezafibrate ($C_{19}H_{20}ClNO_4$), add 100 mL of ammonia-methanol TS, mix, and allow it to stand on a steam bath for 10 minutes. Add ammonia-methanol TS to make exactly 200 mL, filter, pipet 2 mL of the filtrate, add ammonia-methanol TS to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of bezafibrate RS, add ammonia -methanol TS to make exactly 200 mL. Pipet 2.0 mL of this solution, add the ammonia-methanol TS to make exactly 100 mL, and use this solution as the standard solution. Perform the test with each of the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, determine the absorbances (wavelength: 232 nm), A_T and A_S, of the test solution and the standard solution, respectively.

Amount (mg) of bezafibrate ($C_{19}H_{20}ClNO_4$)
= Amount (mg) of bezafibrate RS× (A_T / A_S)

Packaging and storage Preserve in well-closed containers.

Bifonazole
비포나졸



and enantiomer

$C_{22}H_{18}N_2$: 310.39
1-[[(1,1'-Biphenyl)-4-yl]phenylmethyl]imidazole [*60628-96-8*]

Bifonazole, when dried, contains NLT 98.5% and NMT 101.0% of bifonazole ($C_{22}H_{18}N_2$).

Description Bifonazole occurs as a white to pale yellow powder.
It is odorless and tasteless.
It is freely soluble in dichloromethane, soluble in methanol, sparingly soluble in ethanol(95), slightly soluble in ether and practically insoluble in water.
A solution of Bifonazole in methanol (1 in 100) shows no optical rotation.

Identification (1) Determine the absorption spectra of solutions of Bifonazole and bifonazole RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Bifonazole and bifonazole RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 147 and 151 ℃.

Purity (1) ***Chloride***—Add 40 mL of water to 2.0 g of Bifonazole, warm for 5 minutes, cool it down, and filter. Take 10 mL of the filtrate and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control

solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.021%).

(2) ***Sulfate*—**Take 10 mL of the filtrate obtained from (1) and add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this as the test solution and perform the test. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid (NMT 0.048%).

(3) ***Heavy metals*—**Proceed with 2.0 g of Bifonazole according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Related substances*—**Perform the test using light-resistant containers, protected from direct sunlight. Dissolve 0.10 g of Bifonazole in 10 mL of methanol and use this solution as the test solution. Pipet 3 mL of the test solution and add methanol to make exactly 100 mL. Pipet 25 mL and 5 mL each of this solution, add methanol to make exactly 50 mL, and use these solutions as the standard solution (1) and the standard (2), respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution, the standard solution (1) and the standard solution (2) on a silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate and ammonia water(28) (49 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet rays (main wavelength: 254 nm); the spots with an R_f value of about 0.20 obtained from the test solution are not more intense than the spots from the standard solution (1). The principal spot and the spots other than the above spots obtained from the test solution are not more intense than the spots from the standard solution (2).

Loss on drying NMT 0.5% (0.5 g, in vacuum, phosphorus pentoxide, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.15 g of Bifonazole, previously dried, and dissolve in dichloromethane to make exactly 50 mL. Take exactly 5 mL of this solution, transfer to an Erlenmeyer flask with a stopper, add 10 mL of water, 5 mL of dilute sulfuric acid and 25 mL of dichloromethane, and add again 2 to 3 drops of a solution of methyl yellow in dichloromethane (1 in 500) as an indicator. Shake well to mix and titrate with 0.01 mol/L sodium lauryl sulfate VS using a burette with a minimum calibration of 0.02 mL. Add 1 drop each of 0.01 mol/L sodium lauryl sulfate, shake well to mix, and allow it to stand for some time; the endpoint titration is when the dichloromethane layer turns orange from yellow.

Each mL of 0.01 mol/L sodium lauryl sulfate VS
= 3.1039 mg of $C_{22}H_{18}N_2$

Packaging and storage Preserve in light-resistant, tight containers.

Bifonazole Solution
비포나졸 액

Bifonazole Solution contains NLT 90.0% and NMT 110.0% of the labeled amount of bifonazole ($C_{22}H_{18}N_2$: 310.39).

Method of preparation Prepare as directed under the Liquids, with Bifonazole.

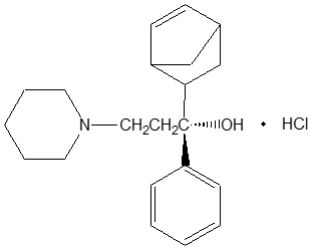
Identification To 1 mL of Bifonazole Solution, add a mixture of methanol and dichloromethane (1 : 1) to make 25 mL and use this solution as the test solution. Separately, weigh 25 mg of bifonazole RS, dissolve in a mixture of methanol and dichloromethane (1 : 1) to make 25 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of toluene, ethyl acetate and diethylamine (6 : 3 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly Dragendorff's TS or examine the plate under ultraviolet rays (main wavelength: 254 nm); the R_f value and the color of the spots obtained from the test solution and the standard solutions are the same.

Assay Weigh accurately an amount of Bifonazole Solution, equivalent to 150 mg of bifonazole ($C_{22}H_{18}N_2$), according to the labeled amount, and dissolve in 50 mL of chloroform. Transfer this solution in a 150-mL beaker, add 35 mL of water, 5 mL of 10% sulfuric acid, and 1 mL of N,N′-dimethyl-*ρ*-(m-torylazo)-aniline indicator, and titrate with 0.004 mol/L sodium lauryl sulfate VS. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.004 mol/L sodium lauryl sulfate VS
= 1.2416 mg of $C_{22}H_{18}N_2$

Packaging and storage Preserve in well-closed containers.

Biperiden Hydrochloride
비페리덴염산염



and enantiomer

$C_{21}H_{29}NO \cdot HCl$: 347.92

1-(Bicyclo[2.2.1]hept-2-en-5-yl)-1-phenyl-3-(piperidin-1-yl)propan-1-ol hydrochloride [*1235-82-1*]

Biperiden Hydrochloride, when dried, contains NLT 99.0% and NMT 101.0% of biperiden hydrochloride ($C_{21}H_{29}NO \cdot HCl$).

Description Biperiden Hydrochloride occurs as a white to yellowish white crystalline powder.
It is freely soluble in formic acid, slightly soluble in water, methanol or ethanol(95), and practically insoluble in ether.

Melting point—About 270 °C (with decomposition).

Identification (1) Dissolve 20 mg of Biperiden Hydrochloride in 5 mL of phosphoric acid; the resulting solution is green.

(2) To 10 mg of Biperiden Hydrochloride, add 4 mL of water, heat, dissolve, and cool it down. Add between 5 and 6 drops of bromine TS; a yellow precipitate is formed.

(3) Determine the absorption spectra of solutions of Biperiden Hydrochloride and biperiden hydrochloride RS (1 in 2000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared spectra of Biperiden Hydrochloride and biperiden hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(5) To 20 mg of Biperiden Hydrochloride, add 10 mL of water, heat, dissolve, and cool; it responds to the Qualitative Analysis for chloride.

Purity (1) ***Acidity or alkalinity***—To 1.0 g of Biperiden Hydrochloride, add 50 mL of water, shake strongly to mix, filter, and add 1 drop of methyl red TS to 20 mL of the filtrate; the solution does not exhibit a red or yellow color.

(2) ***Heavy metals***—Proceed with 1.0 g of Valsartan according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Prepare the test solution with 1.0 g of Biperiden Hydrochloride according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.10 g of Biperiden Hydrochloride in 20 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 200 mL, and use it as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 50 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, methanol and ammonia water(28) (80 : 15 : 2) (as the developing solvent) to about 15 cm, and air-dry the plate. Spray evenly Dragendorff's TS on the plate; the spots other than the principal spot from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 °C, 3 hours).

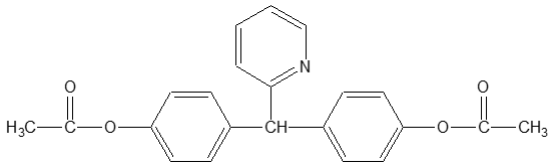
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Biperiden Hydrochloride, previously dried, and dissolve in 5 mL of formic acid, add 60 mL of acetic anhydride and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 34.792 mg of $C_{21}H_{29}NO \cdot HCl$

Packaging and storage Preserve in light-resistant, well-closed containers.

Bisacodyl
비사코딜



$C_{22}H_{19}NO_4$: 361.39

4,4'-(2-Pyridinylmethylene)bisphenol-1,1'-diacetate [*603-50-9*]

Bisacodyl, when dried, contains NLT 98.5% and NMT 101.0% of bisacodyl ($C_{22}H_{19}NO_4$).

Description Bisacodyl occurs as a white, crystalline powder.
It is freely soluble in acetic acid(100), soluble in acetone, slightly soluble in ethanol(95) or ether, and practically insoluble in water.
It dissolves in dilute hydrochloric acid.

Identification (1) Determine the absorption spectra of solutions of Bisacodyl and bisacodyl RS in ethanol(95) (3 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Bisacodyl and bisacodyl RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 132 and 136 ℃.

Purity (1) ***Chloride***—Dissolve 1.0 g of Bisacodyl in 30 mL of acetone and add 6 mL of dilute nitric acid and water to make 50 mL. Use this as the test solution and perform the test. Prepare the control solution by putting 30 mL of acetone, 6 mL of dilute nitric acid and water into 0.35 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.012%).

(2) ***Sulfate***—Dissolve 1.0 g of Bisacodyl in 2 mL of dilute hydrochloric acid and add water to make 50 mL. Use this as the test solution and perform the test. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid VS and 2 mL of dilute hydrochloric acid, and add water to make 50 mL (NMT 0.017%).

(3) ***Heavy metals***—Proceed with 2.0 g of Bisacodyl as directed under Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Related substances***—Dissolve 0.20 g of Bisacodyl in 10 mL of acetone and use this solution as the test solution. Pipet 1 mL of the test, add acetone to make exactly 200 mL and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and standard solution on a plate of silica gel with a fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of 2-butanone, chloroform and xylene (1 : 1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); any spot other than the principal spot obtained from the test solution is not more intense than that from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 h.).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Bisacodyl, previously dried, dissolve it in 50 mL of acetic acid(100) and titrate with 0.1 mol/L perchloric acid VS (Indicator: 0.5 mL of 1-naphtholbenzein TS). The endpoint of the titration is determined to be the point where the color of the solution changes from orange-yellow to green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 36.139 mg of $C_{22}H_{19}NO_4$

Packaging and storage Preserve in well-closed containers.

Bisacodyl Suppositories
비사코딜 좌제

Bisacodyl Suppositories contain NLT 90.0% and NMT 110.0% of the labeled amount of bisacodyl ($C_{22}H_{19}NO_4$: 361.39).

Method of preparation Prepare as directed under Suppositories, with Bisacodyl.

Identification (1) Weigh an amount of Bisacodyl Suppositories, equivalent to 6 mg of bisacodyl, according to the labeled amount, add 20 mL of ethanol(95), and warm on a steam bath for 10 minutes. Shake vigorously for 10 minutes, and allow to stand in iced water for 1 hour. Next, centrifuge to filter the clear supernatant, and add ethanol(95) to 2 mL of the filtrate to make 20 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelengths between 261 nm and 265 nm.

(2) Use the filtrate in (1) as the test solution. Separately, dissolve 6 mg of bisacodyl RS in ethanol(95), and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of 2-butanone, chloroform and xylene (1 : 1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values of the spots from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units It meets the requirements when the Content uniformity test is performed according to the following procedure. Take 1 Bisacodyl Suppositories, add tetrahydrofuran to make a solution containing about 0.2 mg of bisacodyl ($C_{22}H_{19}NO_4$) per mL, warm at 40 °C, and shake well to dissolve. After cooling, add tetrahydrofuran again so that the solution contains about 10 μg of bisacodyl ($C_{22}H_{19}NO_4$) per mL to make exactly *V* mL. Pipet 5 mL of this solution, and perform the test under the Assay.

Amount (mg) of bisacodyl ($C_{22}H_{19}NO_4$)

= Amount (mg) of bisacodyl RS× $\frac{Q_T}{Q_S} \times \frac{V}{50}$

Internal standard solution—A solution of ethylparaben in acetonitrile (3 in 100000).

Assay Weigh accurately the mass of NLT 20 Bisacodyl Suppositories, break carefully into small pieces, and mix evenly. Weigh accurately an amount equivalent to about 10 mg of bisacodyl ($C_{22}H_{19}NO_4$), add 40 mL of tetrahydrofuran, warm at 40 °C, and shake to dissolve. After cooling, add tetrahydrofuran again to make exactly 50 mL. Pipet 5 mL of this solution, and add exactly 5 mL of the internal standard solution and then the mobile phase again to make exactly 100 mL. Cool this solution with ice for 30 minutes, centrifuge, and filter the clear supernatant through a membrane filter with a pore size of 0.5 μm. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 10 mg of bisacodyl RS (previously dried at 105 °C for 2 hours), and dissolve in tetrahydrofuran to make exactly 50 mL. Pipet 5 mL of this solution, proceed in the same manner as the test solution, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak area of bisacodyl to that of the internal standard, Q_T and Q_S.

Amount (mg) of bisacodyl ($C_{22}H_{19}NO_4$)
= Amount (mg) of bisacodyl RS× $\frac{Q_T}{Q_S}$

Internal standard solution—A solution of ethylparaben in acetonitrile (3 in 100000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of 0.01 mol/L citric acid TS, acetonitrile and methanol (2 : 1 : 1).

Flow rate: Adjust the flow rate so that the retention time of bisacodyl is about 8 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the internal standard and bisacodyl are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the ratios of the peak area of bisacodyl to that of the internal standard is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Bisacodyl Tablets
비사코딜 정

Bisacodyl Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of bisacodyl ($C_{22}H_{19}NO_4$: 361.39).

Bisacodyl Tablets are delayed-release preparations.

Method of preparation Prepare as directed under Tablets, with Bisacodyl.

Identification Weigh an amount of Bisacodyl Tablets, previously powdered, equivalent to about 0.3 g of bisacodyl, add 100 mL of acetone, and shake to mix. Heat on a steam bath to boiling, filter and evaporate to about 20 mL. To this solution, add 200 mL of water, and evaporate acetone by warming on a steam bath, through the nitrogen gas. Cool, filter with a glass filter (G4) after 30 minutes and discard the filtrate. Dissolve the residue on the filter in 50 mL of acetone and evaporate to about 15 mL. Add about 75 mL of water, heat on a steam bath for 15 minutes and cool. Crystallize by scratching the wall of the beaker, filter, dry at 105 ℃ for about 15 minutes and perform the test with the residue as directed under the Identification (2) under Bisacodyl.

Disintegration Meets the requirements. However, the tablets are disintegrated within 60 minutes by Solution 1, and within 45 minutes by Solution 2.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Bisacodyl Tablets, and powder. Weigh accurately an amount of the powder, equivalent to about 25 mg of bisacodyl ($C_{22}H_{19}NO_4$), add 10 mL of water, shake to mix for 15 minutes, and shake vigorously again to mix for another 15 minutes. To this solution, add 30 mL of acetonitrile and shake to mix for 15 minutes. Shake vigorously again to mix for another 15 minutes, add acetonitrile to make exactly 50 mL, mix and filter. Discard the first 10 mL of the filtrate, take 5 mL of the subsequent filtrate, add 5.0 mL of the internal standard solution, and use this solution as the test solution. Separately, weigh accurately about 25 mg of bisacodyl RS, previously dried at 105 ℃ for 2 hours, and dissolve in acetonitrile to make exactly 50 mL. Take exactly 5 mL of this solution, proceed in the same manner as the solution, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of bisacodyl to the peak area of the internal standard.

Amount (mg) of bisacodyl ($C_{22}H_{19}NO_4$)

$$= \text{Amount (mg) of bisacodyl RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of ethylparaben in acetonitrile (3 in 100000).

Operating conditions

Proceed as directed under the Operating conditions in the Assay under Bisacodyl Suppositories.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the internal standard and bisacodyl are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio of bisacodyl to the peak area of the internal standard is NMT 2.0%.

Packaging and storage Preserve in well-closed containers and store at below 30 ℃.

Bisacodyl and Docusate Sodium Tablets
비사코딜·도큐세이트나트륨 정

Bisacodyl and Docusate Sodium Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of bisacodyl ($C_{22}H_{19}NO_4$: 361.39) and docusate sodium ($C_{20}H_{37}NaO_7S$: 444.56).

Bisacodyl and Docusate Sodium Tablets are delayed-release preparations.

Method of preparation Prepare as directed under Tablets, with Bisacodyl and Docusate Sodium.

Identification (1) ***Bisacodyl***—Weigh an amount of Bisacodyl and Docusate Sodium Tablets, previously powdered, equivalent to about 5 mg of bisacodyl, add 5 mL of acetone, and shake to mix. Filter and use the filtrate as the test solution. Weigh 5 mg of bisacodyl RS, add 5 mL of acetone, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol and strong ammonia water (100 : 1.5) as the developing solvent and air-dry the plate. Spray hexachloroplatinic(IV) acid-potassium iodide TS evenly onto the plate; the R_f values and the color of the spots obtained from the test solution and the standard solution are the same.

(2) ***Docusate sodium***—Weigh an amount of Bisacodyl and Docusate Sodium Tablets, previously powdered, equivalent to about 50 mg of docusate sodium, add 10 mL of ethanol, and shake to mix. Filter and use the filtrate as the test solution. Weigh 50 mg of docusate sodium RS, add 10 mL of ethanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of cellulose. Next, develop the plate with a mixture of water and methanol (5 : 5) as the developing solvent, and air-dry the plate. Spray evenly a solution prepared by dissolving 50 mg of Rhodamine B in a mixture of an equal amount of ethanol and water and making 100 mL; the R_f values and the color of the spots obtained from the test solution and the standard solution are the same.

Dissolution (1) ***Test in an acidic solution***—Perform the test with 1 tablet of Bisacodyl and Docusate Sodium Tablets at 100 revolutions per minute according to Method 1, using 500 mL of 0.1 mol/L hydrochloric acid TS as the dissolution medium. Filter the dissolved solution, 2 hours after the start of the test, with a membrane filter with a pore size of 0.45 μm, and use the filtrate as the test solution. Separately, weigh accurately about 50 mg of bisacodyl RS, add 50 mL of methanol with 1 drop of dilute phosphoric acid, and use this solution as the standard bisacodyl stock solution. Separately, weigh accurately about 47 mg of docusate sodium RS, transfer to a 100-mL volumetric flask, and add 20 mL of ethanol. Add methanol with 1 drop of dilute phosphoric acid to make 100 mL, and use this solution as the standard docusate sodium stock solution. Take 1.0 mL of the solution prepared by diluting 5.0 mL of the standard bisacodyl stock solution with the dissolution medium to make 100 mL and 10.0 mL of the solution prepared by diluting 5.0 mL of the standard docusate sodium stock solution with the dissolution medium to make 100 mL, add dissolution medium to make 100 mL, and use this solution as the standard solution. Perform the test with 100 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of bisacodyl and docusate sodium in each solution. Determine according to Table 3 of Delayed-release preparations determination method 1.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 3.0 mm in internal diameter and about 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: Dissolve 8.9 g of sodium dihydrogen phosphate dihydrate and 10 g of sodium lauryl sulfate in 800 mL of water, adjust the pH to 7.5 with 1 mol/L hydrochloric acid solution, and add water to make 1000 mL. To 600 mL of this solution, add 400 mL of acetonitrile.

Flow rate: 1.1 mL/min

System suitability

System performance: Proceed with 100 μL of the standard solution according to the above conditions; the number of theoretical plate and the symmetry factor of bisacodyl are NLT 3000 and NMT 1.3, respectively.

System repeatability: Repeat the test 5 times with 100 μL of the standard solution according to the above conditions; the relative standard deviation of peak areas of bisacodyl and docusate sodium is NMT 2.0%.

(2) ***Test in a buffer solution***—After completing the test in (1), dip a basket with the samples in 100-mL beaker containing 80 mL of water and remove from the beaker. When the water is drained, take 1 tablet each of the sample taken out from the basket, and perform the test at 100 revolutions per minute according to Method 2, using 900 mL of pH 7.5 phosphate buffer solution as the dissolution medium. Filter the dissolved solution, 60 minutes after the start of the test, through a membrane filter with pore diameter of 0.45 μm, and use the filtrate as the test solution. Add 8.0 mL of the solution prepared by adding the dissolution medium to 7.0 mL of the standard bisacodyl stock solution in (1) to make 100 mL and 4.0 mL of the standard docusate sodium stock solution in (1) to make 100 mL, and use this solution as the standard solution. Perform the test with 100 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the conditions in (1), and determine peak areas of bisacodyl and docusate sodium in each solution. Determine according to Table 4 of Delayed-release preparations determination method 1.
The acceptable dissolution criterion is NLT 75% (Q) of the labeled amount of Bisacodyl and Docusate Sodium Tablets dissolved in 60 minutes.

pH 7.5 phosphate buffer solution—Dissolve 8.9 g of sodium dihydrogen phosphate dihydrate and 10 g of sodium lauryl sulfate in 800 mL of water, adjust pH to 7.5 with 1 mol/L hydrochloric acid solution, and add water to make 1 L.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Bisacodyl and Docusate Sodium Tablets, and powder. Weigh accurately an amount equivalent to 10 mg of bisacodyl ($C_{22}H_{19}NO_4$) and 32.5 mg of docusate sodium ($C_{20}H_{37}NaO_7S$), dissolve in the mobile phase to make 50 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 10 mg of bisacodyl RS, and about 32.5 mg of docusate sodium RS, add the mobile phase to make 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_{T1}, A_{T2}, A_{S1} and A_{S2}, of bisacodyl and docusate sodium in each solution.

$$\text{Amount (mg) of bisacodyl } (C_{22}H_{19}NO_4) = \text{Amount (mg) of bisacodyl RS} \times \frac{A_{T1}}{A_{S1}}$$

$$\text{Amount (mg) of docusate sodium } (C_{20}H_{37}NaO_7S) = \text{Amount (mg) of docusate sodium RS} \times \frac{A_{T2}}{A_{S2}}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

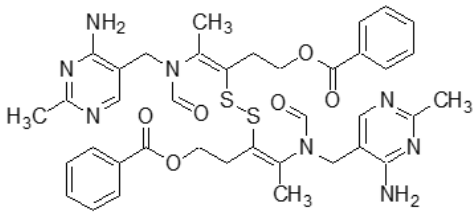
Column: A stainless steel column about 3.9 nm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of 0.005 mol/L tetrabutylammonium phosphate, acetonitrile and methanol (26 : 23 : 1).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in well-closed containers.

Bisbentiamine
비스벤티아민



$C_{38}H_{42}N_8O_6S_2$: 770.92

N-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-*N*-[2-[[2-[[(4-amino-2-methyl-5-pyrimidinyl)methyl]formylamino]-1-[2-(benzoyloxy)ethyl]-1-propen-1-yl]dithio]-4-(benzoyloxy)-1-methyl-1-buten-1-yl]-formamide, [*2667-89-2*]

Bisbentiamine, when dried, contains NLT 98.0% and NMT 102.0% of bisbentiamine ($C_{38}H_{42}N_8O_6S_2$).

Description Bisbentiamine occurs as white crystals or a crystalline powder.
It is odorless.
It is freely soluble in chloroform, sparingly soluble in methanol, slightly soluble in ethanol(95), practically insoluble in water, and soluble in dilute hydrochloric acid.

Melting point—Between 140 and 144 °C (with decomposition).

Identification (1) Weigh 5 mg of Bisbentiamine, dissolve in 1 mL of methanol, add 2 mL of water, 2 mL of L-Cysteine hydrochloride (1 in 100) and 1 mL of 0.5 mol/L sodium hydroxide, shake vigorously to mix, and

allow to stand for 5 minutes. Add 1 mL of potassium ferricyanide TS, 5 mL of 0.5 mol/L sodium hydroxide and 5 mL of isobutanol, shake vigorously to mix for 2 minutes, and allow to stand. Next, expose the solution under ultraviolet light and examine the upper portion of the upper liquid layer in the direction perpendicular to the direction of exposure; the isobutanol layer exhibits a violet fluorescence.

(2) Weigh 50 mg of Bisbentiamine, dissolve in 5 mL of methanol by warming, and add 2 mL of a mixture of hydroxylamine hydrochloride (3 in 20) and sodium hydroxide (3 in 20) in equal amounts. Warm at 50 °C to 60 °C on a steam bath for 2 minutes, add 0.8 mL of hydrochloric acid and 0.5 mL of Iron(III) chloride TS, and add 8 mL of water; the solution exhibits a reddish purple color.

Purity (1) ***Clarity and color of solution***—Weigh 1.0 g of Bisbentiamine, dissolve in 20 mL of methanol on a steam bath by warming at 50°C; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Bisbentiamine according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Thiochrome-positive substances***—Weigh accurately about 0.1 g of Bisbentiamine, previously dried, dissolve in 10 mL of hydrochloric acid TS, add acidic potassium chloride TS to make 200 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of thiamine hydrochloride RS (calculated on the anhydrous basis), and add 0.001 mol/L hydrochloric acid TS to make 1000 mL. Pipet 2.0 mL of this solution, add acidic potassium chloride TS to make 100 mL, and use this solution as the standard solution. Transfer 5.0 mL each of the test solution and the standard solution to stoppered centrifugal separation tubes T, T', S and S', proceed with them in the same manner as in the Assay, and determine fluorescences, F_T, $F_{T'}$, F_S and $F_{S'}$ of each isobutanol layer. Calculate with the following equation; the amount of thiochrome-positive substances is NMT 0.2%.

Amount (mg) of thiochrome-positive substances
= Amount (mg) of thiochrome-positive substances (calculated on the anhydrous basis)$\times \frac{F_T - F_{T'}}{F_S - F_{S'}} \times \frac{1}{250}$

Loss on drying NMT 0.5% (1 g, in Vacuum, phosphorus pentoxide, 24 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 50 mg of Bisbentiamine and bisbentiamine RS, previously dried, dissolve in 25 mL of 1 mol/L hydrochloric acid TS, and add the mobile phase to make exactly 100 mL. Pipet 2 mL each of these solutions, and add the mobile phase to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S of bisbentiamine.

Amount (mg) of bisbentiamine ($C_{38}H_{42}N_8O_6S_2$)
= Amount (mg) of bisbentiamine RS × A_T / A_S

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless-steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter), or an equivalent column.

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 1 g of sodium 1-pentanesulfonate in 600 mL of dilute acetic acid(100) (1 in 100), and add 400 mL of acetonitrile.

Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of bisbentiamine is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Bismuth Subgallate
비스무트차갈르산염

Bismuth Subgallate, when dried, contains NLT 47.0% and NMT 51.0% of bismuth (Bi : 208.98).

Description Bismuth Subgallate occurs as a yellow powder, and is odorless and tasteless.
It is practically insoluble in water, ethanol(95) or ether.
It dissolves in warmed dilute hydrochloric acid, dilute nitric acid or dilute sulfuric acid, and also dissolves in sodium hydroxide TS to form a clear, yellow solution, which immediately turns red.
It is affected by light.

Identification (1) Ignite 0.5 g of Bismuth Subgallate; it chars at first and leaves finally a yellow residue. The residue responds to the Qualitative Analysis for bismuth salt.

(2) To 0.5 g of Bismuth Subgallate, add 25 mL of water and 20 mL of hydrogen sulfide TS, shake well to mix, discard the resulting blackish brown precipitate by filtering, and add 1 drop of iron(III) chloride TS to the filtrate; the solution exhibits a bluish black color.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Bismuth Subgallate in 40 mL of diluted sodium hydroxide TS (1 in 8); the solution is clear.

(2) ***Nitrate***—To 0.5 g of Bismuth Subgallate, add 5 mL of dilute sulfuric acid and 25 mL of iron(II) sulfate TS, shake well to mix, filter, and superimpose 5 mL of the filtrate on the sulfuric acid; the boundary layer does not exhibit a reddish brown color.

(3) ***Sulfate***—Ignite 3.0 g of Bismuth Subgallate in a crucible, dissolve cautiously the residue in 2.5 mL of nitric acid by warming. Add the resulting solution in 100 mL of water, shake to mix, and filter. Evaporate 50 mL of the filtrate on a steam bath to make 15 mL, add water to make 20 mL, filter again, and use the filtrate as the test solution. To 5 mL of the test solution, add 2 to 3 drops of barium nitrate TS; no turbidity is produced.

(4) ***Ammonium***—Dissolve 1.0 g of Bismuth Subgallate in 5 mL of sodium hydroxide TS and heat; the gas evolved does not change the color of a moistened red litmus paper to blue.

(5) ***Copper***—To 5 mL of the test solution obtained in (2), add 1 mL of ammonia TS and filter; the filtrate does not exhibit a blue color.

(6) ***Lead***—Ignite 1.0 g of Bismuth Subgallate at about 500 ºC in a crucible, dissolve the residue in the smallest possible amount of nitric acid added dropwise, evaporate over a low flame to dryness, and allow to cool. Add 5 mL of a solution of potassium hydroxide (1 in 6) to the residue, boil carefully for 2 minutes, allow to cool, and centrifuge. Take the clear supernatant in a test tube, add 10 drops of potassium chromate TS, and acidify the solution by adding acetic acid(100) dropwise; neither turbidity nor a yellow precipitate is produced.

(7) ***Silver***—To 5 mL of the test solution obtained in (2), add 0.5 mL of nitric acid and 2 to 3 drops of dilute hydrochloric acid; no turbidity is produced.

(8) ***Alkaline earth metals and alkali metals***—Boil 1.0 g of Bismuth Subgallate with 40 mL of diluted acetic acid (1 in 2) for 2 minutes, allow to cool, add water to make 40 mL, and filter. To 20 mL of the filtrate, add 2 mL of dilute hydrochloric acid, boil, immediately pass hydrogen sulfide thoroughly through the solution, filter the precipitate produced, and wash with water. Combine the filtrate and the washings, add 5 drops of sulfuric acid, evaporate to dryness, and ignite as directed under the Residue on ignition; the weight of the residue is NMT 5.0 mg.

(9) ***Arsenic*—**Mix 0.20 g of Bismuth Subgallate well with 0.20 g of calcium hydroxide and ignite the mixture. Dissolve the residue in 5 mL of dilute hydrochloric acid, use this solution as the test solution, and perform the test (NMT 10 ppm).

(10) ***Gallic acid*—**To 1.0 g of Bismuth Subgallate, add 20 mL of ethanol(95), shake to mix for 1 minute, and filter. Evaporate the filtrate on a steam bath to dryness; the weight of the residue is NMT 5.0 mg.

Loss on drying NMT 6.0% (1 g, 105 ℃, 3 hours).

Assay Weigh accurately 0.5 g of Bismuth Subgallate, previously dried, heat at about 500 ºC for 30 minutes, and allow to cool. Dissolve the residue in 5 mL of diluted nitric acid (2 in 5) by warming and add water to make exactly 100 mL. Pipet 30 mL of this solution, add 200 mL of water, and titrate with 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 2 to 3 drops of xylenol orange TS). The endpoint of the titration is when the color of the solution changes from purple to yellow.

Each mL of 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 4.180 mg of Bi

Packaging and storage Preserve in light-resistant, well-closed containers.

Bismuth Subnitrate
비스무트차질산염

Bismuth Subnitrate, when dried, contains NLT 71.5% and NMT 74.5% of bismuth (Bi : 208.98).

Description Bismuth Subnitrateoccurs as a white powder.
It is practically insoluble in water, ethanol(95) or ether.
It readily dissolves in hydrochloric acid or nitric acid without effervescence.
It is slightly hygroscopic and changes moistened blue litmus paper to red.

Identification Bismuth Subnitrate responds to the Qualitative Analysis for bismuth salt and nitrate.

Purity (1) ***Chloride***—Dissolve 0.7 g of Bismuth Subnitrate in 2 mL of water and 2 mL of nitric acid and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by evaporating 2 mL of nitric acid on a steam bath to dryness and then adding 0.70 mL of 0.01 mol/L hydrochloric acid, 6 mL of dilute nitric acid and water to make 50 mL (NMT 0.035%).

(2) ***Sulfate***—Dissolve 3.0 g of Bismuth Subnitrate in 3.0 mL of warmed nitric acid, pour this solution into 100 mL of water, shake to mix, and filter. Evaporate the filtrate on a steam bath to 30 mL, filter again, and use the filtrate as the test solution. To 5 mL of the test solution, add 2 to 3 drops of barium nitrate TS; no turbidity is produced.

(3) ***Ammonium***—Boil 0.10 g of Bismuth Subnitrate with 5 mL of sodium hydroxide TS; the gas evolved does not change moistened red litmus paper to blue.

(4) ***Copper***—To 5 mL of the test solution in (2), add 2 mL of ammonia TS and filter; the filtrate does not exhibit a blue color.

(5) ***Lead***—To 1.0 g of Bismuth Subnitrate, add 5 mL of a solution of potassium hydroxide (1 in 6), boil carefully for 2 minutes, allow to cool, and then centrifuge. Transfer the clear supernatant to a test tube, add 10

drops of potassium chromate TS, and acidify by adding acetic acid(100) dropwise; no turbidity or yellow precipitate is produced.

(6) ***Silver***—To 5 mL of the test solution obtained in (2), add 0.5 mL of nitric acid and 2 to 3 drops of dilute hydrochloric acid; no turbidity is produced.

(7) ***Alkaline earth metals and alkali metals***—Boil 2.0 g of Bismuth Subnitrate with 40 mL of diluted acetic acid (1 in 2) for 2 minutes, allow to cool, add water to make 40 mL, and filter. To 20 mL of the filtrate, add 2 mL of dilute hydrochloric acid, boil, immediately pass hydrogen sulfide thoroughly through the solution, filter, and wash the residue with water. Combine the filtrate and the washings, add 5 drops of sulfuric acid, evaporate to dryness, and ignite as directed under the Residue on ignition; the weight of the residue is NMT 5.0 mg.

(8) ***Arsenic***—To 0.20 g of Bismuth Subnitrate, add 2 mL of sulfuric acid, heat until white fumes evolve, and dilute cautiously with water to make 5 mL. Use this solution as the test solution and perform the test (NMT 10 ppm).

(9) ***Carbonate***—To 3 g of Bismuth Subnitrate, add 3 mL of warmed nitric acid; almost no bubbles are produced. Add this solution in 100 mL of water; a white precipitate is produced.

Loss on drying NMT 3.0% (2 g, 105 ℃, 2 hours).

Assay Weigh accurately 0.4 g of Bismuth Subnitrate, previously dried, dissolve in 5 mL of diluted nitric acid (2 in 5) by warming, and add water to make exactly 100 mL. Pipet 25 mL of this solution, add 200 mL of water, and titrate with 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 5 drops of xylenol orange TS). The endpoint of the titration when the color of the solution changes from purple to yellow.

Each mL of 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 4.180 mg of Bi

Packaging and storage Preserve in well-closed containers.

Bismuth Subnitrate Tabets
비스무트차질산염 정

Bismuth Subnitrate Tablets contain bismuth (Bi: 208.95) equivalent to NLT 66.0% and NMT 77.2% of the labeled amount of bismuth subnitrate.

Method of preparation Prepare as directed under Tablets, with Bismuth Subnitrate.

Identification Bismuth Subnitrate Tablets respond to the Qualitative Analysis for bismuth salt and nitrate.

Disintegration Meets the requirements.

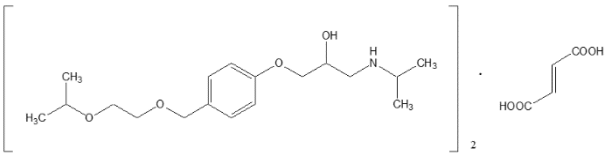
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Bismuth Subnitrate Tablets, and powder the tablets. Weigh accurately an amount equivalent to about 0.4 g of bismuth subnitrate, add 5 mL of nitric acid solution (2 in 5), warm the solution to dissolve, and add water to make exactly 100 mL. Take 25.0 mL of this solution, add 200 mL of water and titrate with 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 5 drops of xylenol orange TS) The endpoint of the titration is when the color of the solution changes from reddish purple to yellow. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 4.180 mg of Bi

Packaging and storage Preserve in well-closed containers.

Bisoprolol Fumarate
비소프롤롤푸마르산염



$(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4$: 766.96

2-Hydroxy-3-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-*N*-[(1-methylethyl)propanamine (2*E*)-2-butenedioate [*104344-23-2*]

Bisoprolol Fumarate contains NLT 97.5% and NMT 102.0% of bisoprolol fumarate $[(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4]$, calculated on the anhydrous basis.

Description Bisoprolol Fumarate occurs as a white, crystalline powder.
It is very soluble in water or methanol, and freely soluble in ethanol(99.5) or acetic acid(100).
A aqueous solution of Bisoprolol Fumarate (1 in 10) shows no optical rotation.

Identification (1) Determine the infrared spectra of Bisoprolol Fumarate and bisoprolol fumarate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention times of the major peaks obtained from the test solution and standard solution in the Assay are the same.

Melting point Between 101 and 105 ℃.

Optical rotation $[\alpha]_D^{20}$: Between -0.2° and +0.2° (0.2 g, 20 mL of methanol, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Bisoprolol Fumarate according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Fumaric acid***—Weigh accurately about 0.5 g of Bisoprolol Fumarate, dissolve in 70 mL of ethanol(99.5), add accurately 8.0 mL of 0.1 mol/L tetrabutylammonium hydroxide, shake for 2 minutes, and titrate with 0.1 mol/L tetrabutylammonium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction (14.8% - 15.4%).

Each mL of 0.1 mol/L tetrabutylammonium hydroxide VS
= 5.804 mg of $C_4H_4O_4$

(3) ***Related substance***—Prepare solutions as directed under the preparation of the test solution under the Related substances of the Assay and use each of these solutions as the test solutions. Perform the test with 10 μL of the test solutions as directed under the Liquid Chromatography according to the conditions under the Assay, determine the areas of each peak, and calculate the total amount of related substances; it is NMT 0.5%.

$$\text{Total content (\%) of related substances} = 100 \times \frac{A_i}{A_S}$$

A_i: All peak areas other than peak areas of fumaric acid and bisoprolol.

A_S: The total areas of all peaks in the chromatogram.

Loss on drying NMT 0.5% (1 g, in vacuum, phosphorus oxide, 80 ℃, 5hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg of Bisoprolol Fumarate, dissolve in 35 vol% acetonitrile solution to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of bisoprolol fumarate RS, dissolve in 35 vol% acetonitrile solution to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of bisoprolol fumarate from each solution.

$$\text{Amount (mg) of bisoprolol fumarate } [(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4] = 50 \times C \times \frac{A_T}{A_S}$$

C: Concentration (mg/mL) of bisoprolol fumarate RS in the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 273 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 125 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm - 10 μm in particle diameter).

Mobile phase: To 1000 mL of 35 vol% acetonitrile solution, add 5 mL of heptafluorobutyric acid and 5 mL of formic acid, mix, and filter.

Flow rate: 1.0 mL/min

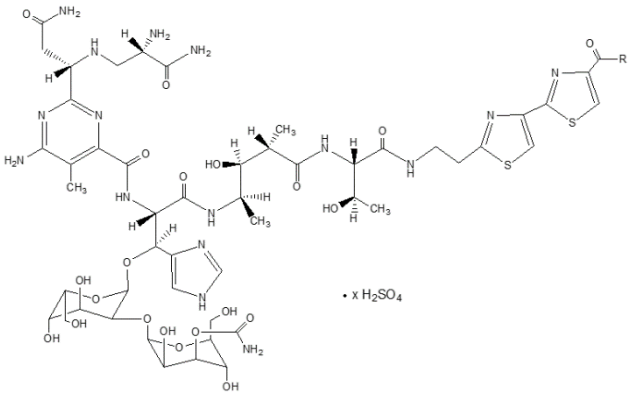
System suitability

System performance: Weigh accurately 25.0 mg of propranolol hydrochloride and 50.0 mg of bisoprolol fumarate and dissolve in 35 vol% acetonitrile solution to make exactly 50 mL. Proceed with 10 μL of this solution according to the above conditions; the resolution between the peaks of bisoprolol and propranolol is NLT 7.0. Additionally, proceed with 10 μL of the standard solution according to the above conditions; the symmetry factor is NMT 2.0.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Bleomycin Sulfate
블레오마이신황산염



Bleomycin acid : R = OH

Bleomycin A_1 : R = $NHCH_2CH_2CH_2SOCH_3$

Bleomycin dimethyl A_2 : R = $NHCH_2CH_2CH_2SCH_3$

Bleomycin A_2 : R = $NHCH_2CH_2CH_2S^+(CH_3)_2 \cdot X^-$

Bleomycin $A_{2'\text{-}a}$: R = $NHCH_2CH_2CH_2CH_2NH_2$
Bleomycin $A_{2'\text{-}b}$: R = $NHCH_2CH_2CH_2NH_2$
Bleomycin A_5 : R = $NH(CH_2)_3NH(CH_2)_4NH_2$
Bleomycin B_1 : R = NH_2
Bleomycin B_2 : R = $NH(CH_2)_4NHC(NH)NH_2$
Bleomycin B_4 : R=
$NH(CH_2)_4NHC(NH)NH(CH_2)_4NHC(NH)NH_2$
Bleomycin Sulfate
Bleomycin acid : 1-Bleomycinoic acid sulfate
Bleomycin A_1 : N^1-[3-(Methylsulfinyl)propyl] bleomycinamide sulfate
Bleomycin dimethyl A_2 : N^1-[3-(Methylsulfanyl)propyl]bleomycinamide sulfate
Bleomycin A_2 N^1-[3-(Dimethylsulfonio)propyl] Bleomycinamide sulfate
Bleomycin $A_{2'\text{-}a}$: N^1-(4-Aminobutyl)bleomycinamide sulfate
Bleomycin $A_{2'\text{-}b}$: N^1-(3-Aminopropyl)bleomycinamide sulfate
Bleomycin A_5 : N^1-{3-[(4-Aminobutyl)amino] propyl}bleomycinamide sulfate
Bleomycin $B_{1'}$: Bleomycinamide sulfate
Bleomycin B_2 : N^1-(4-Guanidinobutyl)bleomycinamide sulfate
Bleomycin B_4: N^1-{4-[3-(4-Guanidinobutyl)guanidino]butyl}-bleomycinamide sulfate [*9041-93-4*]

Bleomycin Sulfate is a sulfate of a mixture of substances having antitumor activity produced by the growth of *Streptomyces verticillus*.

Bleomycin Sulfate contains NLT 1400 μg (potency) and NMT 2000 μg (potency) of bleomycin A_2 ($C_{55}H_{84}ClN_{17}O_{21}S_3$: 1451.01) per mg, calculated on the dried basis.

Description Bleomycin Sulfate occurs as a white to yellowish white powder.
It is freely soluble in water and slightly soluble in ethanol(95).
It is hygroscopic.

Identification (1) Dissolve 4 mg of Bleomycin Sulfate and bleomycin sulfate RS in 5 μL of copper(II) sulfate TS and water to make 100 mL. Determine the absorption spectra of this solution as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the absorption spectra of Bleomycin Sulfate and bleomycin sulfate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Bleomycin Sulfate (1 in 200) responds to the Qualitative Analysis (1) and (2) for sulfate.

pH Dissolve 10 g of Bleomycin Sulfate in 20 mL of water; the pH of this solution is between 4.5 and 6.0.

Purity (1) ***Clarity and color of solution***—Dissolve 80 mg of Bleomycin Sulfate in 4 mL of water; the resulting solution is clear and colorless.

(2) ***Copper***—Weigh accurately 75 mg of Bleomycin Sulfate, dissolve in 10 mL of diluted nitric acid (1 in 100), and use this solution as the test solution. Separately, take exactly 15 mL of the copper standard solution, add diluted nitric acid (1 in 100) to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances of the test solution and the standard solution according to the following conditions as directed under the Atomic Absorption Spectroscopy; the absorbance of the test solution is not greater than the absorbance of the standard solution (NMT 200 ppm).

Gas: Air–acetylene
Lamp: Copper hollow cathode lamp
Wavelength: 324.8 nm

Loss on drying NMT 3.0% (60 mg, in vacuum, phosphorus pentoxide, 60 °C, 3 hours).

Sterility It meets the requirements when used in the manufacturing of sterile preparations.

Bacterial endotoxins Less than 10 EU per mg (potency) of bleomycin when used in the manufacturing of sterile preparations.

Histamine It meets the requirements when used in the manufacturing of sterile preparations. Weigh an appropriate amount of Minocycline Hydrochloride to prepare a solution containing 300 (potency) per mL, and use this solution as the test solution.

Bleomycin content ratio of the active principle Weigh accurately about 10 mg (potency) of Bleomycin Sulfate, dissolve in 20 mL of water, and use this solution as the test solution. Take 20 μL of the test solution and perform the test as directed under the Liquid Chromatography according to the following conditions, and calculate each of the peak areas. Calculate their amount according to the percentage of area; bleomycin A_2 (initial major peak constituent) is between 55% and 70%, bleomycin B_2 (second major peak constituent) is between 25% and 32%, the sum of bleomycin A_2 and bleomycin B_2 is NLT 85%, dimethyl bleomycin A_2 (the relative retention time of bleomycin A_2 is between 1.5 and 2.5) is NMT 5.5%, and the total amount of other peaks is NMT 9.5%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (7 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Use mobile phases A and B to control a step or gradient elution as follows.

Mobile phase A: A mixture of mobile phase stock solution and methanol (9 : 1).

Mobile phase B: A mixture of mobile phase stock solution and methanol (3 : 2).

Time (min)	Mobile Phase A (vol%)	Mobile Phase B (vol%)
0 - 60	100 → 0	0 → 100
60 - 75	0	100

Flow rate: About 1.2 mL/min.

System suitability

System performance: Proceed with 20 μL of the test solution according to the above conditions; bleomycin A_2 and bleomycin B_2 are eluted in this order with the resolution being NLT 5.

System repeatability: Repeat the test 6 times with 20 μL each of the test solutions according to the above conditions; the relative standard deviation of the peak area of bleomycin A_2 is NMT 2.0%.

Time span of measurement: About 20 minutes after the efflux of dimethyl bleomycin A_2 after the melting peak.

Mobile phase stock solution—Dissolve 0.96 g of sodium 1-pentanesulfonate and 1.86 g of ethylenediamine acetic acid disodium dihydrogen dihydrate in 1000 mL of water and 5 mL of acetic acid(100) and adjust the pH to 4.3 by adding ammonia TS.

Assay ***Cylinder-plate method***—(1) Medium

(A) Agar medium for seed layer, base layer and test organism transplantation

Peptone	10.0 g
Glycerin	10.0 g
Meat extract	10.0 g
Agar	15.0 g
Sodium chloride	3.0 g

Weigh the above amount of substances, add purified water to make 1000 mL, and adjust the pH with sodium chloride TS to between 6.9 and 7.1 after sterilizing.

(B) Liquid medium for suspension of test organism

Peptone	10.0 g
Sodium chloride	3.0 g
Meat extract	10.0 g
Glycerin	10.0 g

Weigh the above amount of substances, add purified water to make 1000 mL, and adjust the pH with sodium chloride TS to between 6.9 and 7.1 after sterilizing.

(2) Test organism Use *Mycobacterium smegmatis* ATCC 607 as the test organism.

(3) Test microbial suspension Transplant the above test organism in the medium from (A), incubate at 27 ℃ for between 40 and 48 hours, transplant the organism that grew in this medium to 100 mL of the medium from (B), incubate by shaking for 5 days, and use this as the test microbial suspension. Store the test microbial suspension below 5 ℃ and use it within 14 days. Add 0.5 mL of the test microbial suspension to 100 mL of medium from (A), previously melted and cooled at 48 ℃, shake well to mix, and use this as an agar medium for seed.

(4) Agar plate Follow the Microbial Assays for Antibiotics (A) (5). But the amount of agar medium is 5.0 mL for base and 8.0 mL for seed.

(5) Weigh accurately about 5 mg (potency) of Bleomycin Sulfate, add 0.1 mol/L phosphate buffer solution, pH 6.8, to make solutions that contain 4 μg (potency) and 1 μg (potency) per mL, and use these solutions as the high concentration test solution and low concentration test solution, respectively. Separately, take an appropriate amount of bleomycin hydrochloride A_2 RS dry, weigh accurately about 5 mg (potency), and dissolve in 0.1 mol/L phosphate buffer solution, pH 6.8, to make a standard stock solution containing 150 μg (potency) per mL. Preserve this standard stock solution below 5 ℃ and use it within 30 days. Take accurately an appropriate amount of this standard stock solution, dilute it with 0.1 mol/L phosphate buffer solution, pH 6.8, to make solutions containing 30.0 μg and 15.0 μg (potency) per mL, and use these solutions as the high concentration standard solution and low concentration standard solution, respectively. With these solutions, perform the test as directed under the Microbial Assays for Antibiotics (A) (8).

Packaging and storage Preserve in tight containers.

Boric Acid
붕산

H_3BO_3 : 61.83

Boric acid [*10043-35-3*]

Boric Acid, when dried, contains NLT 99.5% and NMT 101.0% of boric acid (H_3BO_3).

Description Boric Acid occurs as colorless or white crystals or a crystalline powder. It is odorless and has a slight, distinctive taste.

It is freely soluble in warm water, hot ethanol or glycerin, soluble in water or ethanol(95), and practically insoluble in ether.

pH Dissolve 1.0 g of Boric Acid in 20 mL of water; the pH of the solution is between 3.5 to 4.1.

Identification An aqueous solution of Boric Acid (1 in 20) responds to the Qualitative Analysis for borate.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Boric Acid in 25 mL of water or 10 mL of hot ethanol; both solutions is clear and colorless.

(2) ***Heavy metals***—Proceed with 2.0 g of Boric Acid according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Proceed with 0.40 g of Boric Acid according to Method 1 and perform the test (NMT 5 ppm).

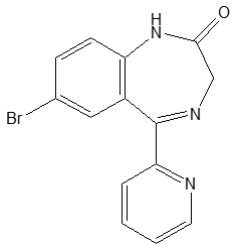
Loss on drying NMT 0.5% (2 g, silica gel, 5 hours).

Assay Weigh accurately about 1.5 g of Boric Acid, previously dried, dissolve it in 15 g of sorbitol and 50 mL of water, and titrate with 1 mol/L sodium hydroxide VS (Indicator: 2 drops of phenolphthalein TS).

Each mL of 1 mol/L sodium hydroxide VS
= 61.83 mg of H_3BO_3

Packaging and storage Preserve in well-closed containers.

Bromazepam
브로마제팜



$C_{14}H_{10}BrN_3O$: 316.15
7-Bromo-5-(pyridin-2-yl)-1,3-dihydro-1,4-benzodiazepin-2-one [*1812-30-2*]

Bromazepam, when dried, contains NLT 99.0% and NMT 101.0% of bromazepam ($C_{14}H_{10}BrN_3O$).

Description Bromazepam occurs as white to pale yellowish white crystals or a crystalline powder.
It is odorless.
It is freely soluble in *N*,*N*-dimethylformamide or acetic acid(100), sparingly soluble in chloroform, slightly soluble in methanol or ethanol(99.5), very slightly soluble in ether, and practically insoluble in water.
It dissolves in dilute hydrochloric acid.

Melting point—About 245 °C (with decomposition).

Identification (1) Determine the absorption spectra of solutions of Bromazepam and bromazepam RS in ethanol(99.5) (1 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Bromazepam and bromazepam RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Bromazepam in a platinum crucible according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 50 mg of Bromazepam in 5 mL of a mixture of acetone and methanol (3 : 2) and use this solution as the test solution. Pipet 1 mL of the test solution and add a mixture of acetone and methanol (3 : 2) to make exactly 50 mL. Pipet 5 mL of this solution, add a mixture of acetone and methanol (3 : 2) to make exactly 50 mL and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solutions and standard solutions on a plate of silica gel with a fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, ethanol(99.5) and ammonia water(28) (38 : 1 : 1) to a distance of about 12 cm, and air-dry the plate. The number of spots obtained from the test solution, other than the principal spot and the spot of the origin point, is NMT 2, and they are not more intense than the spots obtained from the standard solution.

Loss on drying NMT 0.2% (1 g, 105 ℃, 4 h.).

Residue on Ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Bromazepam, previously dried, and dissolve in 80 mL of acetic acid(100). Titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 31.615 mg of $C_{14}H_{10}BrN_3O$

Packaging and storage Preserve in well-closed containers.

Bromazepam Tablets
브로마제팜 정

Bromazepam Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of bromazepam ($C_{14}H_{10}BrN_3O$: 316.15).

Method of preparation Prepare as directed under Tablets, with Bromazepam.

Identification Weigh an amount of Bromazepam Tablets equivalent to 10 mg of bromazepam according to the labeled amount, add 5 mL of chloroform, shake for 3 minutes to mix, and filter. Use this solution as the test solution. Separately, dissolve 60 mg of bromazepam RS in chloroform to make 25 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot

10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate and ammonia water(28) (100 : 1) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light, spray 1% ferrous sulfate TS (prepare before use), dry, and spray evenly 10% ammonia TS; the R_f values of the violet spots obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately 20 tablets of Bromazepam Tablets and powder them. Weigh accurately an amount equivalent to about 15 mg of bromazepam ($C_{14}H_{10}BrN_3O$), add 80 mL of 0.1 mol/L methanolic sulfuric acid and shake to mix for 15 minutes. Add 0.1 mol/L methanolic sulfuric acid to make exactly 100 mL and filter. Pipet 10 mL of the filtrate, add 0.05 mol/L methanolic sulfuric acid to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 15 mg of bromazepam RS, proceed in the same manner as in the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy and determine the absorbances, A_T and A_S, at the wavelength of 285 nm.

Amount (mg) of bromazepam ($C_{14}H_{10}BrN_3O$)
= Amount (mg) of bromazepam RS × (A_T / A_S)

Packaging and storage Preserve in well-closed containers.

Bromelain
브로멜라인

Bromelain is a proteolytic enzyme preparation, derived from the juice or leaves and stems of pineapples obtained by pressing. Bromelain, when dried, contains NLT 500 bromelain units per mg.

Description Bromelain occurs as a pale yellow to pale grayish brown powder.
It has a sight, distinctive odor.

Identification Add 10 mg of Bromelain to 10 mL of 20% skim-milk powder solution with pH adjusted to 5.5 using diluted acetic acid and warm the mixture at 37 ℃; the solution coagulates.

Purity (1) ***Lead***—Put about 1.6 g of Bromelain in a crucible and heat gently to carbonize. After cooling, add 2mL of nitric acid and 5 drops of sulfuric acid, heat until white fumes are evolved, and incinerate by ignition at between 500 and 600 °C. After cooling, add 2 mL of hydrochloric acid and 5 mL of water, dissolve by warming, and filter if necessary. Wash the residue with water, combine the washings with the filtrate, and add ammonium citrate solution (9 in 20) and water to make exactly 50 mL. Pipette exactly 25 mL of this solution, transfer it to a separatory funnel, add 10 mL of ammonium sulfate solution (2 in 5) and 5 drops of thymol blue TS. Neutralize with ammonia TS, and then add 2.5 mL of ammonia TS again. Add 20.0 mL of dithizone in n-butyl acetate solution (1:500) to this solution, shake to mix for 10 minutes, and use the obtained n-butyl acetate layer as the test solution. Pipet 10 mL of this solution, and add diluted hydrochloric acid (1 in 100) to make exactly 50 mL. Perform the test with the test solution and the standard solutions as directed under the Atomic Absorption Spectroscopy according to the following conditions; the absorbance of the test solution is NMT that of the standard solution (NMT 10 ppm).

Gas: Air–acetylen or hydrogen
Lamp: Lead hollow-cathode lamp
Wavelength: 283.3 nm

(2) ***Arsenic***—Put 1.0 g of Bromelain into a crucible, add 10 mL of a solution of magnesium nitrate in ethanol(95) (1:10), ignite with ethanol(95) to combust, and then gradually heat to incinerate. After cooling, add 3 mL of hydrochloric acid to the residue, dissolve by warming on a steam bath, and use this solution as the test solution. Proceed with the test solution and perform the test according to Method 4 (NMT 2 ppm).

(3) ***Cyanide***—Put 5.0 g of Bromelain in a distillation flask, add 2 g of tartaric acid, 50 mL of water, and if necessary, 1 drop of silicon resin, and connect the flask to a distillation apparatus. Add 2 mL of sodium hydroxide TS and 10 mL of water, immerse the bottom of a cooler in this solution, then cool with water, and distill until 25 mL of distillate is obtained. Next, add water to make 50 mL. To 25 mL of this solution, add 0.5 mL of iron(II) sulfate TS, 0.5 mL of dilute iron(III) chloride TS, and 1 mL of dilute sulfuric acid; the solution does not exhibit a blue color.

Loss on drying NMT 5.0% (1 g, in vacuum, phosphorus oxide (V) 5 hours).

Residue on Ignition NMT 25.0% (1 g).

Assay Weigh accurately 0.1 g of Bromelain, transfer it into a mortar, add an appropriate amount of enzyme dilute solution, mix by stirring, and then transfer the mixture to a 100-mL volumetric flask. Wash thoroughly the mortar with about 50 mL of enzyme diluent solution, combine the washings in a volumetric flask, and then add enzyme diluent solution to make exactly 100 mL. Centrifuge this solution, and dilute the clear supernatant obtained from the centrifugation, dilute with the enzyme

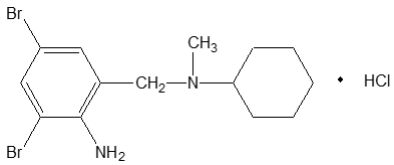
diluent solution to prepare a solution containing 30 to 50 bromelain units per mL. Use this solution as the test solution. Pipet 1.0 mL of the test solution and transfer it into a test tube, and then keep the temperature at 37 ± 0.5 ℃ for 5 minutes. Add 5 mL of substrate solution, previously warmed at 37 ± 0.5 ℃, quickly into the test tube containing the test solution, and initiate the enzyme reaction. After exactly 10 minutes, add 5 mL of the precipitating reagent, shake well to mix, allow to stand at 37 ± 1 ℃ for 40 minutes, and then filter using a filter paper for Assay. Discard 3 mL of the first filtrate and determine the absorbance A of this solution at the wavelength of 660 nm within 2 hours, using water as a control solution. Pipet 1.0 mL of the test solution separately, add 5 mL of the precipitating reagent, shake well to mix, and then add 5 mL of the substrate solution. Proceed with this solution in the same manner for as described above and determine the absorbance A_0. Dissolve tyrosine RS, weighed accurately, in 0.1 mol/L hydrochloric acid TS, and prepare a solution containing 50.0 μg of tyrosine in 1 mL of the solution. With this solution, determine the absorbance AS at a wavelength of 275 nm using water as a control solution.

The number of units in each mg of Bromelain
= [(A - A_0) / A_S] × 55 × [1 / amount (mg) of sample in Each mL of test solution]

Unit of activity—1 bromelain unit is defined as the amount of enzyme that generates a reactant equivalent to 1 μg of tyrosine for 1 minute under the above reaction conditions.

Packaging and storage Preserve in tight containers.

Bromhexine Hydrochloride
브롬헥신염산염



$C_{14}H_{20}Br_2N_2 \cdot HCl$: 412.59

2,4-Dibromo-6-{[cyclohexyl(methyl)amino] methyl}aniline hydrochloride [*611-75-6*]

Bromhexine Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of bromhexine hydrochloride ($C_{14}H_{20}Br_2N_2 \cdot HCl$).

Description Bromhexine Hydrochloride occurs as white crystals or a crystalline powder. It is odorless and tasteless.

It is freely soluble in formic acid, sparingly soluble in methanol and slightly soluble in water or ethanol(95).

The pH of a saturated solution of Bromhexine Hydrochloride is between 3.0 and 5.0.

Melting point—About 239 °C (with decomposition).

Identification (1) Dissolve 3 mg of Bromhexine Hydrochloride and bromhexine hydrochloride RS in 0.01 mol/L hydrochloric acid TS to make 100 mL, and determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Bromhexine Hydrochloride and bromhexine hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 1 g of Bromhexine Hydrochloride in 20 mL of water, shake well to mix, add 3 mL of sodium hydroxide TS, and extract with four 20 mL portions of ether. Take the water layer and neutralize with dilute nitric acid; the resulting solution responds to the Chemical identification reaction (2) for chloride.

Purity (1) ***Heavy metals*—**Proceed with 2.0 g of Bromhexine Hydrochloride as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Perform the test without exposure to light, using light-resistant containers. Dissolve 50 mg of Bromhexine Hydrochloride in 10 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution and add the mobile phase to make exactly 20 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of each solution by the automatic integration method; the peak areas other than the major peak from the test solution are not larger than the major peak area from each of the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 245 nm).

Column: A stainless steel column about 5 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 1.0 g of potassium dihydrogen phosphate in 900 mL of water, adjust the pH to 7.0 with 0.5 mol/L sodium hydroxide TS, and add water to make 1000 mL. To 200 mL of this solution, add 800 mL of acetonitile.

Flow rate: Adjust the flow rate so that the retention time of bromhexine is about 6 minutes.

System suitability

Detection sensitivity: Adjust the sensitivity so that the peak height of bromhexine obtained from 5 μL of the standard solution is between 5 mm and 15 mm.

System performance: To 50 mg of bamethan sulfate, add 0.5 mL of the test solution, and dissolve in the mobile phase to make 10 mL. Proceed with 5 μL of this solution according to the above conditions; bamethan and bromhexine are eluted in this order with the resolution being NLT 7.

Time span of measurement: About twice the retention time of bromhexine after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 °C, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Bromhexine Hydrochloride, previously dried, dissolve in 2 mL of formic acid, add 60 mL of acetic anhydride, and heat on a steam bath at 50 ℃ for 15 minutes. Cool it down and titrate with 0.1 mol/L perchloric acid (indicator: 2 drops of methylrosaniline chloride TS). The endpoint of the titration is when the violet color of this solution turns to bluish green and finally to yellowish green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 41.26 mg of $C_{14}H_{20}Br_2N_2 \cdot HCl$

Packaging and storage Preserve in light-resistant, well-closed containers.

Bromhexine Hydrochloride Tablets
브롬헥신염산염 정

Bromhexine Hydrochloride Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of bromhexine hydrochloride ($C_{14}H_{20}Br_2N_2 \cdot HCl$: 412.59).

Method of preparation Prepare as directed under Tablets, with Bromhexine Hydrochloride.

Identification The retention time of the major peak and the ultraviolet absorption spectra at 200 to 400 nm obtained from the test solution and the standard solution from the Assay are the same.

Dissolution Perform the test with 1 tablet of Bromhexine Hydrochloride Tablets at 50 revolutions per minute according to Method 2, using 900 mL of Solution 1 in the Dissolution as the dissolution medium. Filter the medium 30 minutes after starting the test. Discard the first 10 mL of the filtrate and Take *V* mL of the subsequent filtrate. Add water to make exactly *V* ' mL so that the solution contains about 8.9 μg of bromhexine hydrochloride per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 16 mg of bromhexine hydrochloride RS and dissolve in 80% methanol to make 100 mL. Pipet 5 mL of this solution, add the dissolved solution to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and measure the peak areas A_T and A_S of bromhexine hydrochloride ($C_{14}H_{20}Br_2N_2 \cdot HCl$) in each solution. The dissolution rate in 30 minutes of Bromhexine Hydrochloride Tablets is NLT 75%.

Dissolution rate (%) of the labeled amount of bromhexine hydrochloride ($C_{14}H_{20}Br_2N_2 \cdot HCl$)

$$= W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 45$$

W_S: Amount (mg) of bromhexine hydrochloride RS

C: Labeled amount (mg) of bromhexine hydrochloride ($C_{14}H_{20}Br_2N_2 \cdot HCl$) in 1 tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: A mixture of 0.02 mol/L potassium dihydrogen phosphate solution(pH 3.5) and methanol (1 : 1).

Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area for bromhexine hydrochloride is NMT 2.0%.

0.02 mol/L potassium dihydrogen phosphate solution (pH 3.5)—Dissolve 2.72 g of potassium dihydrogen phosphate in about 900 mL of water, adjust the pH to 3.5 with phosphoric acid, and add water to make 1000 mL.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Bromhexine Hydrochloride Tablets, and powder the tablets. Weigh accurately an amount equivalent to about 8 mg of bromhexine hydrochloride ($C_{14}H_{20}Br_2N_2 \cdot HCl$), add 40 mL of 80% methanol, shake vigorously for 20 minutes to mix, and add 80% methanol to make exactly 100 mL. Filter through a membrane filter with a pore NMT 0.45 μm and use this solution as the test solution. Separately, weigh accurately about 32 mg of bromhexine hydrochloride RS and add 80% methanol to make exactly 100 mL. Take 25 mL of this solution, add 80% methanol to make exactly

100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of bromhexine hydrochloride in each solution.

$$\text{Amount (mg) of bromhexine hydrochloride } (C_{14}H_{20}Br_2N_2\cdot HCl) = \text{Amount (mg) of bromhexine hydrochloride RS} \times \frac{A_T}{A_S} \times \frac{1}{4}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 205 nm). However, a photo-diode array detector (200 nm to 400 nm) is used when the Identification is performed.

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: 40 ℃

Mobile phase: A mixture of 0.02 mol/L potassium dihydrogen phosphate TS (pH 3.5) and methanol (1 : 1).

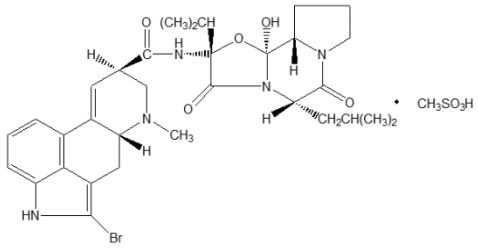
Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of bromhexine hydrochloride is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Bromocriptine Mesilate
브로모크립틴메실산염



$C_{32}H_{40}BrN_5O_5\cdot CH_4O_3S$: 750.70

(5'*S*)-2-Bromo-12'-hydroxy-2'-(1-methylethyl)-5'-(2-methylpropyl)ergotaman-3',6',18-trione; monomethanesulfonic acid [*22260-51-1*]

Bromocriptine Mesilate contains NLT 98.0% and NMT 101.0% of bromocriptine mesilate ($C_{32}H_{40}BrN_5O_5\cdot CH_4O_3S$), calculated on the dried basis.

Method of preparation If there is any possibility of alkyl methanesulfonate esters (methyl, ethyl, isopropyl, etc.) to be formed as the potential impurities by the manufacturing process of Bromocriptine Mesilate, take caution with starting material, manufacturing process, and intermediate material control to minimize the residue of impurities in consideration of risk assessment results. If needed, the manufacturing process can be verified by the test data proving that there is no quality risk in final drug substances.

Description Bromocriptine Mesilate occurs as a white to pale yellowish white or pale brownish white crystalline powder.
It is odorless or has a slight characteristic odor.
It is very soluble in acetic acid(100), freely soluble in methanol, sparingly soluble in ethanol(95), very slightly soluble in acetic anhydride, dichloromethane, or chloroform, and practically insoluble in water or ether.
It is gradually colored by light.

Identification (1) Dissolve 2 mg of Bromocriptine Mesilate in 1 mL of methanol, add 2 mL of p-Dimethylaminobenzaldehyde-iron(III) chloride TS, and shake well to mix; the resulting solution exhibits a violetish blue color.

(2) Determine the absorption spectra of the solutions of Bromocriptine Mesilate and bromocriptine mesilate RS in methanol (3 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths

(3) Determine the infrared spectra of Bromocriptine Mesilate and bromocriptine mesilate RS, previously dried, as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) Perform the test with Bromocriptine Mesilate as directed under the Flame Coloration (2); it exhibits a green color.

Optical rotation $[\alpha]_D^{20}$: Between +95° and +105° [0.1 g, calculated on the dried basis, a mixture of methanol and dichloromethane (1 : 1), 10 mL, 100 mm].

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Bromocriptine Mesilate in 10 mL of methanol; the resulting solution is clear and it's color is not more intense than the following control solution.

Control solution—To 2.5 mL of the colorimetric stock solution of cobalt(II) chloride hexahydrate, 6.0 mL of the colorimetric stock solution of iron(III) chloride hexahydrate and 1.0 mL of the colorimetric stock solution of copper(II) sulfate pentahydrate, add diluted hydrochloric acid (1 in 40) to make exactly 100 mL.

(2) ***Heavy metals*—**Proceed with 1.0 g of Bromocriptine Mesilate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Perform the test without

exposure to daylight, using light-resistant containers. Dissolve 0.10 g of Bromocriptine Mesilate in 10 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 200 mL, and use this solution as the standard solution (1). Pipet 1.0 mL of this solution, add water to make exactly 20 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution, the standard solution (1) and the standard solution (2), as a band with 1 cm in width, on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of toluene, acetone and ammonia water(28) (500 : 150 : 50 : 1) (as the developing solvent) to a distance of about 10 cm, and air-dry the plate in vacuum for 30 minutes. Spray evenly Dragendorff's TS for spraying on the plate, spray evenly hydrogen peroxide TS, cover the plate with a glass plate, and observe; the spots other than the principal spot obtained from the test solution are not more intense than the spots obtained from the standard solution (1), and the number of the spots other than the principal spot that are more intense than the spots obtained from the standard solution (2) are NMT 1.

Loss on drying NMT 3.0% (1 g, NMT 0.67 kPA, 80 °C, 5 hours).

Residue on ignition NMT 0.1% (1 g).

Content of mesylate Weigh accurately 0.4 g of Bromocriptine Mesilate, dissolve in 70 mL of methanol, and titrate with 0.1 mol/L potassium hydroxide-methanol TS with the aid of a current of nitrogen (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction. The content of mesylate, calculated on the dried basis, is between 12.5% and 13.4%.

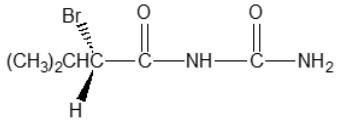
Each mL of 0.1 mol/L potassium hydroxide-methanol TS
= 9.61 mg of CH_3SO_3H

Assay Weigh accurately 0.6 g of Bromocriptine Mesilate, dissolve in 80 mL of a mixture of acetic acid(100) and acetic anhydride (7 : 1) and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 75.07 mg of $C_{32}H_{40}BrN_5O_5 \cdot CH_4O_3S$

Packaging and storage Preserve in light-resistant, tight containers at below -18 ℃.

Bromovalerylurea
브로모발레릴우레아



and enantiomer

$C_6H_{11}BrN_2O_2$: 223.07
2-Bromo-*N*-carbamoyl-3-methylbutanamide [*496-67-3*]

Bromovalerylurea, when dried, contains NLT 98.0% and NMT 101.0% of bromovalerylurea ($C_6H_{11}BrN_2O_2$).

Description Bromovalerylurea occurs as colorless to white crystals or a crystalline powder. It is odorless and has a slightly bitter taste.
It is soluble in ethanol(95), sparingly soluble in ether, and very slightly soluble in water.
It dissolves in sulfuric acid, nitric acid or hydrochloric acid, but precipitates are formed when adding water to the resulting solutions.
It dissolves in sodium hydroxide TS.

Identification (1) To 0.2 g of Bromovalerylurea, add 5 mL of sodium hydroxide (1 in 10), and boil; the resulting gas changes the moistened red litmus paper to blue. To this solution, add an excess of dilute sulfuric acid and boil; the odor of valeric acid is perceptible.

(2) To 0.1 g of Bromovalerylurea, add 0.5 g of anhydrous sodium carbonate, decompose completely by heating slowly, and dissolve the residue in 5 mL of hot water. Cool it down, acidify with acetic acid, and filter. The filtrate responds to the Qualitative Analysis (2) for bromide.

Melting point Between 151 and 155 ℃.

Purity (1) ***Acidity or alkalinity*—**To 1.5 g of Bromovalerylurea, add 30 mL of water, shake well to mix for 5 minutes, and filter; the resulting solution is neutral.

(2) ***Chloride*—**Take 10 mL of the filtrate from (1) and perform the test. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid (NMT 0.028%).

(3) ***Sulfate*—**Take 10 mL of the filtrate from (1) and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid (NMT 0.038%).

(4) ***Heavy metals*—**Proceed with 2.0 g of Bromovalerylurea according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Arsenic*—**Dissolve 0.5 g of Bromovalerylurea in 5 mL of sodium hydroxide TS, use this solution as the test solution, and perform the test (NMT 4 ppm).

(6) ***Readily carbonizable substances***—Perform the test with 0.5 g of Bromovalerylurea. The color of the solution is not more intense than matching fluid A for

color.

Loss on drying NMT 0.5% (1 g, 80 °C, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Bromovalerylurea, previously dried, transfer to a 300-mL Erlenmeyer flask, add 40 mL of sodium hydroxide TS, and boil gently under a reflux condenser for 20 minutes. After cooling, wash the bottom of the reflux condenser and the top of the Erlenmeyer flask with 30 mL of water, add the washings in the Erlenmeyer flask, add 5 mL of nitric acid and exactly 30 mL of 0.1 mol/L silver nitrate solution, and titrate the excess silver nitrate with 0.1 mol/L ammonium thiocyanate VS (indicator: ammonium iron(III) sulfate TS). Perform a blank test in the same manner.

Each mL of 0.1 mol/L silver nitrate solution
= 22.307 mg of $C_6H_{11}BrN_2O_2$

Packaging and storage Preserve in well-closed containers.

Bromperidol Tablets
브롬페리돌 정

Bromperidol Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of bromperidol ($C_{21}H_{23}BrFNO_2$: 420.32).

Method of preparation Prepare as directed under Tablets, with Bromperidol.

Identification (1) Weigh an amount equivalent to about 1 mg of bromperidol according to the labeled amount of Bromperidol Tablets, add 10 mL of chloroform, filter, and use the filtrate as the test solution. Separately, weigh about 10 mg of bromperidol RS, dissolve in 10 mL of chloroform, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, formic acid and methanol (17 : 2 : 1) and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm) or spray evenly iodine vapor; the R_f values and the color of the spots obtained from the test solution and the standard solution are the same.

(2) Determine the absorption spectra of the test solution and the standard solution under the Assay as directed under the Ultraviolet-visible Spectroscopy with 0.25 mol/L sulfuric acid as a control solution; both spectra exhibit similar intensities of absorption at the same wavelengths.

Disintegration Meets the requirements.

Uniformity of dosage units It meets the requirement when the Content uniformity test is performed according to the following procedure.

Take 1 tablet of Bromperidol Tablets, put into a 50-mL volumetric flask, add 10 mL of 0.25 mol/L sulfuric acid, and shake to mix until complete disintegration. Then, add methanol to fill up to the gauge line of the flask and filter. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 50 mg of bromperidol RS, and add methanol to make exactly 100 mL. Take 10.0 mL of this solution, add 10 mL of 0.25 mol/L sulfuric acid, and methanol to make exactly 50 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy and determine the absorbances, A_T and A_S, at the wavelength of 245 nm.

Amount (mg) of bromperidol ($C_{21}H_{23}BrFNO_2$)
= Amount (mg) of bromperidol RS × (A_T / A_S) × 0.1

Assay Weigh accurately the mass of NLT 20 Bromperidol Tablets, and powder. Weigh accurately an amount equivalent to about 1.5 mg of bromperidol ($C_{21}H_{23}BrFNO_2$), put into a separatory funnel, add 20 mL of 0.05 mol/L sulfuric acid, and shake to mix for 5 minutes. To this solution, add 20 mL of ether, shake to extract and take the water layer. To the ether layer, add 10 mL of 0.05 mol/L sulfuric acid to extract, take the water layer and combine the two layers. To the extracted water solution, add 1 mol/L sodium hydroxide solution to alkalize, extract twice with 50 mL each of ether, combine with the ether layer, and wash with 20 mL of water. Next, extract twice with 20 mL and 5 mL of 0.25 mol/L sulfuric acid, respectively, collect the water layer, add 0.25 mol/L sulfuric acid to make exactly 100 mL in total, and use this solution as the test solution. Separately, weigh accurately about 30 mg of bromperidol RS, and add 0.25 mol/L sulfuric acid to make exactly 100 mL. Take 5.0 mL of this solution, add 0.25 mol/L sulfuric acid to make exactly 100 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy and determine the absorbances, A_T and A_S, at the wavelength of 245 nm.

Amount (mg) of bromperidol ($C_{21}H_{23}BrFNO_2$)
= Amount (mg) of bromperidol RS × (A_T / A_S) × 0.05

Packaging and storage Preserve in well-closed containers.

Buflomedil Hydrochloride Injection
부플로메딜염산염 주사액

Buflomedil Hydrochloride Injection contains NLT 95.0% and NMT 105.0% of the labeled amount of buflomedil hydrochloride ($C_{17}H_{25}NO_4 \cdot HCl$: 343.85).

Method of preparation Prepare as directed under Injections, with Buflomedil Hydrochloride.

Identification (1) Take 1 mL of Buflomedil Hydrochloride Injection, add 250 mL of methanol, and determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 273 nm and 277 nm.

(2) Weigh 1 mL of Buflomedil Hydrochloride Injection and about 10 mg of buflomedil hydrochloride RS, dissolve them in 100 mL of methanol, and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Develop the plate with a mixture of methanol, chloroform and ammonia water (6 : 6 : 0.1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Exposure the plate under ultraviolet rays (major wavelength: 254 nm) or spray Dragendorff's TS onto the plate; the R_f values and the colors of the spots obtained from the test solution and the standard solution are identical.

pH Between 3.3 and 5.3.

Pyrogen It meets the requirements when tested as directed under the Pyrogen. In this case, the administered dose is 1 mL (10 mg as buflomedil hydrochloride) per kg.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Take exactly a volume of Buflomedil Hydrochloride Injection, equivalent to 50 mg of buflomedil hydrochloride ($C_{17}H_{25}NO_4 \cdot HCl$), and dissolve with methanol to make exactly 50 mL. Pipet 5 mL of this solution, add 0.1 mol/L hydrochloric acid to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of buflomedil hydrochloride RS, dissolve in methanol to make exactly 50 mL, pipet 5 mL of this solution, add 0.1 mol/L hydrochloric acid to make exactly 100 mL, and use this solution as the standard solution. With the test solution and the standard solution, perform the test as directed under the Ultraviolet-visible Spectroscopy using 0.1 mol/L hydrochloric acid TS as a control solution, and determine the absorbances, A_T and A_S, at 280 nm.

$$\text{Amount (mg) of buflomedil hydrochloride } (C_{17}H_{25}NO_4 \cdot HCl) = \text{Amount (mg) of buflomedil hydrochloride RS} \times (A_T / A_S)$$

Packaging and storage Preserve in hermetic containers.

Buflomedil Hydrochloride Tablets
부플로메딜염산염 정

Buflomedil Hydrochloride Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of buflomedil hydrochloride ($C_{17}H_{25}NO_4 \cdot HCl$: 343.85).

Method of preparation Prepare as directed under Tablets, with Buflomedil Hydrochloride.

Identification (1) Weigh an amount of Buflomedil Hydrochloride Tablets, equivalent to 10 mg of buflomedil hydrochloride, according to the labeled amount, dissolve in methanol to make 100 mL, filter, and use the filtrate as the test solution. Separately, dissolve about 10 mg of buflomedil hydrochloride RS in methanol to make 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of methanol, chloroform and ammonia water (6 : 6 : 0.1) and air-dry the plate. Examine the plate under ultraviolet light or spray Dragendorff's TS on the plate; the R_f values and the color of the spots obtained from the test solution and the standard solution are the same.

(2) Weigh an amount of Buflomedil Hydrochloride Tablets, equivalent to 10 mg of buflomedil hydrochloride according to the labeled amount, dissolve in methanol to make 250 mL, and filter. Determine the absorption spectrum of the filtrate as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at around 280 nm.

Dissolution Perform the test with 1 tablet of Buflomedil Hydrochloride Tablets at 75 revolutions per minute according to Method 2, using 900 mL of Solution 1 in the Dissolution as the dissolution medium. Filter the medium 45 minutes after starting the test. Discard the first 10 mL of the filtrate, Take V mL of the subsequent filtrate, add Solution 1 in the Dissolution so that 1 mL contains about

120 μg of buflomedil hydrochloride according to the labeled amount to make exactly V' mL, and use this solution as the test solution. Separately, weigh accurately about 24 mg of buflomedil hydrochloride RS, dissolve in Solution 1 in the Dissolution to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and measure the peak areas, A_T and A_S, of buflomedil hydrochloride ($C_{17}H_{25}NO_4 \cdot HCl$) in each solution. The dissolution rate in 45 minutes of Buflomedil Hydrochloride Tablets is NLT 80%.

Dissolution rate (%) of the labeled amount of buflomedil hydrochloride ($C_{17}H_{25}NO_4 \cdot HCl$)
$= W_S \times (V' / V) \times (A_T / A_S) \times (1 / C) \times 450$

W_S: Amount (mg) of buflomedil hydrochloride RS
C: Labeled amount (mg) of buflomedil hydrochloride ($C_{17}H_{25}NO_4 \cdot HCl$) in 1 tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: A mixture of 0.01 mol/L potassium dihydrogen phosphate TS and acetonitrile (3 : 2).

Flow rate: 0.7 mL/min

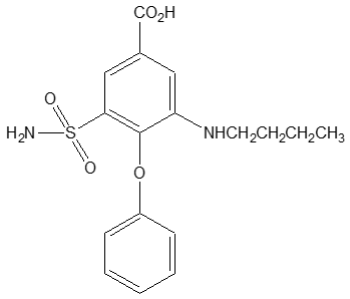
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Buflomedil Hydrochloride Tablets, and powder the tablets. Weigh accurately an amount equivalent to about 50 mg of buflomedil hydrochloride ($C_{17}H_{25}NO_4 \cdot HCl$), and dissolve in methanol to make exactly 50 mL. Take 5.0 mL of this solution, add 0.1 mol/L hydrochloric acid to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of buflomedil hydrochloride RS, dissolve in methanol to make 50 mL, Take 5.0 mL of this solution, add 0.1 mol/L hydrochloric acid to make exactly 100 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy using 0.1 mol/L hydrochloric acid TS as a control solution, and determine the absorbances, A_T and A_S, at the wavelength of 280 nm.

Amount (mg) of buflomedil hydrochloride ($C_{17}H_{25}NO_4 \cdot HCl$)
= Amount (mg) of buflomedil hydrochloride RS
$\times (A_T / A_S)$

Packaging and storage Preserve in tight containers.

Bumetanide
부메타니드



$C_{17}H_{20}N_2O_5S$: 364.42
3-(Butylamino)-4-phenoxy-5-sulfamoylbenzoic acid [*28395-03-1*]

Bumetanide, when dried, contains NLT 98.5% and NMT 101.0% of bumetanide ($C_{17}H_{20}N_2O_5S$).

Description Bumetanide occurs as white crystals or a crystalline powder.
It is freely soluble in pyridine, soluble in methanol or in ethanol(95), slightly soluble in ether and practically insoluble in water.
It dissolves in potassium hydroxide TS.
It is gradually colored by light.

Identification (1) Dissolve 10 mg of Bumetanide in 1 mL of pyridine, add 2 drops of copper(II) sulfate TS, and shake to mix. Add 3 mL of water and 5 mL of chloroform, shake to mix, and allow to stand; the chloroform layer exhibits a pale blue color.

(2) Dissolve 40 mg each of Bumetanide and bumetanide RS in 100 mL of phosphate buffer solution, pH 7.0. To 10 mL each of these solutions, add water to make 100 mL. Determine the absorption spectra of the resulting solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Bumetanide and bumetanide RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 232 and 237 ℃.

Purity (1) ***Clarity and color of solution*—**Dissolve 50 mg of Bumetanide in 2 mL of a solution of potassium hydroxide (1 in 30) and 8 mL of water; the resulting solution is clear and the color of this solution is not more intense than that of the following control solution.

Control solutions—Pipet 0.5 mL each of co-

baltous(II) chloride hexahydrate colorimetric stock solution, iron(III) chloride CS and copper(II) sulfate pentahydrate colorimetric stock solution, mix them, and add diluted hydrochloric acid (1 in 40) to make exactly 100 mL.

(2) ***Chloride***—Thoroughly mix 0.5 g of Bumetanide with 0.7 g of potassium nitrate and 1.2 g of anhydrous sodium carbonate, transfer the mixture in small portions into a red hot platinum crucible, and heat until the reaction is complete. After cooling, add 14 mL of dilute sulfuric acid and 6 mL of water to the residue, boil for 5 minutes, filter, and wash the residue with 10 mL of water. Then, combine the filtrate and the washings and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.021%).

(3) ***Heavy metals***—Proceed with 2.0 g of Bumetanide as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Proceed with 1.0 g of Bumetanide as directed under Method 3 and perform the test (NMT 2 ppm).

(5) ***Related substances***—Perform the test without exposure to direct sunlight using light-resistant containers. Dissolve 0.10 g of Bumetanide in 10 mL of methanol, and use this solution as the test solution. Pipet 1 mL of the test solution and add methanol to make exactly 100 mL. Pipet 2 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, acetic acid(100), cyclohexane and methanol (32 : 4 : 4 : 1) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solutions.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

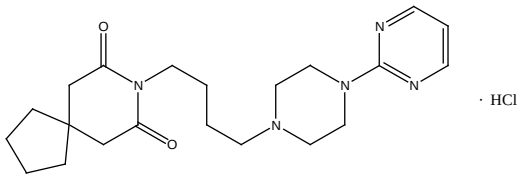
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Bumetanide, previously dried, dissolve in 50 mL of ethanol(95), and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 36.442 mg of $C_{17}H_{20}N_2O_5S$

Packaging and storage Preserve in light-resistant, tight containers.

Buspirone Hydrochloride
부스피론염산염



$C_{21}H_{31}N_5O_2 \cdot HCl$: 421.96
8-[4-(4-Pyrimidin-2-ylpiperazin-1-yl)butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride[*33386-08-2*]

Buspirone Hydrochloride contains NLT 97.5% and NMT 102.5% of buspirone hydrochloride ($C_{21}H_{31}N_5O_2 \cdot HCl$), calculated on the anhydrous basis.

Description Buspirone Hydrochloride occurs as a white, crystalline powder.
It is very soluble in water, freely soluble in methanol or dichlormethane, sparingly soluble in ethanol(95) or acetonitrile, very slightly soluble in ethyl acetate, and practically insoluble in hexane.

Identification (1) Determine the infrared spectra of Buspirone Hydrochloride and buspirone hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention times of the major peaks obtained from the test solution and standard solution in the Assay are the same.

(3) An aqueous solution of Buspirone Hydrochloride (1 in 100) responds to the Qualitative Analysis (2) for chloride.

Purity ***Heavy metals*—**Proceed with 1.0 g of Buspirone Hydrochloride according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Water NMT 0.5% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.5% (1 g).

Assay Dissolve about 50 mg each of Buspirone Hydrochloride and buspirone hydrochloride RS, accurately weighed, in 25 mL of 1 mol/L hydrochloric acid TS, and add water to make exactly 100 mL, respectively. To 10 mL of each of these solutions, add 10 mL of the internal standard and add water to make exactly 50 mL, respectively. Use these solutions as the test solution and the standard solution, respectively. Perform the test with 25

μL each of the test solution and the standard solution, under the following conditions under the Liquid Chromatography, and calculate the ratios, Q_T and Q_S, of the peak area of buspirone hydrochloride to that of the internal standard for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of buspirone hydrochloride } (C_{21}H_{31}N_5O_2\cdot HCl) = \text{Amount of (mg) buspirone hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Dissolve 0.25 g of propyl p-hydroxybenzoate in methanol to make 100 mL. Add water to 25.0 mL of this solution to make 500 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 3.0 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of phosphate buffer solution and acetonitrile (60 : 40).

Flow rate: 2 mL/min

System suitability

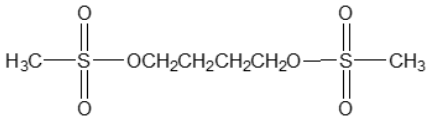
System performance: Proceed with 25 μL of the standard solution according to the above conditions; the resolution between the peaks of buspirone hydrochloride and the internal standard is NLT 4.

System repeatability: Repeat the test 5 times with 25 μL each of the standard solution under the above conditions; the relative standard deviation of the ratios of the peak area of buspirone hydrochloride to that of the internal standard is NMT 2.0%.

Phosphate buffer solution—Dissolve 1.36 g of potassium dihydrogen phosphate in water to make 1000 mL, and adjust the pH to 7.5 with 10 w/v% sodium hydroxide solution.

Packaging and storage Preserve in light-resistant, tight containers.

Busulfan
부설판



$C_6H_{14}O_6S_2$: 246.30

4-Methylsulfonyloxybutyl methanesulfonate [*55-98-1*]

Busulfan contains NLT 98.5% and NMT 101.0% of busulfan ($C_6H_{14}O_6S_2$), calculated on the dried basis.

Description Busulfan occurs as a white, crystalline powder.

It is slightly soluble in ether, very slightly soluble in ethanol(95), and practically insoluble in water.

Identification (1) Add 10 mL of water and 5 mL of sodium hydroxide TS to 0.1 g of Busulfan, dissolve by heating, and use this solution as the test solution.

(i) Add 1 drop of potassium permanganate TS to 7 mL of the test solution; the purple color of potassium permanganate TS turns bluish purple through blue to green.

(ii) Acidify 7 mL of the test solution with dilute sulfuric acid, and then add 1 drop of potassium permanganate TS; the color of potassium permanganate TS remains unchanged.

(2) Determine the infrared spectra of Busulfan and busulfan RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 115 and 118 ℃.

Purity (1) ***Sulfate***—Add 40 mL of water to 1.0 g of Busulfan and dissolve by heating. Cool in ice for 15 minutes and filter. Wash the residue with 5 mL of water, combine the washings and the filtrate, and add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid VS (NMT 0.019%).

(2) ***Heavy metals*—**Proceed with 1.0 g of Busulfan according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Loss on drying NMT 2.0% (1, in vacuum, phosphorus oxide, 60 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Busulfan, add 40 mL of water and boil gently under a reflux condenser for 30 minutes. After cooling, titrate with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of phenolphthalein TS).

$$\text{Each mL of 0.1 mol/L sodium hydroxide VS} = 12.315 \text{ mg of } C_6H_{14}O_6S_2$$

Packaging and storage Preserve in light-resistant, well-closed containers.

Busulfan Tablets
부설판 정

Busulfan Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of busulfan ($C_6H_{14}O_6S_2$: 246.30).

Method of preparation Prepare as directed under Tablets, with Busulfan.

Identification Powder Busulfan Tablets and extract the powder several times with acetone. Collect and combine these extracts and evaporate to dryness on a steam bath, with the aid of a current of air. Perform the test with the residue as directed under the Identification (1) and (2) of Busulfan. The melting point of the residue is about 115 ℃.

Disintegration Meets the requirements.

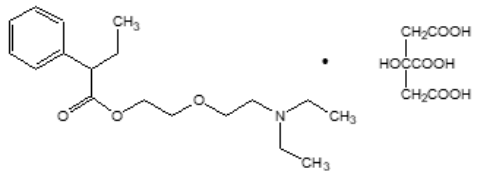
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 40 tablets of Busulfan Tablets and powder (caution: guard against accidental inhalation of fine powder). Weigh accurately an amount of the powder equivalent to about 80 mg of busulfan ($C_6H_{14}O_6S_2$) and transfer to a beaker. Extract four times with 20 mL each of acetone. At each time of extraction, stir the mixture well, then allow the insoluble matter to settle, decant the clear supernatant, and filter through a glass filter (G4). Collect all of the acetone extracts, evaporate to about 10 mL, add phenolphthalein TS, and neutralize with 0.1 mol/L sodium hydroxide solution. Evaporate to dryness, add about 30 mL of water and perform the test under a reflux condenser as directed under the Assay of Busulfan according to the following (indicator: 3 drops of phenolphthalein TS).

Each mL of 0.1 mol/L sodium hydroxide VS
= 12.315 mg of $C_6H_{14}O_6S_2$

Packaging and storage Preserve in light-resistant, well-closed containers.

Butamirate Citrate
부타미레이트시트르산염



$C_{18}H_8NO_3 \cdot C_6H_8O_7$: 499.55
2-(2-Diethylaminoethyloxy)ethyl 2-phenylbutanoate 2-hydroxypropane 1,2,3-tricarboxylic acid, [*18109-81-4*]

Butamirate Citrate, when dried, contains NLT 98.0% and NMT 101.0% of butamirate citrate ($C_{18}H_{29}NO_3 \cdot C_6H_8O_7$).

Description Butamirate Citrate occurs as a yellowish white lump with a faint amine odor.
It is soluble in water.

Melting point—Between 75 and 77 ℃.

Identification (1) ***Citric acid***—Heat the test solution (1 mL) from Purity on a steam bath along with 1 mL of 0.1 mol/L potassium permanganate and 1 mL of 2 mol/L acetic acid(100) without boiling until it is decolorized. Add 1 mL of bromine water to the clear solution; a white precipitate is formed.

(2) ***Diethylaminoethoxyethanol***—Add 1 mL of the test solution in Purity to a test tube containing 3 mL of 2 mol/L sodium hydroxide TS, and direct the vapor produced onto a piece of red litmus paper soaked with water; the paper turns blue.

(3) Perform the test as directed under the Thin Layer Chromatography under Purity; the Rf value and the color of the spots obtained from the test solution and the standard solution are the same.

(4) Weigh 0.2 g of Butamirate Citrate, transfer it into a 100-mL volumetric flask, dissolve it with 70% ethanol, and dilute with 70% ethanol to 100 mL. Then, determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy using 70% ethanol as the control solution; it exhibits an absorption maximum at a wavelength of 249 nm.

Purity Weigh about 2.5 g of Butamirate Citrate and dissolve in warm water to make 50 mL. After cooling, use this solution as the test solution.

(1) ***Chloride***—Pipet 5 mL of the test solution, transfer it into a Nessler tube and perform the test as directed under Chloride. Prepare the control solution with 0.35 mL of 0.01 mol/L hydrochloric acid (NMT 0.05%).

(2) ***Sulfate***—Pipet 5 mL of the test solution, transfer it into a Nessler tube, and then perform the test as directed under Sulfate; no turbidity is produced.

(3) ***Heavy metals***—Proceed with 1 g of Butamirate Citrate according to Method 1 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Related substances***—Weigh about 0.1 g of Butamirate Citrate, place in a separatory funnel, dissolve in 20 mL of water and 10 mL of 2 mol/L ammonia water, and extract 3 times with 20 mL each of n-hexane. After passing the extract through an anhydrous sodium sulfate layer, transfer it into a 300 mL round-bottom flask, dry in vacuum at 50 ℃, and dissolve the residue in 5 mL of methanol. Use this solution as the test solution. Separately, use a 2% methanol solution of butamirate citrate and a 0.05% methanol solution of diethylaminoethoxyethanol as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture

of ethyl acetate, methyl ethyl ketone, water and concentrated formic acid (5 : 3 : 1 : 1) as the developing solvent to a distance of about 10 cm and air-dry the plate. After drying the plate at 100 ℃ for 15 minutes, place it in a developing chamber saturated with iodine, for 30 minutes; Butamirate citrate appears as a brown spot with an Rf value of around 0.56, and diethylaminoethoxyethanol or other related substances are not observed. However, free citric acid appears as a spot elongated from the starting point of butamirate citrate.

pH Between 3.5 and 3.9 (1% aqueous solution).

Loss on drying NMT 1.0% (1 g, 40 ℃, phosphorus pentoxide, vacuum desiccator, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.6 g of Butamirate Citrate, previously dried, transfer it to a 250-mL Erlenmeyer flask, dissolve in 50 mL of acetic acid(100), and add 5 mL of acetic anhydride. Next, titrate with 0.1 mol/L perchloric acid VS until a pure blue color appears. Use 3 to 4 drops of 0.1% methylrosaniline chloride in acetic acid as the indicator. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 49.95 mg of $C_{18}H_{29}NO_3 \cdot C_6H_8O_7$

Packaging and storage Preserve in tight containers.

Butamirate Citrate Syrup
부타미레이트시트르산염 시럽

Butamirate Citrate Syrup contains NLT 95.0% and NMT 105.0% of the labeled amount of butamirate citrate ($C_{18}H_{29}NO_3 \cdot C_6H_8O_7$: 499.52).

Method of preparation Prepare as directed under Syrups, with Butamirate Citrate.

Identification Weigh about 6.0 mL of Butamirate Citrate Syrup, transfer to a 100 mL separatory funnel, add 10 mL of 2 mol/L ammonia water, mix, and extract 4 times with each 20 mL of chloroform. Combine all extracts, pass through a layer of anhydrous sodium sulfate, and filter to a 300 mL round bottom flask. Wash the anhydrous sodium sulfate layer with 10 mL of chloroform, combine the washing with the extracts obtained in the previous step, evaporate at 50 ℃ in vacuum, and dissolve the residue in 1 mL of methanol. Use the resulting solution as the test solution. Use 2% butamirate citrate in methanol as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, methyl ethyl ketone, water and concentrated formic acid (5 : 3 : 1 : 1) as the developing solvent to a distance of about 10 cm and air-dry the plate. After drying, allow to stand in a developing chamber saturated with Iodine for 30 minutes; the R_f values and the colors of the spots from the test solution and the standard solution are the same.

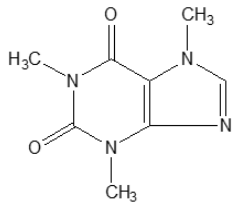
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately an amount of Butamirate Citrate Syrup, equivalent to 75 mg of butamirate citrate ($C_{18}H_{29}NO_3 \cdot C_6H_8O_7$), transfer to a 100 mL separatory funnel, add phosphate buffer (pH 7.0), and mix. Extract 4 times with each 20 mL of chloroform, combine the extracts, pass through a layer of anhydrous sodium sulfate, and filter to a 300-mL round bottom flask. Wash the anhydrous sodium sulfate layer with 10 mL of chloroform, combine the washing with the extracts obtained in the previous step, and evaporate to dryness at 50 ℃ in vacuum. Dissolve the residue in 20 mL of acetic acid(100), add 10 mL of acetic anhydride, mix well, and titrate with 0.01 mol/L perchloric acid VS as directed in the potentiometric titration under the Titrimetry. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.01 mol/L perchloric acid VS
= 4.995 mg of $C_{18}H_{29}NO_3 \cdot C_6H_8O_7$

Packaging and storage Preserve in tight containers.

Anhydrous Caffeine
카페인무수물



$C_8H_{10}N_4O_2$: 194.19
1,3,7-Trimethylpurine-2,6-dione [*58-08-2*]

Anhydrous Caffeine, when dried, contains NLT 98.5% and NMT 101.0% of anhydrous caffeine ($C_8H_{10}N_4O_2$).

Description Anhydrous Caffeine occurs as white crystals or a powder.
It is odorless and has a bitter taste.
It is freely soluble in chloroform, sparingly soluble in water, acetic acid(100), or acetic anhydride, and slightly soluble in ethanol(95) or ether.

Dissolve 1.0 g of Anhydrous Caffeine in 100 mL of water; the pH of this solution is between 5.5 and 6.5.

Identification (1) To 2 mL of an aqueous solution of Anhydrous Caffeine (1 in 500), add dropwise of tannic acid TS; a white precipitate forms and this precipitate dissolves when adding dropwise tannic acid TS again.

(2) To 10 mg of Anhydrous Caffeine, add 10 drops of hydrogen peroxide TS and 1 drop of hydrochloric acid, and evaporate to dryness on a steam bath; the residue exhibits a yellowish red color. Also, transfer this residue into a container containing 2 to 3 drops of ammonia TS; the resulting residue changes to a purple color, which disappears upon the addition of 2 to 3 drops of sodium hydroxide TS.

(3) Dissolve 10 mg of Anhydrous Caffeine in water to make 50 mL. To 5 mL of this solution, add 3 mL of diluted acetic acid (3 in 100) and 5 mL of diluted pyridine (1 in 10) to mix, add 2 mL of diluted sodium hypochlorite TS (1 in 5), and allow to stand for 1 minute. To this solution, add 2 mL of sodium thiosulfate TS and 5 mL of sodium hydroxide TS; the resulting solution exhibits a yellow color.

Melting point Between 235 and 238 ℃.

Purity (1) ***Chloride***—Dissolve 2.0 g of Anhydrous Caffeine in 80 mL of hot water, cool quickly to 20 ℃, add water to make 100 mL, and use this solution as the sample stock solution. To 40 mL of the sample stock solution, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid (NMT 0.011%).

(2) ***Chloride***—To 40 mL of the sample stock solution (1), add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid (NMT 0.024%).

(3) ***Heavy metals***—Proceed with 2.0 g of Anhydrous Caffeine according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Related substances***—Dissolve 0.10 g of Anhydrous Caffeine in 10 mL of chloroform, and use this solution as the test solution. Pipet 1 mL of this solution and add chloroform to make exactly 100 mL. Pipet 1 mL of this solution, add chloroform to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform and ethanol(95) (9 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots obtained from the standard solution.

(5) ***Readily carbonizable substances***—Proceed with 0.5 g of Anhydrous Caffeine and perform the test. The color of the solution is not more intense than that of the Matching Fluid for Color D.

Loss on drying NMT 0.5% (1 g, 80 ℃, 4 hours).

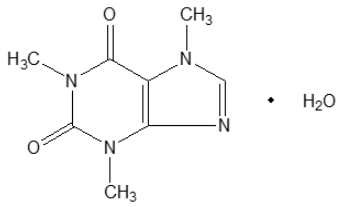
Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh exactly about 0.4 g of Anhydrous Caffeine, previously dried, dissolve in 70 mL of a mixture of acetic anhydride and acetic acid(100) (6 : 1), and titrate with 0.1 mol/L perchloric acid VS (indicator: 3 drops of methylrosaniline chloride TS). However, the endpoint of the titration is when the purple color of this solution changes to green and then finally to yellow. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 19.419 mg of $C_8H_{10}N_4O_2$

Packaging and storage Preserve in tight containers.

Caffeine Hydrate
카페인수화물



Caffeine $C_8H10N_4O_2 \cdot H_2O$: 212.21
1,3,7-Trimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione hydrate [*5743-12-4*]

Caffeine Hydrate, when dried, contains NLT 98.5% and NMT 101.0% of caffeine hydrate ($C_8H10N_4O_2$: 194.19).

Description Caffeine Hydrate occurs as soft white crystals or a powder.
It is odorless and has a slightly bitter taste.
It is freely soluble in chloroform, sparingly soluble in water, acetic (100), or acetic anhydride, slightly soluble in ethanol(95), and very slightly soluble in ether.
Dissolve 1.0 g of Caffeine Hydrate in 100 mL of water; the pH of this solution is between 5.5 and 6.5.
It effloresces in dry air.

Identification (1) To 2 mL of an aqueous solution of Caffeine Hydrate (1 in 500), add tannic acid TS dropwise; a white precipitate forms and this precipitate dissolves when adding tannic acid TS dropwise again.

(2) To 10 mg of Caffeine Hydrate, add 10 drops of hydrogen peroxide TS and 1 drop of hydrochloric acid, and evaporate to dryness on a steam bath; the residue exhibits a yellowish red color. Also, transfer this residue into a container containing 2 to 3 drops of ammonia TS; the resulting residue changes to a purple color, which disappears upon the addition of 2 to 3 drops of sodium hydroxide TS.

(3) Dissolve 10 mg of Caffeine Hydrate in water to make 50 mL. To 5 mL of this solution, add 3 mL of diluted acetic acid (3 in 100) and 5 mL of diluted pyridine (1 in 10) to mix, add 2 mL of diluted sodium hypochlorite TS (1 in 5), and allow to stand for 1 minute. To this solution, add 2 mL of sodium thiosulfate TS and 5 mL of sodium hydroxide TS; the resulting solution exhibits a yellow color.

Melting point Between 235 and 238 ℃ (after drying).

Purity (1) ***Chloride***—Dissolve 2.0 g of Caffeine Hydrate in 80 mL of hot water, cool quickly to 20 ℃, add water to make 100 mL, and use this solution as the sample stock solution. To 40 mL of the sample stock solution, add 6 mL of dilute nitric acid and water to make 50 mL, and use this solution as the test solution. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid (NMT 0.011%).

(2) ***Sulfate***—To 40 mL of the sample stock solution (1), add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid (NMT 0.024%).

(3) ***Heavy metals***—Proceed with 2.0 g of Caffeine Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Related substances***—Dissolve 0.10 g of Caffeine Hydrate in 10 mL of chloroform, and use this solution as the test solution. Pipet 1 mL of this solution, and add chloroform to make exactly 100 mL. Pipet 1 mL of this solution, add chloroform to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform and ethanol(95) (9 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

(5) ***Readily carbonizable substances***—Proceed with 0.5 g of Caffeine Hydrate and perform the test. The color of the solution is not more intense than that of the Matching Fluid for Color D.

Loss on drying Between 0.5% and 8.5% (1 g, 80 °C, 4 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh exactly about 0.4 g of Caffeine Hydrate, previously dried, dissolve in 70 mL of a mixture of acetic anhydride and acetic acid(100) (6 : 1), and titrate with 0.1 mol/L perchloric acid VS (indicator: 3 drops of methylrosaniline chloride TS). The endpoint of the titration is when the purple color of this solution changes to green and then finally to yellow. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 19.419 mg of $C_8H_{10}N_4O_2$

Packaging and storage Preserve in tight containers.

Caffeine And Sodium Benzoate
벤조산나트륨카페인

Caffeine and Sodium Benzoate, when dried, contains NLT 48.0% and NMT 50.0% of caffeine ($C_8H_{10}N_4O_2$: 194.19) and contains NLT 50.0% and NMT 52.0% of sodium benzoate ($C_7H_5NaO_2$: 144.10).

Description Caffeine and Sodium Benzoate occurs as a white powder, is odorless, and has a slightly bitter taste.
It is freely soluble in water, soluble in acetic acid(100) or acetic anhydride, sparingly soluble in ethanol(95) and practically insoluble in ether.

Identification (1) Dissolve 1 g of Caffeine and Sodium Benzoate in 10 mL of water in a separatory funnel, add 1 drop of phenolphthalein TS, and add carefully dropwise 0.01 mol/L sodium hydroxide TS until a pale red color appears. Extract three times each time with 20 mL of chloroform by shaking well to mix and separate from the water layer (use the water layer for Test (2) below). Combine the chloroform extracts, filter it and evaporate the filtrate to dryness on a steam bath. Perform the test with the residue as directed below.

(i) To 2 mL of the aqueous solution of the residue (1 in 500), add tannic acid TS; a white precipitate is formed, which dissolves upon further addition of tannic acid TS.

(ii) To 10 mg of the residue, add 10 drops of hydrogen peroxide TS and 1 drop of hydrochloric acid and evaporate to dryness on a steam bath; the resulting residue exhibits a yellowish red color. Transfer this residue into a container containing 2 to 3 drops of ammonia TS; the resulting residue changes to a purple color, which disappears upon the addition of 2 to 3 drops of sodium hydroxide TS.

(iii) Dissolve 10 mg of the residue in water to make 50 mL. To 5 mL of this solution, add 3 mL of diluted acetic acid (3 in 100) and 5 mL of pyridine solution (1 in 10), mix, then add 2 mL of diluted sodium hypochlorite

TS (1 in 5), and allow to stand for 1 minute. To this solution, add 2 mL of sodium thiosulfate TS and 5 mL of sodium hydroxide TS; the resulting solution exhibits a yellow color.

(2) To 5 mL of the water layer obtained in (1), add 5 mL of water; the resulting solution responds to the Qualitative Analysis (2) for benzoate.

(3) Heat Caffeine and Sodium Benzoate; white fumes are produced. Ignite it further and add hydrochloric acid to the resulting residue; bubbles are formed and the resulting solution responds to the Qualitative Analysis (1) for sodium salt.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Caffeine and Sodium Benzoate in 5 mL of water; the resulting solution is colorless and clear.

(2) ***Akali***—Dissolve 1.0 g of Caffeine and Sodium Benzoate in 20 mL of water and add 1 to 2 drops of phenolphthalein TS; the resulting solution does not exhibit a red color.

(3) ***Chloride***—Dissolve 0.5 g of Caffeine and Sodium Benzoate in 10 mL of water and add 30 mL of ethanol(95), 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 30 mL of ethanol(95) and water to 0.70 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.050%).

(4) ***Chlorinated compounds***—Dissolve 1.0 g of Caffeine and Sodium Benzoate in 40 mL of water, add 10 mL of dilute sulfuric acid, and extract twice each time with 20 mL of ether. Allow the combined ether extracts to evaporate at room temperature to dryness. Place the resulting residue and 0.7 g of calcium carbonate in a crucible, mix with a small amount of water, and allow to dry. Next, ignite the resulting residue at about 600 ℃, dissolve in 20 mL of dilute nitric acid, and filter. Wash the residue with 15 mL of water, combine the filtrate and the washings, and add water to make 50 mL. To this solution, add 0.5 mL of silver nitrate TS; the resulting solution is not more turbid than the following control solution.

Control solution—Dissolve 0.7 g of calcium carbonate in 20 mL of dilute nitric acid and filter. Wash the residue with 15 mL of water, combine the filtrate and the washings, and add 1.2 mL of 0.01 mol/L hydrochloric acid and water to make 50 mL, and add 0.5 mL of silver nitrate TS.

(5) ***Heavy metals***—Dissolve 2.0 g of Caffeine and Sodium Benzoate in 47 mL of water, add 3 mL of dilute hydrochloric acid slowly while stirring thoroughly to mix, and filter. Discard the first 5 mL of the filtrate, take the subsequent 25 mL of the filtrate, neutralize with ammonia TS, and add 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 2 mL of dilute acetic acid and water to 2.0 mL of lead standard solution to make 50 mL (NMT 20 ppm).

(6) ***Arsenic***—Proceed with 1.0 g of Caffeine and Sodium Benzoate according to Method 1 and perform the test (NMT 2 ppm).

(7) ***Phthalic acid***—Weigh accurately about 100 mg of Caffeine and Sodium Benzoate, dissolve it in 1 mL of water, add 1 mL of resorcinol-sulfuric acid TS, and evaporate the water by heating in an oil bath at between 120 and 125 ℃, and heat again for 90 minutes. After cooling, dissolve the resulting residue in 5 mL of water. To 1 mL of this solution, add 10 mL of a solution of sodium hydroxide (43 in 500) and use this solution as the test solution. Separately, take exactly 61 mg of potassium hydrogen phthalate and dissolve it in 1000 mL of water. Take 1 mL of this solution and proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbances of these solutions at the wavelength of 495 nm; the absorbance of the test solution is NMT that of the standard solution.

(8) ***Readily carbonizable substances***—Proceed with 0.5 g of Caffeine and Sodium Benzoate and perform the test; the color of the solution is not more intense than that of the matching fluids for color A.

Loss on drying NMT 3.0% (2 g, 80 ℃, 4 hours).

Assay (1) ***Sodium Benzoate***—Weigh accurately about 0.25 g of Caffeine and Sodium Benzoate, previously dried, and dissolve in 20 mL of acetic acid(100) by warming to 50 ℃, if necessary. After cooling, titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). The endpoint of the titration is the first equivalence point. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 14.411 mg of $C_7H_5NaO_2$

(2) ***Caffeine***—Continue with the titration in (1) with 0.1 mol/L perchloric acid VS from the first equivalence point to the second equivalence point (potentiometric titration under the Titrimetry).

Each mL of 0.1 mol/L perchloric acid VS
= 19.419 mg of $C_8H_{10}N_4O_2$

Packaging and storage Preserve in well-closed containers.

Calamine
칼라민

zinc; iron(3+); oxygen(2-) [*8011-96-9*]

Calamine is zinc oxide which contains a small amount of iron(III) oxide. Calamine, when ignited, contains NLT 98.0% and NMT 100.5% of zinc oxide (ZnO :

81.37).

Description Calamine occurs as a pale red, fine powder, which is odorless and has a faint taste.
It is practically insoluble in water.
It dissolves in hydrochloric acid.

Identification (1) Dissolve 1 g of Calamine in 10 mL of hydrochloric acid, and filter; the filtrate responds to the Qualitative Analysis for zinc salt.

(2) Add 10 mL of 3 mol/L hydrochloric acid to 1 g of Calamine, boil, filter, and add 1 to 2 drops of ammonium thiocyanate to the filtrate; the resulting solution exhibits a red color.

Purity (1) ***Acid insoluble matter***—Dissolve 2.0 g of Calamine in 50 mL of 3 mol/L hydrochloric acid and filter. Rinse the residue with water, and dry at 105 ℃ for 1 hour; the amount is NMT 40 mg (NMT 2.0%).

(2) ***Alkalinity***—Add 20 mL of water to 1.0 g of Calamine, heat on a steam bath for 15 minutes, filter, and add 2 drops of phenolphthalein TS and 0.20 mL of 0.05 mol/L sulfuric acid to the filtrate; the resulting solution is colorless.

(3) ***Lead***—Add 15 mL of water to 1 g of Calamine, add 3 mL of acetic acid(100) while stirring to mix, dissolve by heating on a steam bath, and cool. Filter it, and add 5 drops of potassium chromate TS to the filtrate; the resulting solution does not become turbid.

(4) ***Calcium***—Add 25 mL of 3 mol/L hydrochloric acid to 1 g of Calamine, heat for 30 minutes to dissolve, and filter it. add ammonia TS to the filtrate until the first precipitation is dissolved again, and put another 5 mL of ammonia TS. To 10 mL of this solution, add 2 mL of ammonium oxalate TS; the solution has no turbidity or has a slight turbidity.

(5) ***Calcium or magnesium***—Add 2 mL of sodium phosphate TS to 10 mL of the solution from (5); the solution has no turbidity or has a slight turbidity.

(6) ***Arsenic***—Dissolve 0.25 g of Calamine in 35 mL of water, use this solution as the test solution, and perform the test (NMT 8 ppm).

Loss on ignition NMT 2.0% (2 g).

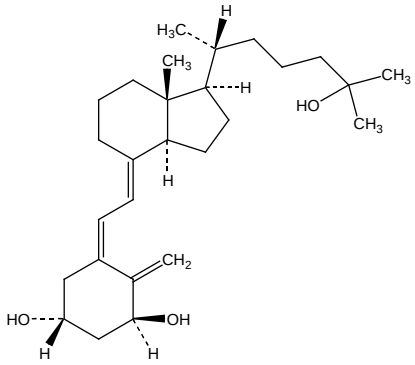
Microbiological examination of non-sterile products The total aerobic microbial count is NMT 1000 CFU, and the total combined yeasts/molds count is NMT 100 CFU per g of Calamine. Also, *Escherichia coli*, *Salmonella*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* are not detected.

Assay Ignite Calamine, weigh accurately about 1.5 g, add accurately 50 mL of 0.5 mol/L sulfuric acid, heat gently to dissolve, and filter. Rince the residue with hot water until the washings become neutral, combine the filtrate with the washings, add 2.5 g of ammonium chloride to cool, and titrate with 1 mol/L sodium hydroxide VS (indicator: 3 drops of methyl orange TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.5 mol/L sulfuric acid VS
= 40.69 mg of ZnO

Packaging and storage Preserve in well-closed containers.

Calcitriol
칼시트리올



$C_{27}H_{44}O_3$: 416.64
(1*R*,3*S*,5*Z*)-5-[(2*E*)-2-[(1*R*,3a*S*,7a*R*)-1-[(2*R*)-6-Hydroxy-6-methylheptan-2-yl]-7a-methyl-2,3,3a,5,6,7-hexahydro-1*H*-inden-4-ylidene]ethylidene]-4-methylidenecyclohexane-1,3-diol [*32222-06-3*]

Calcitriol contains NLT 97.0% and NMT 103.0% of calcitriol ($C_{27}H_{44}O_3$).

Description Calcitriol occurs as white crystals.
It is freely soluble in ethanol(95), soluble in oils and practically insoluble in water.
It is sensitive to air, heat and light,
In solution, it shows a reversible isomerization reaction to pre-calcitriol depending on the temperature and time.

Identification (1) Determine the infrared spectra of Calcitriol and Calcitriol RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention times of the major peaks obtained from the test solution and the standard solution under the Assay are the same.

Purity ***Related substances***—Weigh accurately 10 mg of Calcitriol, dissolve in acetonitrile without heating, put acetonitrile to make 55 mL, and add 2-Amino-2-hydroxymethyl-1,3-propanediol buffer solution to make 100 mL. Use this solution as the test solution. Separately, weigh accurately 10 mg of calcitriol RS, dissolve in acetonitrile without heating, put acetonitrile to make 55 mL, and add 2-Amino-2-hydroxymethyl-1,3-propanediol

buffer solution to make 100 mL. Use this solution as the standard solution. Take 50 μL of the test solution and perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution according to the automatic integration method and determine the peaks other than calcitriol and pre-calcitriol obtained from the test solution according to the percentage peak area method; NMT 0.1% for triazoline adduct of pre-calcitriol with the relative retention time of 0.43; NMT 0.25% for trans-calcitriol {(5*E*,7*E*)-9,10-Secocholesta-5,7,10(19)-trien-1α,3β,25-triol} with the relative retention time of 0.96; NMT 0.1% for 1β-calcitriol {(5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-trien-1β,3β,25-triol} with the relative retention time of 1.15; NMT 0.25% for Methylene Calcitriol {(5*Z*,7*E*)-1α,3β-dihydroxy-17-((*R*)-7-hydroxy-7-methyl-octan-2-yl)-9,10-secoandrosta-5,7,10(19)-triene} with the relative retention time of 1.5; NMT 0.1% for each of other unidentified related substances; and the sum of total peak areas of the related substances is NMT 1.0%. However, exclude any peaks smaller than 0.1%.

2-Amino-2-hydroxymethyl-1,3-propanediol buffer solution—Dissolve 1.0 g of 2-Amino-2-hydroxymethyl-1,3-propanediol in 900 mL of water, add phosphoric acid to adjust the pH to 7.0 to 7.5, and add water to make 1000 mL.

Operating conditions

Proceed as directed under the Assay under Calcitriol.

System suitability

System performance: Proceed with 50 μL of the system suitability solution under the above operating conditions; the relative retention time of pre-calcitriol with respect to calcitriol is 0.9 with the resolution being NLT 3.5. Also, proceed with 50 μL of the standard solution under the above operating conditions; the number of theoretical plates is NLT 10000 plates.

System repeatability: Repeat the test 5 times according to the above conditions with 50 μL of the standard solution each time; the relative standard deviation is NMT 1.0%

Time span of measurement: About 2 times the retention time of Calcitriol.

System suitability solution—A solution prepared by taking 2 mL of the standard solution and warming at 80 ℃ for 30 minutes.

Assay Perform the test quickly while protected from light and air. Weigh accurately 1 mg of Calcitriol, dissolve in the mobile phase to make exactly 10 mL, and use this solution as the test solution. Weigh accurately 1 mg of calcitriol RS, dissolve in the mobile phase to make exactly 10 mL, and use this solution as the standard solution (1). Pipet 1.0 mL of this solution, dilute with the mobile phase to make exactly 100 mL, and use this solution as the standard solution (2). Pipet 2 mL of the standard solution (1), allow to stand at 80 ℃ for 30 minutes, and use this solution as the standard solution (3). Perform the test with 50 μL each of the test solution and the standard solution (1) as directed under the Liquid Chromatography, and determine the peak areas A_T and A_S of calcitriol for each solution.

$$\text{Amount (mg) calcitriol } (C_{27}H_{44}O_3) = 10 \times C \times \frac{A_T}{A_S}$$

C: Concentration (mg/mL) of calcitriol in standard solution (1)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of acetonitrile and 2-Amino-2-hydroxymethyl-1,3-propanediol buffer solution (550 : 450).

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 50 μL of the standard solution (3) under the above conditions; the relative retention times of the pre-calcitriol peak to the retention time of calcitriol peak is about 0.9, and the resolution between these peaks are NLT 3.5. Proceed with 50 μL of the standard solution (1) under the above operating conditions; the number of theoretical plates is NLT 10000.

System repeatability: Repeat the test 6 times with 50 μL each of standard solution (1) under the above operating conditions; the relative standard deviation of the peak area of calcitriol is NMT 1%.

2-Amino-2-hydroxymethyl-1,3-propanediol buffer solution—Dissolve 1.0 g of 2-Amino-2-hydroxymethyl-1,3-propanediol in 1000 mL of water, and add phosphoric acid to adjust the pH to 7.0 to 7.5.

Packaging and storage Preserve in light-resistant, tight containers under nitrogen atmosphere at 2 ℃ to 8 ℃. Use immediately the contents after opening the container.

Precipitated Calcium Carbonate
침강탄산칼슘

$CaCO_3$: 100.09

[*471-34-1*]

Precipitated Calcium Carbonate, when dried, contains NLT 98.5% and NMT 101.0% of calcium carbonate ($CaCO_3$).

Description Precipitated Calcium Carbonate occurs as a white, fine crystalline powder, and is odorless and tasteless.
It is practically insoluble in water, but its solubility increases when carbon dioxide is present.
It is practically insoluble in ethanol(95) or ether.
It dissolves with effervescence in dilute acetic acid, dilute hydrochloric acid or dilute nitric acid.

Identification (1) Dissolve 0.5 g of Precipitated Calcium Carbonate in 10 mL of dilute hydrochloric acid, boil, then cool, and add ammonia TS to neutralize; the solution responds to the Qualitative Analysis for calcium salt.

(2) Precipitated Calcium Carbonate responds to the Qualitative Analysis (1) for carbonate.

Purity (1) ***Acid-insoluble substances***—To 5.0 g of Precipitated Calcium Carbonate, add 50 mL of water, then add 20 mL of hydrochloric acid dropwise with stirring, boil for 5 minutes, cool, add water to make 200 mL and filter using filter paper. Wash the residue until the washings show no turbidity when silver nitrate TS is added and ignite the residue with the filter paper to incinerate; the amount of the residue is NMT 10.0 mg.

(2) ***Heavy metals***—Mix 2.0 g of Precipitated Calcium Carbonate with 5 mL of water, add slowly 6 mL of dilute hydrochloric acid, and evaporate on a steam bath to dryness. Dissolve the residue in 50 mL of water and filter. To 25 mL of the filtrate, add 2 mL of dilute acetic acid, 1 drop of ammonia TS and water to make 50 mL, and perform the test using this solution as the test solution. For the control solution, evaporate 3 mL of hydrochloric acid on a steam bath to dryness, and add 2 mL of dilute acetic acid, 2.0 mL of lead standard solution and water to make 50 mL (NMT 20 ppm).

(3) ***Lead***—Weigh accurately 1.0 g of Precipitated Calcium Carbonate, mix with 5 mL of water, and slowly add 8 mL of 3 mol/L hydrochloric acid TS. Evaporate to dryness on a steam bath, dissolve the residue in 5 mL of water, and use this solution as the test solution. Transfer the test solution to a separatory funnel, wash with 10 mL of water, add 6 mL of a diammonium hydrogen citrate solution, 2 mL of hydroxylamine hydrochloride TS and 2 drops of phenol red TS, and add ammonia water(28) until the solution is alkalified. Cool the solution if necessary, add 2 mL of a potassium cyanide solution, extract with 5 mL each of extracting dithizone solution until the extract exhibits a green color, and combine the extracts in another separatory funnel. To the combined extracts, add 20 mL of diluted nitric acid (1 in 1000), shake for 30 seconds, and discard the chloroform layer. To the nitric acid layer, add 5.0 mL of standard dithizone solution and 4 mL of ammonia-cyanide TS, and shake for 30 seconds; the purple color of the chloroform layer is not more intense than the color obtained with 3 mL of diluted lead standard solution (1 in 10) in the same manner as the test solution (NMT 3 ppm).

(4) ***Magnesium and alkali metals***—Dissolve 1.0 g of Precipitated Calcium Carbonate in a mixture of 20 mL of water and 10 mL of dilute hydrochloric acid, boil, neutralize with ammonia TS, and add ammonium oxalate TS dropwise until precipitation of calcium oxalate is completed. Heat the mixture on a steam bath for 1 hour, cool, add water to make 100 mL, shake well and filter. To 50 mL of the filtrate, add 0.5 mL of sulfuric acid, evaporate to dryness and ignite the residue on evaporation at 600 °C to a constant mass; the amount of the residue is NMT 5.0 mg.

(5) ***Barium***—Mix 1.0 g of Precipitated Calcium Carbonate with 10 mL of water, add 4 mL of hydrochloric acid in small portions with stirring, boil for 5 minutes, cool, add water to make 40 mL and filter. With the filtrate, perform the test as directed under the Flame Coloration (1); it does not exhibit a green color.

(6) ***Iron***—Weigh accurately about 40 mg of Precipitated Calcium Carbonate, dissolve in 5 mL of 2 mol/L hydrochloric acid TS, transfer to a beaker, add water to make 10 mL, and use this solution as the test solution. Separately, put 4.0 mL of iron standard solution into a beaker, add water to make 10 mL, and use this solution as the standard solution. To each beaker, add 2 mL of a solution of citric acid (1 in 5) and 2 drops of thioglycolic acid, adjust the pH to 9.5 ± 0.1 with ammonia TS, add water to make 20 mL, mix, and allow to stand for 5 minutes. Again, add water to make 50 mL, and mix well. Immediately, with the test solution and standard solution, determine the absorbances at the absorbance maximum wavelength at about 530 nm as directed under the Ultraviolet-visible Spectroscopy using water as the blank test solution; the absorbance of the test solution is NMT that of the standard solution (NMT 0.1%).

(7) ***Arsenic***—Moisten 0.67 g of Precipitated Calcium Carbonate with 1 mL of water, then dissolve in 4 mL of dilute hydrochloric acid, use this solution as the test solution and perform the test (NMT 3 ppm).

Loss on drying NMT 1.0% (1 g, 180 °C, 4 hours).

Assay Weigh accurately about 0.12 g of Precipitated Calcium Carbonate, previously dried, and dissolve in 20 mL of water and 3 mL of dilute hydrochloric acid. Add 80 mL of water, 15 mL of a solution of potassium hydroxide (1 in 10) and 50 mg of NN indicator, and titrate immediately with 0.05 mol/L disodium ethylenediaminetetraacetate VS. The endpoint of titration is when the color of the solution changes from purple to blue.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 5.004 mg of $CaCO_3$

Packaging and storage Preserve in tight containers.

Calcium Chloride Hydrate
염화칼슘수화물

$CaCl_2 \cdot 2H_2O$: 147.02

Calcium Chloride Hydrate contains NLT 96.7% and NMT 103.3% of calcium chloride ($CaCl_2 \cdot 2H_2O$).

Description Calcium Chloride Hydrate occurs as a white grain or a mass, which is odorless.
It is very soluble in water, soluble in ethanol(95) and practically insoluble in ether.
It is deliquescent.

Identification An aqueous solution of Calcium Chloride Hydrate (1 in 10) responds to the Qualitative Analysis for calcium salt and chloride.

pH Dissolve 1.0 g of Calcium Chloride Hydrate in 20 mL of freshly boiled and cooled water; the pH of this solution is between 4.5 and 9.2.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Calcium Chloride Hydrate in 20 mL of water; the solution is clear and colorless.

(2) ***hypochlorous acid***—Dissolve 0.5 g of Calcium Chloride Hydrate in 5 mL of water, add 2 to 3 drops of dilute hydrochloric acid and 2 to 3 drops of zinc iodide-starch TS; the resulting solution does not exhibit a blue color immediately.

(3) ***Sulfate***—Perform the test with 1.0 g of Calcium Chloride Hydrate. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid (NMT 0.024%).

(4) ***Heavy metals***—Proceed with 2.0 g of Calcium Chloride Hydrate according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Magnesium and alkali metals***—Dissolve 1 g of Calcium Chloride Hydrate in 50 mL of water, add 0.5 g of ammonium chloride, and heat for 1 minute. Add immediately 40 mL of oxalic acid TS to this solution, stir until its precipitation is formed, and add 2 drops of methyl red TS before it is cooled. Add ammonia TS drop by drop until it turns alkaline, cool to room temperature, add water to make 100 mL, mix well, and allow to stand for 4 hours to overnight. Filter this solution, place 50 mL of the clear filtrate into the platinum plate, and add 0.5 mL of sulfuric acid. Evaporate to dryness on a steam bath, and heat gently and ignite until the ammonium is volatilized and the residue reaches a constant weight; the amount is NMT 5 mg (NMT 1.0%).

(6) ***Valium***—Dissolve 0.5 g of Calcium Chloride Hydrate in 5 mL of water, add 2 drops of dilute hydrochloric acid and 2 mL of potassium sulfate TS, and allow to stand for 10 minutes; the solution does not become turbid.

(7) ***Iron, aluminum and phosphate***—Put 1.0 g of Calcium Chloride Hydrate into a Nestler tube and dissolve in 20 mL of water and 1 drop of dilute hydrochloric acid, and heat. After cooling, add 3 drops of ammonia TS, and heat to boiling; the solution does not become turbid or produces no precipitation.

(8) ***Arsenic***—Proceed with 1.0 g of Calcium Chloride Hydrate according to Method 1 and perform the test (NMT 2 ppm).

Assay Weigh accurately about 0.4 g of Calcium Chloride Hydrate and dissolve in water to make 200 mL exactly. Pipet 20 mL of this solution, add 40 mL of water, 2 mL of 8 mol/L potassium hydroxide TS and 0.1 g of NN indicator, and immediately titrate with 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS. The endpoint of titration is when the color of the solution changes from purple to blue.

Each mL of 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.9402 mg of $CaCl_2 \cdot 2H_2O$

Packaging and storage Preserve in tight containers.

Calcium Chloride Injection
염화칼슘 주사액

Calcium Chloride Injection is an aqueous solution for injection and contains NLT 95.0% and NMT 105.0% of the labeled amount of calcium chloride (CaCl2: 110.98).
The concentration of Calcium Chloride Injection is expressed as the amount of calcium chloride ($CaCl_2$).

Method of preparation Prepare as directed under Injections, with Calcium Chloride.

Description Calcium Chloride Injection occurs as a clear, colorless liquid.

Identification Calcium Chloride Injection responds to the Qualitative Analysis for calcium salt and chloride.

pH Between 4.5 and 7.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.30 EU per mg of Calcium Chloride Injection.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

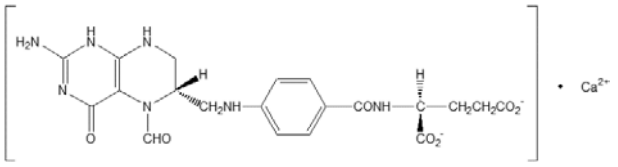
Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Calcium Chloride Injection equivalent to about 0.4 g of calcium chloride ($CaCl_2$), and perform the test as directed under the Assay of Calcium Chloride.

Each mL of 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.2197 mg of $CaCl_2$

Packaging and storage Preserve in hermetic containers.

Calcium Folinate
폴리네이트칼슘



Leucovorin Calcium $C_{20}H_{21}CaN_7O_7$: 511.50
Calcium(2*S*)-2-{[4-[(*R*)-2-amino-5-formyl-4-oxo-5,6,7,8-tetrahydro-1*H*-pteridin-6-yl)methyl-amino]benzoyl]amino}pentanedioate [*1492-18-8*]

Calcium Folinate contains NLT 95.0% and NMT 102.0% of calcium folinate ($C_{20}H_{21}CaN_7O_7$), calculated on the anhydrous basis.

Description Calcium Folinate occurs as a white to pale yellow powder.
It is odorless and tasteless.
It is very soluble in water, freely soluble in acetic acid(100), and practically insoluble in ethanol(95) or ether.
It is gradually affected by light.

Identification (1) Determine the absorption spectra of aqueous solutions of Calcium Folinate and calcium folinate RS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Calcium Folinate and calcium folinate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Calcium Folinate (1 in 100) responds to the Qualitative Analysis (2) and (3) for calcium salt.

Optical rotation $[\alpha]_D^{20}$: Between +14° and +19° (0.1 g calculated on the anhydrous basis, water, 10 mL, 100 mm).

pH To 1.25 g of Calcium Folinate, add 50 mL of freshly boiled and cooled water, and dissolve by warming at 40 ℃, if necessary; the pH of this solution is between 6.8 and 8.0.

Purity (1) ***Clarity and color of solution***—To 1.25 g of Calcium Folinate, add 50 mL of freshly boiled and cooled water, and dissolve by warming at 40 ℃, if necessary; the resulting solution is clear. Determine the absorbance of this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at a wavelength of 420 nm is NMT 0.25.

(2) ***Heavy metals***—Proceed with 0.40 g of Calcium Folinate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 50 ppm).

(3) ***Related substances***—Weigh accurately 10 mg of Calcium Folinate, dissolve exactly in 25 mL of water, and use this solution as the test solution. Pipet 2 mL of the test solution, dissolve in water to make exactly 200 mL, and use this solution as the standard solution. With 20 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions and determine the peak areas of each solution by the automatic integration method; the peak areas other than the folinate from the test solution are not greater than the peak area of the folinate from the standard solution. Also, the sum of peak areas other than folinate from the test solution is not greater than 5 times the peak area of folinate from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed under the conditions under the Assay.

System suitability

System performance: Proceed as directed under the system suitability under the Assay.

Test for required detectability: Pipet 5 mL of the standard solution and add water to exactly 50 mL. Confirm that the peak area of folinate obtained from 20 μL of this solution is equivalent within the range between 7% and 13% of the peak area of folinate obtained from the standard solution.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above operating conditions; the relative standard deviation of the peak areas of folinate is NMT 2.0%.

Time span of measurement: About 2.5 times the retention time of folinate after the solvent peak.

Water Between 7.0% and 17.0% (0.2 g, volumetric titration, direct titration).

Assay Weigh accurately 10 mg of Calcium Folinate and calcium folinate RS (previously determine water content), dissolve each in the water to make exactly 25 mL, pipet 5 mL of these solutions, add the mobile phase to make exactly 25 mL, and use these solutions as the test solution and the standard solution. Perform the test with 20 μL each of the test solution and the standard solution

as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of folinate from each of the solutions.

$$\text{Amount (mg) of calcium folinate } (C_{20}H_{21}CaN_7O_7) = \text{Amount (mg) of calcium folinate RS, calculated on the anhydrous basis} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 45 °C.

Mobile phase: To a mixture of sodium hydrogen phosphate docahydrate (287 in 100000), methanol and tetrabutylammonium hydroxide TS (385 : 110 : 4), add phosphoric acid to adjust the pH to 7.5.

Flow rate: Adjust the flow rate so that the retention time of calcium folinate is about 10 minutes.

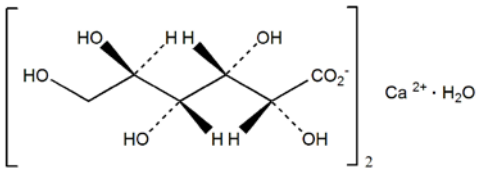
System suitability

System performance: Dissolve 10 mg each of Calcium Folinate and folic acid in 100 mL of the mobile phase. Proceed with 20 μL of this solution under the above operating conditions; calcium folinate and folic acid are eluted in this order with the resolution being NLT 10.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above operating conditions; the relative standard deviation of the peak areas of calcium folinate is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Calcium Gluconate Hydrate
글루콘산칼슘수화물



Calcium Gluconate $C_{12}H_{22}CaO_{14}\cdot H_2O$: 448.39
Calcium(2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanoate, hydrate [*299-28-5*]

Calcium Gluconate Hydrate, when dried, contains NLT 99.0% and NMT 104.0% of calcium gluconate hydrate ($C_{12}H_{22}CaO_{14}\cdot H_2O$).

Description Calcium Gluconate Hydrate occurs as a white crystalline powder or granule.
It is soluble in water and practically insoluble in ethanol(99.5).

Identification (1) Weigh 10 mg of Calcium Gluconate Hydrate and calcium gluconate hydrate RS respectively in 1 mL of water, and dissolve by warming, and use these solutions as the test solution and the standard solution, respectively. With the solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethanol(95), water, ammonia water and ethyl acetate (5 : 3 : 1 : 1) to a distance of about 10 cm, air-dry the plate, and heat it at 110 °C for 20 minutes. After cooling, spray a mixture of ammonium molybdate TS and cerium sulfate TS evenly onto the plate, air-dry, and heat it at 110 °C for 20 minutes; the spots from the test solution and the standard solution are the same in the R_f value and color tone.

(2) The aqueous solution of Calcium Gluconate Hydrate (1 in 40) responds to the Qualitative Analysis for calcium salt.

Optical rotation $[\alpha]_D^{20}$: Between +6° and +11° (after drying, 0.5 g, 25 mL of water, cooling after warming, 100 mm).

pH Dissolve 1.0 g of Calcium Gluconate Hydrate in 20 mL of water by warming. The pH of the solution is between 6.0 and 8.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Calcium Gluconate Hydrate in 50 mL of water by warming; the resulting solution is clear.

(2) ***Chloride***—Weigh 0.40 g of Calcium Gluconate Hydrate and perform the test. Prepare the control solution with 0.80 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.071%).

(3) ***Sulfate***—Weigh 1.0 g of this drug and perform the test. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid VS (NMT 0.048%).

(4) ***Phosphate***—Weigh 10.0 g of Calcium Gluconate Hydrate to 90 mL of water at between about 70 and 80 ℃ and boil for 10 seconds until the solution becomes clear. Pipet 1 mL of this solution, add water to make 100 mL and use this solution as the test solution. Separately, weigh accurately a suitable amount of potassium dihydrogen phosphate and dissolve in water to make a solution having a concentration of 0.716 mg/mL in 1 mL. Pipet 1.0 mL of this solution and add water to make 100 mL. Pipet 2.0 mL of this solution, add water to make 100 mL and use this solution as the standard solution. Add 4 mL of sulfomolybdic acid TS and 0.1 mL of a mixture containing 3 mol/L hydrochloric acid TS and acidic tin(II) chloride TS (10 : 1) to the test solution and the standard solution respectively to mix, and allow to stand for 10 minutes. The color observed from the test

solution is not darker than that from the standard solution (NMT 0.01%).

(5) ***Heavy metals***—Weigh 1.0 g of Calcium Gluconate Hydrate to 30 mL of water and 2 mL of dilute acetic acid, and dissolve it by heating. After cooling it down, add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 2 mL of dilute acetic acid and water to 2.0 mL of lead standard solution to make 50 mL (NMT 20 ppm).

(6) ***Iron***—Weigh 1.0 g of Calcium Gluconate Hydrate, put it in a 100 mL quartz glass flask, add 20 mL of 12 mol/L nitric acid TS, and heat until smoke appears. Add 0.5 mL of 30% hydrogen peroxide to this and heat again until smoke appears. Repeat this procedure until the volume decreases to about 5 mL. Then, cool it down, add 1.0 mL of perchloric acid, and boil. Avoid heating at NLT 190 ℃ or evaporating to dryness as it may cause explosion. Add 2 mol/L hydrochloric acid TS to this solution to make 25 mL and use this solution as the test solution. Separately, pipet 2.0 mL, 4.0 mL and 10.0 mL of iron standard solution, respectively, put each of them in a 100-mL volumetric flask, add 1.37 g of calcium chloride dihydrate to the flask, and dilute with 2 mol/L hydrochloric acid TS to make 100 mL. Use these solutions as the standard solution (1), (2) and (3). Separately, repeat the process of preparing the test solution by using 0.34 g of calcium chloride dihydrate instead and use the resulting solution as the blank test solution. Perform the test with the test solution and the standard solutions (1), (2) and (3) as directed under Atomic Absorption Spectroscopy according to the following conditions and obtain the content of iron in the test solution using the calibration curve derived from the standard solution absorbance; the result is NMT 5 ppm.

Gas: Air–acetylene
Lamp: Iron hollow cathode lamp
Wavelength: 248.3 nm

(7) ***Magnesium and alkali metals***—Completely dissolve 1.0 g of Calcium Gluconate Hydrate in 100 mL of boiling water, and add 10 mL of ammonium chloride TS, 1 mL of ammonia water(28), and 50 mL of ammonium oxalate TS of the temperature between about 70 and 80 ℃. Allow it to stand for 4 hours, add water to make 200 mL, and filter it. Evaporate 100 mL of the filtrate to dryness and ignite to a constant mass: the residue is NMT 2 mg (NMT 0.4%).

(8) ***Arsenic***—Dissolve 0.6 g of Calcium Gluconate Hydrate in 5 mL of water by warming, add 5 mL of dilute sulfuric acid and 1 mL of bromine TS and heat to concentration on a steam bath to 5 mL. Use this solution as the test solution (NMT 3.3 ppm).

(9) ***Sucrose and reducing sugars***—Weigh 0.5 g of Calcium Gluconate Hydrate, put it to 10 mL of water and 2 mL of hydrochloric acid, and boil the solution for 2 minutes. After cooling, add 5 mL of sodium carbonate TS, allow to stand for 5 minutes, add water to make 20 mL and filter. Add 2 mL of Fehling's TS to 5 mL of the filtrate and boil for 1 minute; no orange to red precipitate is formed immediately.

Loss on drying NMT 1.0% (1 g, 80 ℃, 2 hours).

Assay Weigh accurately about 0.4 g of Calcium Gluconate Hydrate, previously dried, dissolve in 100 mL of water, add 2 mL of 8 mol/L potassium hydroxide TS and 0.1 g of NN indicator and titrate immediately with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS The endpoint is reached when the color of the solution changes from purple to blue.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 22.420 mg of $C_{12}H_{22}CaO_{14}\cdot H_2O$

Packaging and storage Preserve in well-closed containers.

Calcium Gluconate Injection
글루콘산칼슘 주사액

An aqueous solution for injection, Calcium Gluconate Injection contains NLT 95.0% and NMT 105.0% of the labeled amount of calcium in total (Ca: 40.08).
A small amount of calcium saccharate or other suitable calcium salts may be added to Calcium Gluconate Injection as a stabilizer.

Method of preparation Prepare Calcium Gluconate Injection as directed under Injections, with Calcium Gluconate Hydrate. However, when adding a stabilizer, state the total amount of calcium.

Description Calcium Gluconate Injection occurs as a clear, colorless liquid.

Identification (1) Pipet 5 mL of Calcium Gluconate Injection, heat, add 0.7 mL of acetic acid(100) and 1 mL of freshly distilled phenylhydrazine, and heat on a steam bath for 30 minutes. After cooling, proceed as directed under the Identification (1) for Calcium Gluconate Hydrate hereinafter.

(2) An aqueous solution of Calcium Gluconate Injection (1 in 5) responds to the Qualitative Analysis for calcium salt.

pH Between 6.0 and 8.2.

Sterility Meets the requirements.

Bacterial endotoxins Bacterial endotoxins in Calcium Gluconate Injection is less than 0.17 EU per mg of calcium gluconate hydrate.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

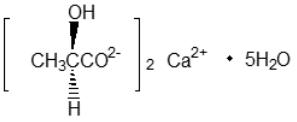
Extractable volume of injections Meets the requirements.

Assay Take an exact amount of Calcium Gluconate Injection equivalent to about 0.4 g of calcium gluconate ($C_{12}H_{22}CaO_{14}$), add 100 mL of water, 2 mL of 8 mol/L potassium hydroxide TS, and 0.1 g of NN indicator, and immediately titrate with 0.05 mol/L ethylenediamine tetraacetate disodium VS. The endpoint of titration is reached when the color of the solution changes from purple to blue.

Each mL of 0.05 mol/L disodium ethylenediaminetetraacetate VS
= 2.0040 mg of Ca

Packaging and storage Preserve in hermetic containers.

Calcium Lactate Hydrate
락트산칼슘수화물



and enantiomer

Calcium Lactate $C_6H_{10}CaO_6 \cdot 5H_2O$: 308.29
Calcium (*RS*)-2-hydroxypropanoate pentahydrate [*5743-47-5*]

Calcium Lactate Hydrate, when dried, contains NLT 97.0% and NMT 101.0% of calcium lactate ($C_6H_{10}CaO_6$: 218.22).

Description Calcium Lactate Hydrate occurs as a white powder or grain.
It is odorless and has a slight sour taste.
1 g of Calcium Lactate Hydrate is slowly soluble in 20 mL of water, slightly soluble in ethanol(95) and practically insoluble in ether.
It is efflorescent at room temperature and becomes an anhydrous matter at 120 ℃.

Identification An aqueous solution of Calcium Lactate Hydrate (1 in 20) responds to the Qualitative Analysis for calcium salt and lactate.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Calcium Lactate Hydrate in 20 mL of water by heating; the resulting solution is clear.

(2) ***Acidity or alkalinity***—Add 2 drops of phenolphthalein TS in the solution in (1); the resulting solution does not exhibit a red color. Add 0.50 mL of 0.1 mol/L sodium hydroxide VS; the resulting solution does not exhibit a red color.

(3) ***Heavy metals***—Add 30 mL of water and 5 mL of dilute acetic acid to 1.0 g of Calcium Lactate Hydrate and dissolve by heating. After cooling, add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 2 mL of dilute acetic acid and water to make 50 mL (NMT 20 ppm).

(4) ***Magnesium or alkaline metals***—Dissolve about 1.0 g of Calcium Lactate Hydrate in 40 mL of water, add 0.5 g of ammonium chloride, boil, and add 20 mL of ammonium oxalate TS. Heat on a steam bath for 1 hour, cool it down, add water to make 100 mL, and filter. Add 0.5 mL of sulfuric acid to 50 mL of the filtrate, evaporate to dryness to a constant mass, ignite at a temperature between 450 and 550 ℃; the residue is NMT 5 mg.

(5) ***Arsenic***—Dissolve about 0.5 g of Calcium Lactate Hydrate in 2 mL of water and 3 mL of hydrochloric acid. Use this solution as the test solution and perform the test (NMT 4 ppm).

(6) ***Volatile fatty acid***—Add 2 mL of sulfuric acid to about 1.0 g of Calcium Lactate Hydrate, and heat; the solution does not have the same odor as the acetic acid or butyric acid.

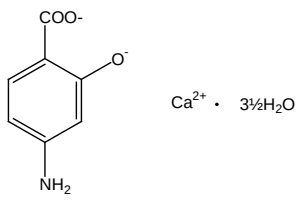
Loss on drying Between 25.0% and 30.0% (1 g, 1 hour from the start at 80 ℃, nest 4 hours at 120 ℃).

Assay Weigh accurately about 0.5 g of Calcium Lactate Hydrate, previously dried, dissolve in water by heating, cool it down, and add water to make exactly 100 mL. Pipet 20 mL of this solution, add 80 mL of water and 1.5 mL of 8 mol/L potassium hydroxide TS, allow it to stand for 3 to 5 minutes, and add 0.1 g of NN indicator. Titrate immediately with 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS. However, the endpoint of the titration is when the red color of this solution turns blue.

Each mL of 0.02 mol/L disodium ethylenediaminetetraacetate VS
= 4.3644 mg of $C_6H_{10}CaO_6$

Packaging and storage Preserve in tight containers.

Calcium *p*-Aminosalicylate Hydrate
파라아미노살리실산칼슘수화물



PAS-calcium
Calcium p-Aminosalicylate

$C_7H_5CaNO_3 \cdot 3½H_2O$: 254.25

Calcium 4-amino-2-hydroxybenzoate hydrate [*133-15-3*, anhydrous]

Calcium p-Aminosalicylate Hydrate contains NLT 97.0% and NMT 103.0% of calcium p-aminosalicylate ($C_7H_5CaNO_3$: 191.20), calculated on the anhydrous basis.

Description Calcium p-Aminosalicylate Hydrate occurs as a white or slightly colored powder and has a slightly bitter taste.
It is very slightly soluble in water and practically insoluble in ethanol(95) or methanol.
It is gradually changed to brown by light.

Identification (1) To 50 mg of Calcium p-Aminosalicylate Hydrate, add 100 mL of water, shake well to mix, and filter. Add 1 mL of 1 mol/L hydrochloric acid TS to 10 mL of the filtrate, shake to mix, and then add 1 drop of iron(III) chloride TS; the resulting solution exhibits a purple color.

(2) Determine the infrared spectra of Calcium p-Aminosalicylate Hydrate and calcium p-aminosalicylate hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers

(3) To 3 g of Calcium p-Aminosalicylate Hydrate, add 15 mL of ammonium chloride TS and 15 mL of water, heat on a steam bath for 10 minutes, cool, and then filter; the filtrate responds to the Qualitative Analysis (1), (2), and (3) for calcium salt.

Purity (1) ***Chloride*—**Dissolve 1.0 g of Calcium p-Aminosalicylate Hydrate in 15 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.70 mL of 0.01 mol/L hydrochloric acid (NMT 0.025%).

(2) ***Heavy metal***—Proceed with 1.0 g of Calcium p-Aminosalicylate Hydrate according to Method 3 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic*—**Dissolve 0.40 g of Calcium p-Aminosalicylate Hydrate in 20 mL of 0.1 mol/L hydrochloric acid TS by warming in on a steam bath, and perform the test using this solution as the test solution (NMT 5 ppm).

(4) ***3-aminophenol***—To 0.10 g of Calcium p-Aminosalicylate Hydrate, add 5 mL of 0.1 mol/L ethylenediaminetetraacetic acid disodium salt TS, previously cooled in iced water, and shake vigorously to dissolve. Immediately add 3 mL of ammonia-ammonium chloride buffer solution, pH 11.0, previously cooled in iced water, and shake to mix. Next, add 2 mL of 4-amino-*N*,*N*-diethylaniline sulfate TS, shake to mix, and add 10.0 mL of cyclohexane and 4 mL of diluted potassium hexacyanoferrate(III) TS (1 in 10). Then immediately shake for 20 seconds to mix. Centrifuge this solution, take the cyclohexane layer separately, wash it twice with 5 mL of diluted ammonia TS (1 in 14) each time, add 1 g of anhydrous sodium sulfate, shake to mix, and allow to stand for 5 minutes; the color of the clear cyclohexane layer is not more intense than the following control solution.

Control solution—Dissolve 50 mg of 3-aminophenol in water to make exactly 500 mL. Pipet 20 mL of this solution and add water to make exactly 100 mL. Take 5.0 mL of this solution, add 3 mL of ammonia-ammonium chloride buffer solution (pH 11.0), previously cooled in iced water, shake to mix, and proceed in the same manner.

Water Between 23.3% and 26.3% (0.1 g, volumetric titration, direct titration).

Assay Weigh accurately about 0.2 g of Calcium p-Aminosalicylate Hydrate, add 60 mL of water and 0.75 mL of dilute hydrochloric acid, and heat on a steam bath to dissolve. After cooling, add water to make exactly 100 mL, and use this solution as the test solution. Take exactly 30 mL of the test solution, put it in an iodine bottle, and then add exactly 25 mL of 0.05 mol/L bromine solution. Next, add 20 mL of potassium bromide solution (1 in 4), then quickly add 14 mL of a mixture of acetic acid(100) and hydrochloric acid (5 : 2), and immediately stopper the bottle. Allow to stand for 10 minutes, shaking occasionally to mix. Then add cautiously 6 mL of potassium iodide TS, immediately stopper the bottle, and shake gently to mix. Allow to stand for 5 minutes and titrate the released iodine with 0.1 mol/L sodium thiosulfate VS (indicator: 1 mL of starch TS). Perform a blank test in the same manner.

Each mL of 0.05 mol/L bromine solution VS
= 3.187 mg of $C_7H_5CaNO_3$

Packaging and storage Preserve in light-resistant, tight containers.

Calcium *p*-Aminosalicylate Granules
파라아미노살리실산칼슘 과립

PAS-calcium Granules

Calcium p-aminosalicylate Granules contain NLT 95.0% and NMT 105.0% of the labeled amount of calcium p-aminosalicylate hydrate ($C_7H_5CaNO_3 \cdot 3½H_2O$: 254.25).

Method of preparation Prepare as directed under Granules with Calcium *p*-Aminosalicylate Hydrate.

Identification Powder Calcium *p*-Aminosalicylate Granules, weigh an appropriate amount, equivalent to 50

mg of Calcium *p*-aminosalicylate, according to the labeled amount, add 100 mL of water, shake vigorously to mix, and filter. To 10 mL of the filtrate, add 1 mL of 1 mol/L hydrochloric acid TS, shake to mix, and add 1 drop of iron(III) chloride TS; the solution exhibits a purple color.

Dissolution Weigh accurately an amount of calcium *p*-aminosalicylate hydrate ($C_7H_5CaNO_3 \cdot 3½H_2O$) equivalent to about 250 mg according to the labeled amount, perform the test at 75 revolutions per minute according to Method 2, using 900 mL of water as the dissolution medium. Take NLT 20 mL of the dissolved solution after 60 minutes from the start of the dissolution test, and filter through a membrane filter with a pore size of NMT 0.5 μm. Discard the first 10 mL of the filtrate, pipet 5 mL of the subsequent filtrate, add water to make exactly make 100 mL, and use this solution as the test solution. Separately, weigh accurately an amount of calcium *p*-aminosalicylate hydrate RS, previously determined for Water content, equivalent to about 28 mg, and dissolve in water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, AT and AS, of the test solution and the standard solution at the absorbance maximum wavelength near 300 nm as directed under Ultraviolet-visible Spectrophotometry. It meets the requirements if the dissolution rate of Calcium *p*-Aminosalicylate Granules in 60 minutes is NLT 75%.

Dissolution rate (%) with respect to the labeled amount of calcium *p*-aminosalicylate hydrate ($C_7H_5CaNO_3 \cdot 3½H_2O$)

$$= \frac{W_S}{W_T} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 900 \times 1.330$$

W_S: Taken amount (g) of *p*-aminosalicylic acid ($C_7H_5CaNO_3$), as calculated on the anhydrous basis, in calcium *p*-aminosalicylate hydrate RS

W_T: Taken amount (g) of Calcium *p*-Aminosalicylate Granules

C: Labeled amount (mg) of calcium *p*-aminosalicylate hydrate $C_7H_5CaNO_3 \cdot 3½H_2O$) in 1 g

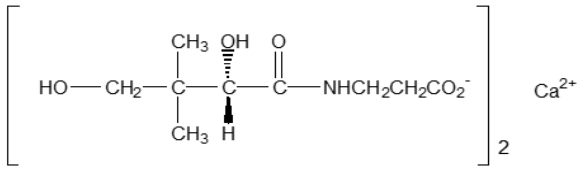
Particle size distribution estimation by analytical sieving Meets the requirements.

Assay Powder Calcium *p*-Aminosalicylate Granules, weigh accurately an amount of calcium p-aminosalicylate hydrate ($C_7H_5CaNO_3 \cdot 3½H_2O$: 254.25) equivalent to about 0.2 g, add 60 mL of water and 0.75 mL of dilute hydrochloric acid, heat on a steam bath to dissolve, cool, add water to make exactly 100 mL, and filter. Pipet 30 mL of the filtrate, place in an iodine bottle, and perform the test as directed under the Assay of Calcium *p*-Aminosalicylate Hydrate.

Each mL of 0.05 mol/L bromine solution VS
= 4.238 mg of $C_7H_5CaNO_3 \cdot 3½H_2O$

Packaging and storage Preserve in light-resistant, tight containers.

Calcium Pantothenate
판토텐산칼슘



$C_{18}H_{32}CaN_2O_{10}$: 476.53

Calcium *bis*(3-{[(2*R*)-2,4-dihydroxy-3,3-dimethylbutanoyl]amino}propanoate) [*137-08-6*]

Calcium Pantothenate, when dried, contains NLT 5.7% and NMT 6.0% of nitrogen (N: 14.01), and NLT 8.2% and NMT 8.6% of calcium (Ca: 40.08).

Description Calcium Pantothenate occurs as a white powder.
It is odorless and has a bitter taste.
It is freely soluble in water, very slightly soluble in ethanol(95), and practically insoluble in ether.
The pH of an aqueous solution of Calcium Pantothenate (1 in 20) is between 7.0 and 9.0.
It is hygroscopic.

Identification (1) Dissolve 50 mg of Calcium Pantothenate in 5 mL of sodium hydroxide TS, and filter. To the filtrate, add 1 drop of copper(II) sulfate TS; the resulting solution exhibits an deep blue color.

(2) To 50 mg of Calcium Pantothenate, add 5 mL of sodium hydroxide TS, and boil for 1 minute. After cooling, add diluted hydrochloric acid (1 in 10) to adjust pH to between 3 and 4, and add 2 drops of iron(III) chloride TS; the resulting solution exhibits a yellow color.

(3) An aqueous solution of Calcium Pantothenate (1 in 10) responds to the Qualitative Analysis for calcium salt.

Optical rotation $[\alpha]_D^{20}$: Between +25.0° and +28.5° (1 g after drying, water, 20 mL, 100 mm).

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Calcium Pantothenate in 20 mL of water; the resulting solution is clear and colorless.

(2) ***Heavy metals*—**Proceed with 1.0 g of Calcium Pantothenate according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Alkaloid*—** Dissolve 50 mg of Calcium Pantothenate in 5 mL of water, and add 0.5 mL of ammonium molybdate TS and 0.5 mL of phosphoric acid solution

(1 in 10); the solution has no white turbidity.

(4) ***Related substances***—Weigh 100 mg of Calcium Pantothenate, add water to make exactly 10 mL, and use this solution as the test solution. Separately, weigh 10 mg of β-alanine RS, dissolve in methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of ethanol(95) and water (65 : 35) as the developing solvent to a distance of about 15 cm, spray evenly a solution of ninhydrin in ethanol(95) (0.2 in 100) on the plate, and air-dry the plate. Heat this thin-layer chromatographic plate at 120 ℃ for 20 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution (NMT 1.0%).

Loss on drying NMT 5.0% (1 g, 105 ℃, 4 hours).

Assay (1) ***Nitrogen***—Weigh accurately about 50 mg of Calcium Pantothenate, previously dried, and perform the test as directed under the Nitrogen Determination.

(2) ***Calcium***—Weigh accurately 0.4 g of Calcium Pantothenate, previously dried, and dissolve in 30 mL of water by heating. After cooling, add exactly 25 mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt, add 10 mL of pH 10.7 ammonia-ammonium chloride buffer solution, and titrate excess ethylenediaminetetraacetic acid disodium salt with 0.05 mol/L magnesium chloride VS (indicator: 40 mg of eryochrome black T in sodium chloride) However, the endpoint of the titration is when the bluish purple color of the solution turns to purple. Perform a blank test in the same manner.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.0039 mg of Ca

Packaging and storage Preserve in tight containers.

Calcium Polystyrene Sulfonate
폴리스티렌설폰산칼슘

Calcium 2-ethenylbenzenesulfonate [*37286-92-3*]

Calcium Polystyrene Sulfonate is a calcium-type cation exchange resin produced by combining a sulfonic acid group with a styrene-divinylbenzene copolymer.

Calcium Polystyrene Sulfonate, when dried, contains NLT 7.0% and NMT 9.0% of calcium (Ca : 40.08).

Each g of Calcium Polystyrene Sulfonate exchanges with 53 to 71 mg of potassium (K: 39.10), calculated on the dried basis.

Description Calcium Polystyrene Sulfonate occurs as a pale yellowish white to pale yellow powder.
It is odorless and tasteless.
It is practically insoluble in water, ethanol(95) or ether.

Identification (1) Determine the infrared spectra of Calcium Polystyrene Sulfonate and calcium polystyrene sulfonate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Mix 0.5 g of Calcium Polystyrene Sulfonate with 10 mL of dilute hydrochloric acid, filter and neutralize the filtrate with ammonia TS; the solution responds to the Qualitative Analysis for calcium salt.

Purity (1) ***Ammonium***—Weigh about 1.0 g of Calcium Polystyrene Sulfonate in a flask, add 5 mL of sodium hydroxide TS, cover the bottom with a watch glass with a wet red litmus test paper attached, and heat for 15 minutes; the gas produced does not change the red litmus test paper to blue. (NMT 5 ppm).

(2) ***Heavy metals***—Proceed with 2.0 g of Calcium Polystyrene Sulfonate according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Calcium Polystyrene Sulfonate according to Method 3, and perform the test (NMT 2 ppm).

(4) ***Styrene***—Weigh 10.0 g of Calcium Polystyrene Sulfonate, add 10 mL of acetone, shake to mix for 30 minutes, and centrifuge. Use the clear supernatant as the test solution. Separately, weigh 10 mg of styrene and add acetone to make exactly 100 mL. Pipet 1 mL of this solution, add acetone to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of styrene of each solution; A_T and A_S; A_T is not greater than A_S.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of water and acetonitrile (1 : 1).

Flow rate: 2.0 mL/min

System performance: Dissolve 20 mg each of styrene and butyl p-hydroxybenzoate in 100 mL of acetone. To 5 mL of this solution, add acetone to make 100 mL. Proceed with 20 μL of this solution according to the above operating conditions; butyl p-hydroxybenzoate and styrene are eluted in this order with the resolution being NLT 5.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of styrene is NMT 2.0%.

(5) ***Sodium*—**Pipet 20 mL from the 50 mL of solution obtained from Assay (1), and add water to make exactly 500 mL, and use this solution as the test solution. Separately, weigh accurately 0.2542 g of sodium chloride, previously dried at 130 °C for 2 hours, and dissolve in 0.02 mol/L hydrochloric acid TS to make exactly 1000 mL. Take an appropriate amount of this solution, add 0.02 mol/L hydrochloric acid TS, dilute accurately to contain 1 to 3 μg of sodium (Na: 22.99) per mL, and use this solution as the standard solution. With the test and standard solutions, perform the test as directed under the Atomic Absorption Spectroscopy according to the following conditions, and determine the sodium content in the test solution using the calibration curve obtained from the standard solution (NMT 1%).

Gas: Air–acetylene
Lamp: Potassium hollow cathode lamp
Wavelength: 589.0 nm

Loss on drying NMT 10.0% (1 g, in vacuum, 80 °C, 5 hours).

Fine particles (1) ***Apparatus*—**Use the apparatus shown in the figure.

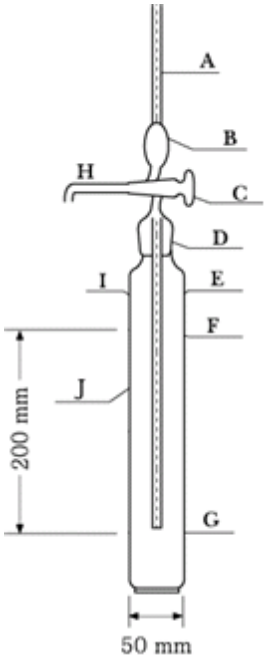
Volume up to the 20 cm mark when inserting the capillary pipet: 550 mL

Volume per inhalation: 10 mL

(2) ***Procedure*—**Weigh accurately about 5.5 g of Calcium Polystyrene Sulfonate, previously dried, add 300 mL of water at 25 °C, and stir to mix for 5 minutes. Transfer this to the sedimentation tube (J) stored at 25 °C, fill water at 25 °C to 2 mm to below the 20 cm mark F of the sedimentation tube (J), and then insert the pipet. Open the three-way cock (C) to release the air, add water from the vent hole (D) to the 20-cm mark (F) exactly, and close the three-way cock (C). Shake the apparatus sufficiently in both vertical and horizontal directions to disperse the content, then open the three-way stopper (C) and allow to stand at 25 ± 1°C for 5 hours and 15 minutes. Next, suck up the suspension in the sedimentation tube (J) exactly up to the pipet port scale (A), and open the three-way cock (C) in the direction of the pipet discharge tube (H) to take it. Repeat the same procedure to combine the result, and take exactly 20 mL of the suspension. Evaporate this solution to dryness on a steam bath, dry it at 105 °C to a constant mass, and then determine the mass W_S (g). Also, pipet 20 mL of the used water, and proceed in the same manner to obtain its mass W_B (g). Determine the amount of fine particles (S) according to the following formula; it is NMT 0.1%.

$$\text{S (\%)} = \frac{|W_S - W_B|(g) \times V(mL)}{20(mL) \times Amount\ of\ sample\ (g)} \times 100$$

V: Internal volume up to the 20 cm mark when inserting the capillary pipet (mL)



Andreasen pipet

A: Mark of pipet bulb	B: Pipet bulb for suction
C: Three-way stopcock	D: Vent-hole
E: Suction tube of pipet	F: Mark of 20 cm
G: Baseline of 0 cm	H: Outlet of pipet
I: Capillary tube of pipet	J: Sedimentation tube

Assay (1) ***Calcium*—**Weigh accurately about 1.0 g of Calcium Polystyrene Sulfonate, previously dried, and add 5 mL of 3 mol/L hydrochloric acid TS, disperse, and place the flask with volume of 50 mL as a receiver at the bottom of a chromatographic tube with an internal diameter of about 12 mm and a height of about 70 mm with glass wool at the bottom. Wash the tube thoroughly using a small amount of 3 mol/L hydrochloric acid TS, and combine the washings with the solution. Again, use 3 mol/L hydrochloric acid TS to elute until the volume reaches about 45 mL. Then, add water to make exactly 50 mL. Pipet 20 mL of this solution, add ammonia TS to exactly adjust the pH to 10, and immediately titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS. (indicator: 40 mg of eriochrome black T-sodium chloride indicator). The endpoint of titration is when the color of the solution changes from purple to blue. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.0039 mg of Ca

(2) ***Potassium exchange capacity*—**Weigh accu-

rately about 1.0 g of Calcium Polystyrene Sulfonate, previously dried, in a glass container with a stopper, add 50 mL of potassium standard stock solution, stir for 120 minutes, and then filter. Discard the first 20 mL of the filtrate, take accurately 5 mL of the subsequent filtrate, and add 0.02 mol/L hydrochloric acid TS to make exactly 100 mL. Pipet 10 mL of this solution, add 0.02 mol/L hydrochloric acid TS to make exactly 1000 mL, and use this solution as the test solution. Separately, pipet an appropriate amount of potassium standard stock solution, add 0.02 mol/L hydrochloric acid TS, dilute accurately to contain 0.5 to 2.5 μg of potassium (K: 39.10) per mL, and use this solution as the standard solution. With the test and standard solutions, perform the test as directed under the Atomic Absorption Spectroscopy according to the following conditions, and determine the potassium content *Y* (mg) in 1000 mL of the test solution using the calibration curve obtained from the standard solution. Determine the potassium exchange capacity per gram of Calcium Polystyrene Sulfonate, calculated on the dried basis, using the following formula.

Potassium exchange capacity (K) (mg) per gram of Calcium Polystyrene Sulfonate, calculated on the dried basis

$$= \frac{X - 100Y}{W}$$

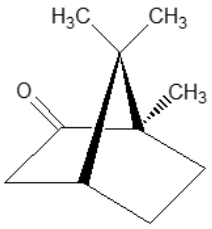
X: Amount (mg) of potassium in 50 mL of potassium standard stock solution before exchange

W: The amount (g) of Calcium Polystyrene Sulfonate taken, calculated on the dried basis

Gas: Air–acetylene
Lamp: Potassium hollow cathode lamp
Wavelength: 766.5 nm

Packaging and storage Preserve in tight containers.

d-Camphor
d-캄파



$C_{10}H_{16}O$: 152.23

(1*R*,4*R*)-4,7,7-Trimethylbicyclo[2.2.1]heptan-3-one [*464-49-3*]

d-Camphor contains NLT 96.0% and NMT 101.0% of *d*-camphor ($C_{10}H_{16}O$).

Description *d*-Camphor occurs as colorless or white translucent crystals or a crystalline powder or a mass, with a characteristic aroma, and a slightly bitter and refreshing taste.
It is freely soluble in ethanol(95), ether or carbon disulfide, and slightly soluble in water.
It slowly volatilizes at room temperature.

Identification Dissolve 0.1 g of *d*-Camphor in 2 mL of methanol, add 1 mL of 2,4-dinitrophenylhydrazine TS, then heat for 5 minutes on a steam bath; orange-red precipitates are formed.

Optical rotation $[\alpha]_D^{20}$: Between +41.0 and +43.0° (5 g, ethanol(95), 50 mL, 100 mm).

Melting point Between 177 and 182 ºC.

Purity (1) ***Water*—**Add 10 mL of carbon disulfide to 1.0 g of *d*-Camphor and shake to mix; the solution exhibits no turbidity.

(2) ***Chlorine compound*—**Weigh about 0.20 g of *d*-Camphor in powder form, transfer to a dried porcelain crucible, add 0.4 g of sodium peroxide and comply decompose by slowly heating over a burner. Dissolve the residue in 20 mL of hot water, acidify by adding 12 mL of dilute nitric acid, filter in a Nessler tube, wash 3 times with 5 mL of hot water each time, combine the filtrate and washings, cool and add water to make 50 mL, add 1 mL of nitric acid TS, shake well to mix, and allow to stand for 5 minutes; the turbidity of the solution is not more intense than that of the following control solution.

Control solution—Proceed in the same manner as for the test solution using 0.20 mL of 0.01 mol/L hydrochloric acid.

(3) ***Non-volatile residue*—**Sublimate 2.0 g of *d*-Camphor by heating on a steam bath, then dry for 3 hours at 105 ℃; the amount of residue is NMT 1.0 mg.

Assay Weigh accurately about 0.1 g each of *d*-Camphor and *d*-camphor RS, add exactly 5 mL of internal standard solution to each, and dissolve in ethanol(99.5) to make 100 mL. Use these solutions as the test solution and the standard solution, respectively. Perform the test with 2 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and determine the ratios of the peak area of *d*-camphor to that of the internal standard, Q_T and Q_S.

Amount (mg) of *d*-camphor ($C_{10}H_{16}O$)
$= \text{Amount (mg) of } d\text{-camphor RS} \times \frac{Q_T}{Q_S}$

Internal standard solution—A solution of methyl salicylate in ethanol(99.5) (1 in 25).

Operating conditions

Detector: A hydrogen flame ionization detector
Column: A column about 3 mm in internal diameter

and about 3 m in length, packed with diatomaceous earth for gas chromatography, 180 to 250 μm in particle diameter, coated with 20 M polyethylene glycol for gas chromatography at the ratio of 10%.

Column temperature: A constant temperature of about 160 °C.

Carrier gas: Nitrogen

Flow rate: Adjust the flow rate so that the retention time of *d*-camphor is about 6 minutes.

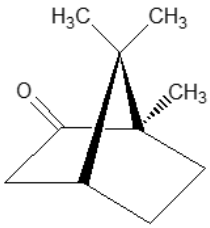
System suitability

System performance: Proceed with 2 μL of the standard solution under the above operating conditions; *d*-camphor and the internal standard are eluted in this order with the resolution being NLT 7.

System repeatability: Repeat the test 6 times with 2 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area of *d*-camphor to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

dl-Camphor
dl-캄파



and enantiomer

Synthetic Camphor $C_{10}H_{16}O_3$: 152.24

4,7,7-Trimethylbicyclo[2.2.1]heptan-3-one [*76-22-2*]

dl-Camphor contains NLT 96.0% and NMT 101.0% of *dl*-camphor ($C_{10}H_{16}O$).

Description *dl*-Camphor occurs as colorless or white translucent crystals or a crystalline powder or a mass, with a characteristic aroma, and a slightly bitter and refreshing taste.

It is freely soluble in ethanol(95), ether or carbon disulfide, and slightly soluble in water.

It slowly volatilizes at room temperature.

Identification (1) Dissolve 0.1 g of *dl*-Camphor in 2 mL of methanol, add 1 mL of 2,4-dinitrophenylhydrazine TS, and heat for 5 minutes on a steam bath; orange-red precipitates are formed.

Optical rotation $[\alpha]_D^{20}$: Between -1.5° and +1.5° (5 g, ethanol(95) 50 mL, 100 mm).

Melting point Between 175 and 180 °C.

Purity (1) ***Water***—Add 10 mL of carbon disulfide to 1.0 g of *dl*-Camphor and shake to mix; the solution exhibits no turbidity.

(2) ***Chlorine compound***—Weigh about 0.20 g of *dl*-camphor in powder form, transfer to a dried porcelain crucible, add 0.4 g of sodium peroxide and comply decompose by slowly heating over a burner. Dissolve the residue in 20 mL of hot water, acidify by adding 12 mL of dilute nitric acid, filter in a Nessler tube, wash 3 times with 5 mL of hot water each time, combine the filtrate and washings, cool and add water to make 50 mL, add 1 mL of nitric acid TS, shake well to mix, and allow to stand for 5 minutes; the turbidity of the solution is not more intense than that of the following control solution.

Control solution—Proceed in the same manner as for the test solution using 0.20 mL of 0.01 mol/L hydrochloric acid.

(3) ***Non-volatile residue***—Sublimate 2.0 g of *dl*-Camphor by heating on a steam bath, and dry for 3 hours at 105 °C; the amount of residue is NMT 1.0 mg.

Assay Weigh accurately 0.1 g each of *dl*-Camphor and *dl*-camphor RS, add exactly 5 mL of internal standard solution to each, and dissolve in ethanol(99.5) to make 100 mL. Use these solutions as the test solution and the standard solution, respectively. Proceed with 2 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak area of *dl*-camphor to that of the internal standard Q_T and Q_S.

$$\text{Amount (mg) of } dl\text{-camphor } (C_{10}H_{16}O) = \text{Amount (mg) of } dl\text{-camphor RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of methyl salicylate in ethanol(99.5) (1 in 25).

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A column about 3 mm in internal diameter and about 3 m in length, packed with diatomaceous earth for gas chromatography, 180 to 250 μm in particle diameter, coated with 20 M polyethylene glycol for gas chromatography at the ratio of 10%.

Column temperature: A constant temperature of about 160 °C.

Carrier gas: Nitrogen

Flow rate: Adjust the flow rate so that the retention time of *dl*-camphor is about 6 minutes.

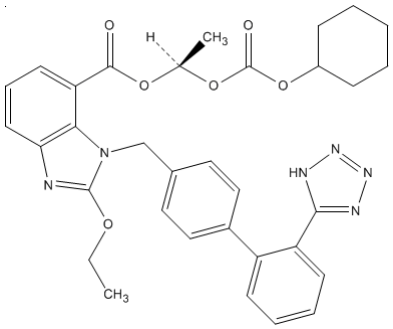
System suitability

System performance: Proceed with 2 μL of the standard solution under the above operating conditions; *dl*-camphor and the internal standard are eluted in this order with the resolution being NLT 7.

System repeatability: Repeat the test 6 times with 2 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area of *dl*-camphor to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Candesartan Cilexetil
칸데사르탄실렉세틸



and enantiomer

$C_{33}H_{34}N_6O_6$: 610.66

1-Cyclohexyloxycarbonyloxyethyl 2-ethoxy-3-[[4-[2-(2*H*-tetrazol-5-yl)phenyl]phenyl]methyl] enzimidazole-4-carboxylate [*145040-37-5*]

Candesartan Cilexetil contains NLT 99.0% and NMT 101.0% of candesartan cilexetil ($C_{33}H_{34}N_6O_6$), calculated on the anhydrous basis.

Description Candesartan Cilexetil occurs as white crystals or a crystalline powder.
It is soluble in acetic acid(100), sparingly soluble in methanol, slightly soluble in ethanol(99.5), and practically insoluble in water.
A solution of Candesartan Cilexetil in methanol (1 in 100) shows no optical rotation.
It shows polymorphism.

Identification (1) Determine the absorption spectra of solutions of Candesartan Cilexetil and Candesartan Cilexetil RS in methanol (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the absorption spectra of Candesartan Cilexetil and Candesartan Cilexetil RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Candesartan Cilexetil according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 20 mg of Candesartan Cilexetil in 50 mL of a mixture of acetonitrile and water (3 : 2), and use this solution as the test solution. Take exactly 1 mL of this solution, add a mixture of acetonitrile and water (3 : 2) to make 100 mL, and use this solution as the standard solution. Take exactly 10 μL each of the test solution and the standard solution, and perform the test as directed under the Liquid Chromatography according to the following conditions. Measure the peak area of each solution according to the automatic integration method, and calculate the amount of related substances; the peak area with the relative retention time of about 0.4 and about 2.0 to the candesartan cilexetil in the test solution is not greater than 1/5 times the peak area of candesartan cilexetil in the standard solution, the peak area with the relative retention time of about 0.5 to the candesartan cilexetil in the test solution is not greater than 3/10 times the peak area of candesartan cilexetil in the standard solution, and the peak areas other than the peak of candesartan cilexetil and the peak mentioned above in the test solution are less than 1/10 times the peak area of candesartan cilexetil in the standard solution. In addition, the sum of peak areas other than candesartan cilexetil in the test solution is not greater than 3/5 times the peak area of candesartan cilexetil in the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (4 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: A mixture of acetonitrile, water and acetic acid(100) (57 : 43 : 1).

Mobile phase B: A mixture of acetonitrile, water and acetic acid(100) (90 : 10 : 1).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 30	100 → 0	0 → 100

Flow rate: 0.8 mL/min

System suitability

Test for required detectability: Pipet 2 mL of the standard solution, and add a mixture of acetonitrile and water (3 : 2) to make exactly 20 mL. Confirm that the peak area of candesartan cilexetil obtained from 10 μL of this solution is equivalent to between 7% and 13% of the peak area of candesartan cilexetil obtained from the standard solution.

System performance: Proceed with 10 μL of the

standard solution under the above operating conditions; the number of theoretical plates and the symmetry factor of the peak of candesartan cilexetil are NLT 12000 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of candesartan cilexetil is NMT 2.0%.

Time span of measurement: During 30 minutes after injection, which is started after the solvent peak.

Water NMT 0.3% (0.5 g, coulometric titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Candesartan Cilexetil, dissolve in 60 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 61.07 mg of $C_{33}H_{34}N_6O_6$

Packaging and storage Preserve in well-closed containers.

Candesartan Cilexetil Tablets
칸데사르탄실렉세틸 정

Candesartan Cilexetil Tablets contain NMT 95.0% and NLT 105.0% of the labeled amount of candesartan cilexetil ($C_{33}H_{34}N_6O_6$: 610.66).

Method of preparation Prepare as directed under Tablets, with Candesartan Cilexetil.

Identification Weigh a portion of powdered Candesartan Cilexetil Tablets, equivalent to 1 mg of candesartan cilexetil according to the labeled amount, add 50 mL of methanol, shake vigorously to mix for 10 minutes, and then filter. Determine the absorption spectrum of this filtrate as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima at the wavelength of 252 nm to 256 nm and 302 nm to 307 nm.

Purity ***Related Substances***—Take NLT 10 tablets of Candesartan Cilexetil Tablets, grind them into powder, weigh accurately an amount of this powder, equivalent to 6 mg of candesartan cilexetil according to the labeled amount, add 15 mL of a mixture of acetonitrile and water (3 : 2), shake vigorously to mix for 10 minutes, and centrifuge. Filter the clear supernatant through a membrane filter with a pore diameter of NMT 0.45 μm. Discard the first 3 mL of the filtrate and use the subsequent filtrate as the test solution. Take 1 mL of this solution, add a mixture of acetonitrile and water (3 : 2) to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas of each solution according to the automatic integration method and calculate the amounts of related substances; the peak area having the relative retention time of about 0.5 to candesartan cilexetil from the test solution is not greater than 1.5 times the peak area of candesartan cilexetil from the standard solution, the peak areas having the relative retention times of about 0.8, about 1.1 and about 1.5 to candesartan cilexetil from the test solution are not greater than 1/2 of the peak area of candesartan cilexetil from the standard solution, respectively, the peak area having the relative retention time of about 2.0 to candesartan cilexetil from the test solution is not larger than the peak area of candesartan cilexetil from the standard solution, the peak areas other than candesartan cilexetil peak, the peak with a relative retention time of about 0.4 to candesartan cilexetil and the above peaks are smaller than 1/10 of the peak area of candesartan cilexetil from the standard solution. Also, the total area of the peaks other than the peak of candesartan cilexetil obtained from the test solution is not larger than 4 times the peak area of candesartan cilexetil obtained from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (4 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase: A mixture of acetonitrile, water and acetic acid(100) (57 : 43 : 1).

Mobile phase: A mixture of acetonitrile, water and acetic acid(100) (90 : 10 : 1).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 30	100 → 0	0 → 100

Flow rate: 0.8 mL/min

System suitability

Test for required detectability: Pipet 2 mL of the standard solution and add a mixture of acetonitrile and water (3 : 2) to make exactly 20 mL. Confirm that the peak area of candesartan cilexetil obtained from 10 μL of this solution is within the range between 7% and 13% of the peak area of candesartan cilexetil from the standard solution.

System performance: Proceed with 10 μL of the

standard solution under the above conditions; the number of theoretical plates and symmetry factor of the peak of candesartan cilexetil are NLT 12000 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of candesartan cilexetil is NMT 2.0%.

Time span of measurement: For 30 minutes after injection, beginning after the solvent peak.

Dissolution Perform the test with 1 tablet of Candesartan Cilexetil Tablets at 50 revolutions per minute according to the Method 2 under the Dissolution Test, using 900 mL of polysorbate 20 solution (1 in 100) as the dissolution medium. Take NLT 20 mL of the dissolved solution after 45 minutes from the start of the dissolution test, and filter through a membrane filter with a pore size of NMT 0.45 μm. Discard the first 5 mL of the filtrate, pipet *V mL* of the subsequent filtrate, add water to make *V'* mL so that each mL contains about 2.2 μg of candesartan cilexetil ($C_{33}H_{34}N_6O_6$) according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 50 mg of candesartan cilexetil RS (previously determined the water content in the same manner as for Candesartan Cilexetil Tablets), dissolve in acetonitrile to make exactly 50 mL. Take exactly 5 mL of this solution and add acetonitrile to make exactly 50 mL. Take exactly 1 mL of this solution, add the dissolution medium to make exactly 50 mL, and use this solution as the standard solution. Take exactly 50 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of candesartan cilexetil for each solution. Meets the requirements if the dissolution rate of Candesartan Cilexetil Tablets in 45 minutes is NLT 75%.

Dissolution rate (%) relative to the labeled amount of candesartan cilexetil ($C_{33}H_{34}N_6O_6$)
= Amount (mg) of candesartan cilexetil RS, calculated on the anhydrous basis

$$\times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times \frac{18}{5}$$

C: Labeled amount (mg) of candesartan cilexetil ($C_{33}H_{34}N_6O_6$) in 1 tablet

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

System performance: Proceed with 50 μL of the standard solution under the above operating conditions; the number of theoretical plates and symmetry factor of the peak of candesartan cilexetil are NLT 7000 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 50 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of candesartan cilexetil is NMT 2.0%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Candesartan Cilexetil Tablets, and powder. Weigh accurately an amount of this powder, equivalent to about 6 mg of candesartan cilexetil ($C_{33}H_{34}N_6O_6$), add exactly 15 mL of internal standard solution, add a mixture of acetonitrile and water (3 : 2) to make 150 mL, shake to mix for 10 minutes, and allow to stand. Filter the clear supernatant through a membrane filter with a pore diameter of not more that 0.45 μm. Discard the first 5 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 50 mg of candesartan cilexetil RS (previously determined the water content in the same manner as for candesartan cilexetil), dissolve in acetonitrile to make exactly 50 mL. Take exactly 4 mL of this solution, add exactly 10 mL of the internal standard solution, add a mixture of acetonitrile and water (3 : 2) to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and calculate the ratios, Q_T and Q_S, of the peak area of candesartan cilexetil to that of the internal standard from the test solution and the standard solution, respectively.

Amount (mg) candesartan cilexetil ($C_{33}H_{34}N_6O_6$)
= Amount (mg) of candesartan cilexetil RS, as calculated on the anhydrous basis

$$\times \frac{Q_T}{Q_S} \times \frac{3}{25}$$

Internal standard solution—A solution of acenaphthene in acetonitrile (1 in 800).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless-steel column about 3.9 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (4 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of acetonitrile, water and acetic acid(100) (57 : 43 : 1).

Flow rate: Adjust the flow rate so that the retention time of candesartan cilexetil is about 13 minutes.

System suitability

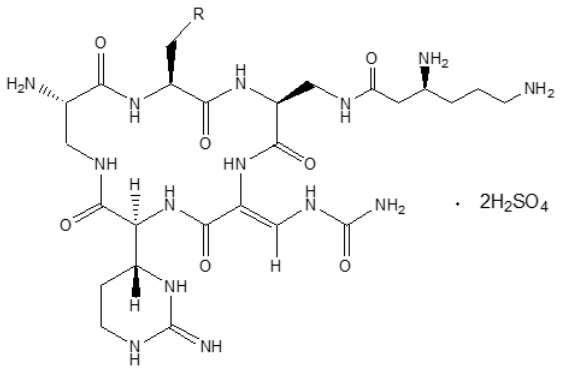
System performance: Proceed with 10 μL of the standard solution under the above conditions; the internal standard and candesartan cilexetil are eluted in this order with the resolution being NLT 5.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above oper-

ating conditions; the relative standard deviation of the peak area ratios of candesartan cilexetil to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Capreomycin Sulfate
카프레오마이신황산염



Capreomycin IA R = OH
Capreomycin IB R = H

Capreomycin IA $C_{25}H_{44}N_{44}O_8 \cdot 2H_2SO_4$: 492.87
Capreomycin IB $C_{25}H_{44}N_{44}O_7 \cdot 2H_2SO_4$: 484.87
3,6-Diamino-*N*-({(2*S*,5*S*,11*S*,15*S*,*Z*)-15-amino-2-(hydroxymethyl)-11-[(*R*)-iminohexahydropyrimidin-4-yl]-3,6,9,12,16-pentaoxo-8-(ureidomethylene)-1,4,7,10,13-pentaazacyclohexadecan-5-yl}methyl)hexanamide [*1405-37-4*]

Capreomycin Sulfate contains NLT 700 μg (potency) per mg of capreomycin, calculated on a dried basis.

Description Capreomycin Sulfate occurs as a white to pale yellowish white crystalline powder or a powder.
It is very soluble in water and practically insoluble in ethanol(95), chloroform, or ether.

Identification (1) Weigh an appropriate amount of Capreomycin Sulfate, dissolve in 0.1 mol/L hydrochloric acid TS to make 0.002% solution, and determine the absorption spectra as directed under the Ultraviolet-visible Spectroscopy in the wavelength range of 230 to 350 nm at the layer length of 200 mm; it exhibits a maximum at the wavelength of about 268 nm.

(2) Weigh an appropriate amount of Capreomycin Sulfate, dissolve in 0.1 mol/L sodium hydroxide TS to make 0.002% solution, and determine the absorption spectra as directed under the Ultraviolet-visible Spectroscopy in the wavelength range of 230 to 350 nm; it exhibits a maximum at the wavelength of about 287 nm.

(3) Weigh each of 5 mg (potency) of Capreomycin Sulfate and capreomycin sulfate RS, transfer into the test tube, dissolve in 0.5 mL of hydrochloric acid and 0.5 mL of water, and close the stopper tightly. Warm at 100 ℃ for 16 hours, and evaporate to dryness on a steam bath until there is no smell of hydrogen chloride gas. To each of the residues, dissolve in 1 mL of water, and use these solutions as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of cellulose for thin-layer chromatography, and develop the plate with a mixture of 2-propanol, methyl ethyl ketone, and 1 mol/L hydrochloric acid TS (60 : 15 : 25) as the developing solvent. Next, remove the plate, air-dry it in a cold airstream for 15 minutes, warm it at 100 °C for 15 minutes, and cool it. Spray evenly cadmium-ninhydrin TS, and warm at 100 °C for 30 minutes; the R_f values of the spots obtained from the test solution and the standard solution are the same.

(4) An aqueous solution of Capreomycin Sulfate responds to the Qualitative Analysis for sulfate.

Optical rotation $[\alpha]_D^{20}$: Between -26° and -36° (0.3 g, water, 30 mL, 200 mm).

pH Dissolve 3 g (potency) of Capreomycin Sulfate in 100 mL of water; the pH of this solution is between 4.5 and 7.5.

Purity ***Heavy metals***—Proceed with 1.0 g of Capreomycin Sulfate and perform the test according to Method 1. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

Loss on drying NMT 10.0% (0.1 g, 0.7 kPa, 100 ℃, 4 hours).

Residue on ignition NMT 3.0% (1 g, 700 ℃).

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins Less than 0.35 EU per mg (potency) of capreomycin when used in the manufacturing of sterile preparations.

Histamine It meets the requirements when used in the manufacturing of sterile preparations under the Histamine. However, weigh an appropriate amount of Capreomycin Sulfate, dissolve in isotonic sodium chloride injection to make a solution containing 3.0 mg (potency) per mL, and use this solution as the test solution.

Capreomycin I Weigh accurately about 0.2 g of Capreomycin Sulfate, transfer it into a 10-mL volumetric flask, and add water exactly to the gauge line. Store the test solution at below 5 °C. Perform the test with the solution as directed under the Paper Chromatography. Use a 300 ×

300 × 600 mm glass vessel for the descending method as the developing chamber. However, fill this glass vessel with a mixture of 1-propanol and water (7 : 3) up to a height of 40 mm from the bottom, and saturate for 2 days. Since the migration rates of capreomycin I and II are influenced by this saturation level, adjust the mixing ratio of the mixture so that the R_f value of capreomycin I is about 0.5, and the R_f value of capreomycin II is about 0.6 after development. Spot 100 μL of the test solution on the 200 × 500 mm or an equivalent Whatman No. 1 filter paper for chromatography, and air-dry with hot air. Separately, develop with the blank test paper using the descending method with a mixture of 1-propanol, water, triethylamine, and acetic acid(100) (75 : 33 : 8 : 8) for 16 hours in the developing chamber, and dry at room temperature for 1 hour. Apply ultraviolet light (wavelength 254 nm) to the dried filter paper; capreomycin I appears at an R_f value of about 0.5, and capreomycin II appears at an R_f value of about 0.6. Mark the region corresponding to the principal spot of the capreomycin, mark the same location in the blank test chromatogram, and then cut out this section. Next, cut each section to be about 1.5 cm^2 in size, transfer it into the 50-mL volumetric flask, and add 0.1 mol/L acetic acid buffer solution (pH 6.2) exactly to the gauge line. Pipet 3.0 mL of this solution, transfer it into the 50-mL volumetric flask, add water exactly to the gauge line, and use this solution as the sample measurement solution. Measure the absorbance of the sample extract and the sample measurement solution at a layer length of 10 mm and a wavelength of 268 nm, respectively, using water as the control solution, and calculate the content of capreomycin I as follows (NLT 90.0% for the total capreomycin). If the content of capreomycin I is NMT 90.0%, perform two more tests, perform the recovery rate test for total capreomycin as follows, and use the average of the results from the three tests as the final result.

$$\text{Content (\%) of capreomycin I} = \frac{A_I - A_b}{A_S} \times 100$$

A_I: Absorbance of the extract from the portion of capreomycin I on the filter paper applied with the sample

A_b: Absorbance of the extract from the portion of capreomycin I on the blank test filter paper applied with the sample

A_S: Absorbance of the sample measurement solution

Recovery rate test of the total capreomycin Spot 100 μL of the test solution on the starting line of the filter paper, dry the filter paper with warm air, cut the spotted area and the area without spotting, again cut each with an area of 1.5 cm^2, and transfer into two 50-mL Erlenmeyer flasks. Perform the test according to the procedure described above, and calculate the total capreomycin recovery rate using the following formula (recovery rate of the total capreomycin 100 ± 2%):

$$\text{Content (\%) of capreomycin I} = \frac{A_T - A_b}{A_S} \times 100$$

A_T: Absorbance of the sample extract solution

A_b: Absorbance of the blank test extract solution

A_S: Absorbance of the sample measurement solution

Assay ***Cylinder plate method*****—**(1) Medium (A) Agar medium for seed and base layer Use the medium in **(A)(2)**(a)②ⓑ under Microbial Assays for Antibiotics.

(2) *Test organism*—Use *Micrococcus luteus* ATCC 9341 as the test organism.

(3) Weigh accurately an appropriate amount of Capreomycin Sulfate, and dissolve in sterile purified water to make a solution containing 8 mg (potency) per mL. Pipet an appropriate amount of this solution, dilute with 0.1 mol/L phosphate buffer solution (pH 8.0) to make solutions containing 800.0 μg and 200.0 μg (potency) per mL, and use these solutions as the high concentration test solution and the low concentration test solution, respectively. Separately, weigh accurately about 80 mg (potency) of capreomycin sulfate RS, and dissolve in sterile purified water to prepare the standard stock solution containing 8 mg (potency) per mL. Store the standard solution at below 5 °C and use it within 7 days. Pipet an appropriate amount of this standard stock solution, dilute with 0.1 mol/L phosphate buffer solution (pH 8.0) to make solutions containing 800.0 μg and 200.0 μg (potency) in 1 mL, and use them as the high concentration standard solution and the low concentration standard solution, respectively. With these solutions, perform the test according to **(A)(8)** under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in tight containers.

Capreomycin Sulfate for Injection
주사용 카프레오마이신황산염

Capreomycin Sulfate for Injection is a preparation for injection, which is dissolved before use. It contains NLT 90.0% and NMT 120.0% of the labeled amount of capreomycin.

Method of preparation Prepare as directed under Injections, with Capreomycin Sulfate.

Description Capreomycin Sulfate for Injection occurs as a white to pale yellowish white powder.

Identification Perform the test according to the Identification (1), (2), and (3) under Capreomycin Sulfate.

pH Dissolve an amount of Capreomycin Sulfate for Injection equivalent to 0.3 mg (potency) of capreomycin in 10 mL of water; the pH of the solution is 4.5 to 7.5.

Purity ***Heavy metals***—Proceed with 1.0 g of Capreomycin Sulfate for Injection according to Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

Loss on drying NMT 10.0% (0.1 g, 0.7 kPa, 60 ℃, 3 hours).

Residue on ignition NMT 3.0% (1.0 g). Moisten the carbonized residue with 2 mL of nitric acid and 5 drops of sulfuric acid.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.35 EU per mg (potency) of capreomycin.

Histamine Meets the requirements of the Histamine under Capreomycin Sulfate.

Particulate contamination: Visible particles Meets the requirements.

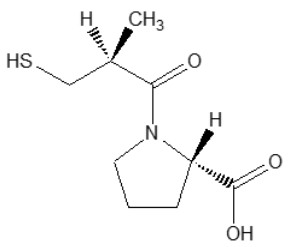
Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay ***Cylinder plate method***—Perform the test as directed under the Assay under Capreomycin Sulfate. Weigh accurately an appropriate amount of Capreomycin Sulfate for Injection, dissolve it in sterile purified water to prepare a solution containing 8 mg (potency) per mL, pipet an appropriate amount of this solution and add 0.1 mol/L phosphate buffer solution (pH 8.0) to make the concentration of (3). Use this solution as the test solution.

Packaging and storage Preserve in hermetic containers.

Captopril
캅토프릴



$C_9H_{15}NO_3S$: 217.29

(2*S*)-1-[(2*S*)-2-Methyl-3-sulfanylpropanoyl] pyrrolidine-2-carboxylic acid [*62571-86-2*]

Captopril, when dried, contains NLT 97.5% and NMT 102.0% of captopril ($C_9H_{15}NO_3S$).

Description Captopril occurs as white crystals or a crystalline powder.

It is very soluble in methanol, freely soluble in ethanol(99.5) and soluble in water.

Melting point—About 106 °C.

Identification Determine the infrared spectra of Captopril and captopril RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -125° and -134° (0.1 g, after drying, ethanol(99.5), 10 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of captopril according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Prepare the test solution with 1.0 g of Captopril and perform the test according to Method 1 (NMT 2 ppm).

(3) ***Related substances***—Weigh 50.0 mg of captopril, dissolve in methanol to make exactly 25 mL, and use this solution as the test solution (use immediately after preparation). Separately, weigh accurately a suitable amount of captopril disulfide RS, dissolve in methanol so that each mL contains 10 μg, and use this solution as the standard solution. Using 20 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions and determine the peak areas A_T and A_S of captopril disulfide for each solution; the amount of captopril disulfide is NMT 1.0%, and the individual peak areas over than those of the solvent, captopril and captopril disulfide are NMT 40% of the major peak area from the standard solution(0.2%), and their total area is not greater than the major peak area of the standard solution (0.5%).

$$\text{Content (\%) of captopril disulfide} = \frac{C_S}{C_U} \times \frac{A_T}{A_S} \times 100$$

C_S: Concentration (μg/mL) of captopril disulfide in the standard solution

C_U: Concentration (μg/mL) of captopril in the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of methanol solution of tetrahydrofuran (9 in 100) and phosphoric acid solution

(1 in 2000) (33 : 67).

Selection of column: Dissolve captopril RS, captopril disulfide RS and 3-acetylthio-2-methylpropanoic acid RS in methanol so that each solution contains 0.1 mg per mL. Pipet a certain amount of each solution and add methanol so that each solution contains 10 μg per mL. Perform the test using 20 μL of these solutions according to the above conditions; captopril, 3-acetylthio-2-methylpropanoic acid and captopril disulfide are eluted in this order, and the resolution between captopril and 3-acetylthio-2-methylpropanoic acid is NLT 3.0.

Loss on drying NMT 1.0% (1 g, in vacuum, 80 ℃, 3 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.3 g of Captopril, dissolve in 100 mL of water, add 20 mL of dilute sulfuric acid and 1 g of potassium iodide, shake well to mix, then titrate with 1/60 mol/L potassium iodide VS (indicator: 2 mL of starch TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1/60 mol/L potassium iodate VS
= 21.729 mg of $C_9H_{15}NO_3S$

Packaging and storage Preserve in tight containers.

Captopril Tablets
캅토프릴 정

Captopril Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of captopril ($C_9H_{15}NO_3S$: 217.29).

Method of preparation Prepare as directed under Tablets, with Captopril.

Identification Weigh an amount, equivalent to 0.1 g of captopril according to the labeled amount Captopril Tablets, previously powdered, put in an Erlenmeyer flask, add 25 mL of methanol, shake to mix well, and centrifuge. Use the clear supernatant as the test solution. Separately, weigh an appropriate amount of captopril RS, dissolve in methanol to obtain a solution containing 4 mg per mL. Use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 50 μL each of the test solution and the standard solution onto the plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of toluene, acetic acid(100) methanol (75 : 25 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray a newly prepared mixture of ammonia water(28) and 0.04% of 5,5'-dithio-bis(2-nitrobenzoic acid) methanol solution (1:6) evenly onto the plate; the R_f value of the principal spot obtained from the test solution is the same as that from the standard solution.

Purity ***Captopril Disulfide***—Use the test solution under the Assay. Separately, weigh accurately an appropriate amount of captopril disulfide RS and dissolve in the mobile phase to obtain a solution containing 50 μg per mL. Use this solution as the standard solution. However, Use the test solution and the standard solution within 8 hours of preparation, protected from air. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area, A_T and A_S, of captopril disulfide in each solution; the amount of captopril disulfide is NMT 3.0%.

$$\text{Content (\%) of captopril disulfide} = \frac{2500C}{W} \times \frac{A_T}{A_S}$$

C: Concentration (mg/mL) of the standard solution
W: Amount (mg) of sample taken

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel (containing 15% CH groups) for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of methanol, water and phosphoric acid (450 : 550 : 0.5).

Flow rate: 1.0 mL/min

System suitability

System performance: Weigh an appropriate amount of captopril RS and captopril disulfide RS and dissolve in the mobile phase to obtain a solution containing 50 μg each per mL. Proceed with 20 μL of this solution as directed under the above operating conditions; captopril and captopril disulfide are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times according to the above conditions with 20 μL each of the standard solution; the relative standard deviation of the peak area is NMT 2.0%

Dissolution Perform the test with 1 tablet of Captopril Tablets at 50 revolutions per minute according to Method 1 under the Dissolution, using 900 mL of 0.01 mol/L hydrochloric acid TS as the dissolution medium. Filter the dissolved solution 20 minutes after starting the test. Use the filtrate as the test solution. Separately, weigh accurately an appropriate amount of captopril RS, dissolve in the dissolution medium to make it the same concentration as the test solution. Use this solution as the standard solution. Determine the absorbances of the test solution and the standard solution, respectively, at wavelength of 212 nm as directed under the Ultraviolet-visible

Spectroscopy, using the dissolution medium as the control solution.
Meets the requirements if the dissolution rate of Glimepiride Tablets in 20 minutes is NLT 80%.

Uniformity of dosage units Meets the requirements.

Assay Take NLT 20 tablets of Captopril Tablets, put in an appropriate volumetric flask, add the mobile phase to fill the flask to about half its capacity, and sonicate for 15 minutes. Fill the mobile phase up to the gauge line, shake well with a shaker for 15 minutes, extract, and filter. Take an appropriate amount of the filtrate and add the mobile phase to obtain a solution containing about 1 mg of captopril per mL. Use this solution as the test solution. Separately, weigh an appropriate amount of captopril RS and captopril disulfide RS, dissolve in the mobile phase to obtain a solution containing 1 mg and 50 μ*g* per mL. Use this solution as the standard solution. However, use the test solution and the standard solution within 8 hours of preparation, protected from air. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of captopril in each solution.

$$\text{Content of captopril } (C_9H_{15}NO_3S) \text{ in 1 mL of test solution (\%)} = C \times \frac{A_T}{A_S}$$

C: Concentration (mg/mL) of the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel (containing 15% CH groups) for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of methanol, water and phosphoric acid (450 : 550 : 0.5).

Flow rate: 1.0 mL/min

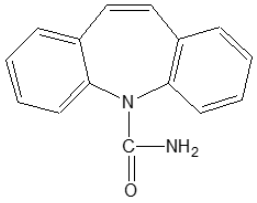
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above operating conditions; captopril and captopril disulfide are eluted in this order with resolution being NLT 2.0.

System repeatability: Repeat the test 6 times according to the above conditions with 20 μL each of the standard solution; the relative standard deviation of the peak area is NMT 2.0%

Packaging and storage Preserve in well-closed containers.

Carbamazepine
카르바마제핀



$C_{15}H_{12}N_2O$: 236.27

2-Azatricyclo[9.4.0.0^{3,8}]pentadeca-1(11),3(8),4,6,9,12,14-heptaene-2-carboxamide [*298-46-4*]

Carbamazepine, when dried, contains NLT 97.0% and NMT 103.0% of carbamazepine ($C_{15}H_{12}N_2O$).

Description Carbamazepine occurs as a white to pale yellow yellowish white powder. It is odorless, and at first, it is tasteless but becomes slightly bitter.
It is freely soluble in chloroform, sparingly soluble in ethanol(95) or acetone, and very slightly soluble in water or ether.

Identification (1) To 0.1 g of Carbamazepine, add 2 mL of nitric acid, and heat on a steam bath for 3 minutes; the resulting solution exhibits a reddish orange color.

(2) To 0.1 g of Carbamazepine, add 2 mL of sulfuric acid, and heat on a steam bath for 3 minutes; the resulting solution exhibits a yellow color and a green fluorescence.

(3) Examine Carbamazepine under ultraviolet light; it exhibits strong blue fluorescence.

(4) Determine the absorption spectra of the solutions of Carbamazepine and Carbamazepine RS in ethanol(95) (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Melting point Between 189 and 193 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Carbamazepine in 10 mL of chloroform; the solution is colorless to pale yellow and clear.

(2) ***Acid***—To 2.0 g of Carbamazepine, add exactly 40 mL of water, shake well for 15 minutes to mix, and filter with a glass filter. Pipet 10 mL of the filtrate, and add 1 drop of phenolphthalein TS and 0.50 mL of 0.01 mol/L sodium hydroxide TS; the resulting solution exhibits a red color.

(3) ***Alkali***—Take exactly 10 mL of the filtrate from (2), and add 1 drop of methyl red TS and 0.50 mL of 0.01 mol/L hydrochloric acid VS; the resulting solution exhibits a red color.

(4) ***Chloride***—Dissolve 0.25 g of Carbamazepine in 30 mL of acetone, add 6 mL of dilute nitric acid and water to make 50 mL, use this solution as the test solution,

and perform the test. Prepare the control solution by adding 30 mL of acetone, 6 mL of dilute nitric acid, and water to 0.20 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.028%).

(5) ***Heavy metals***—Proceed with 2.0 g of Carbamazepine according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(6) ***Related substances***—Dissolve 0.25 g of Carbamazepine in exactly 10 mL of chloroform and use this solution as the test solution. Separately, dissolve 5.0 mg of iminodibenzyl in chloroform to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin-layer chromatography. Spot 10 μL each of the test solution and the standard solution on the plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of toluene and methanol (19 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly potassium dichromate-sulfuric acid TS on the plate; spots other than the principal spot obtained from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

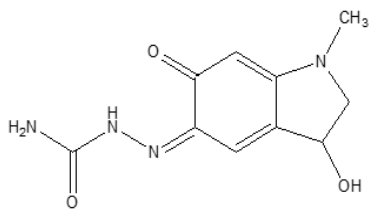
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg of Carbamazepine, previously dried, and dissolve in ethanol(95) to make exactly 250 mL. Pipet 5 mL of the test solution, and add ethanol(95) to make exactly 100 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance, *A* at the absorbance maximum wavelength of about 285 nm.

$$\text{Amount (g) of carbamazepine } (C_{15}H_{12}N_2O) = \frac{A}{490} \times 50000$$

Packaging and storage Preserve in tight containers.

Carbazochrome
카르바조크롬



$C_{10}H_{12}N_4O_3$: 236.23

2-(1,2,3,6-Tetrahydro-3-hydroxy-1-methyl-6-oxo-5*H*-indol-5-ylidene)-hydrazinecarboxamide, [*69-81-8*]

Carbazochrome, when dried, contains NLT 98.0% and NMT 101.0% of carbazochrome ($C_{10}H_{12}N_4O_3$).

Description Carbazochrome occurs as yellowish red to red crystals or a crystalline powder.
It is odorless and has a slightly bitter taste.
It is slightly soluble in acetic acid(100), very slightly soluble in water or ethanol, and practically insoluble in acetic anhydride or ether.

Melting point—About 222 °C (with decomposition).

Identification (1) Dissolve 5 mg of Carbazochrome in 2 mL of sulfuric acid; the resulting solution exhibits an intense green color.

(2) Dissolve 10 mg of Carbazochrome in 2 mL of dilute sulfuric acid (1 in 3); the resulting solution exhibits a yellow color. To this solution, add 0.5 mL of sodium nitrite TS, and shake to mix well; the resulting solution slowly exhibits a reddish brown color.

(3) To 10 mg of Carbazochrome, add 1 mL of aniline, and boil carefully by heating; the gas produced turns moistened red litmus paper blue.

(4) Weigh 2 mg of Carbazochrome, previously dried at 105 ℃ for 5 hours, and determine the infrared absorption spectrum as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; it exhibits absorption at the wavenumbers of about 3350, 1690, 1560, and 1050 cm^{-1}.

Absorbance $E_{1cm}^{1\%}$ (354 nm): Between 1054 and 1130 (after drying, 5 mg, water, 1000 mL).

Purity (1) ***Chloride***—To 1.2 g of Carbazochrome, add 80 mL of water, dissolve by shaking for 5 minutes, and filter. Take 20 mL of the filtrate, add 6 mL of dilute nitric acid, 1 mL of silver nitrate TS and water to make 50 mL, and use this solution as the test solution. Separately, to 20 mL of the filtrate, add 6 mL of dilute nitric acid and 1 mL of silver nitrate TS, allow to stand for 10 minutes, and repeat the filtration process until the solution becomes clear. Wash the residue with 5 mL of water 4 times, combine the filtrate and the washings, add 0.35 mL of 0.01 mol/L hydrochloric acid and water to make 50 mL, and use this solution as the control solution. With the test solution and the control solution, allow to stand for 5 minutes, avoiding direct sunlight, and compare the colors against a black background; the turbidity of the test solution is not more intense than that of the control solution (NMT 0.041%).

(2) ***Heavy metals***—Proceed with 1.0 g of Carbazochrome according to Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(3) ***Iron***—Weigh 0.5 g of Carbazochrome, ignite, and prepare the test solution with this residue according to Method 1 under the Iron. Separately, take 3.0 mL of iron standard solution, proceed in the same manner to prepare the control solution, and perform the test according to Method A under the Iron.

(4) ***Arsenic***—Prepare the test solution with 1.0 g of

Carbazochrome according to Method 3 and perform the test (NMT 2 ppm).

Loss on drying NMT 1.0% (1 g, 105 ℃, 5 hours).

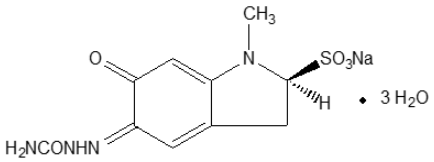
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Carbazochrome, previously dried, dissolve in 30 mL of acetic acid(100) for non-aqueous titration by warming, and add 120 mL of acetic anhydride. After cooling, titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 23.623 mg of $C_{10}H_{12}N_4O_3$

Packaging and storage Preserve in tight containers.

Carbazochrome Sodium Sulfonate Hydrate
카르바조크롬설폰산나트륨수화물



and enantiomer

Carbazochrome Sodium Sulfonate
$C_{10}H_{11}N_4NaO_5S \cdot 3H_2O$: 376.32
Sodium (5*Z*)-5-(carbamoylhydrazono)-1-methyl-6-oxo-2,3,5,6-tetrahydro-1H-indole-2-sulfonate hydrate

Carbazochrome Sodium Sulfonate Hydrate contains NLT 98.0% and NMT 102.0% of carbazochrome sodium sulfonate ($C_{10}H_{11}N_4NaO_5S$: 322.27), calculated on the anhydrous basis.

Description Carbazochrome Sodium Sulfonate Hydrate occurs as orange yellow crystals or a crystalline powder.
It is sparingly soluble in water, very slightly soluble in ethanol(95), and practically insoluble in ether.
An aqueous solution of Carbazochrome Sodium Sulfonate Hydrate (1 in 100) shows no optical rotation.

Melting point—About 210 °C (with decomposition).

Identification (1) Determine the absorption spectra of aqueous solutions of Carbazochrome Sodium Sulfonate Hydrate and carbazochrome sodium sulfonate hydrate RS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelength.

(2) Determine the infrared spectra of Carbazochrome Sodium Sulfonate Hydrate and carbazochrome sodium sulfonate hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Carbazochrome Sodium Sulfonate Hydrate (1 in 100) responds to the Qualitative Analysis (1) for sodium salt.

pH Dissolve 0.8 g of Carbazochrome Sodium Sulfonate Hydrate in 50 mL of water by warming, and cool; the pH of the solution is between 5.0 and 6.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Carbazochrome Sodium Sulfonate Hydrate in 50 mL of water by warming, and allow to stand for cooling; the solution is clear. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at 590 nm is NMT 0.070.

(2) ***Heavy metals***—Proceed with 1.0 g of Carbazochrome Sodium Sulfonate Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve 50 mg of Carbazochrome Sodium Sulfonate Hydrate in 100 mL of water, and use this solution as the test solution. Pipet 2 mL of this solution, add water to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area obtained from each solution according to the automatic integration method; the sum of peak areas other than the major peak for the test solution is not larger than the peak area of the major peak for the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 360 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 1.2 g of ammonium dihydrogen phosphate in 1000 mL of water, take 925 mL of this solution, add 75 mL of ethanol(95), and shake to mix. Add phosphoric acid to adjust the pH to 3.

Flow rate: Adjust the flow rate so that the retention time of carbazochrome sulfonate is 6 to 8 minutes.

System suitability

Detection sensitivity: Adjust the sensitivity so that the peak height of carbazochrome sulfonate from 10 μL of the standard solution is about 5% of the full scale.

Test for required detectability: Pipet 2 mL of the standard solution and add the mobile phase to make exactly 20 mL. Confirm that the peak area of carbazochrome sulfonate obtained from 10 μL of this solution is equivalent to NLT 7% and NMT 13% of the peak area of carbazochrome sulfonate obtained from the standard solution.

System performance: Dissolve 10 mg each of Carbazochrome Sodium Sulfonate Hydrate and carbazochrome in 100 mL of water. Proceed with 10 μL of this solution according to the above conditions; carbazochrome sulfonate and carbazochrome are eluted in this order with the resolution being NLT 3.

Time span of measurement: About 3 times the retention time of carbazochrome sulfonate after the solvent peak.

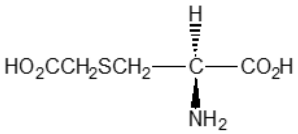
Water Between 13.0% and 16.0% (0.3 g, volumetric titration, direct titration).

Assay Weigh accurately about 0.25 g of Carbazochrome Sodium Sulfonate Hydrate, dissolve in 50 mL of water, transfer into a chromatography column 10 mm in diameter, previously made with 20 mL of strongly acidic ion exchange resin for column chromatography (H type), and elute at the flow rate of about 4 mL per minute. Next, wash the chromatography column with 150 mL of water, combine with the previous eluate, and titrate it with 0.05 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L sodium hydroxide VS
= 16.114 mg of $C_{10}H_{11}N_4NaO_5S \cdot 3H_2O$

Packaging and storage Preserve in well-closed containers.

Carbocisteine
카르보시스테인



S-Carboxymethyl-L-cysteine

$C_5H_9NO_4S$: 179.19

(2*R*)-2-Amino-3-carboxymethyl sulfanylpropanoic acid *[638-23-3]*

Carbocisteine, when dried, contains NLT 98.5% and NMT 101.0% of carbocisteine ($C_5H_9NO_4S$).

Description Carbocisteine occurs as a white crystalline powder.
It is odorless and has a slightly sour taste.
It is very slightly soluble in water and practically insoluble in ethanol(95).
It dissolves in dilute hydrochloric acid or sodium hydroxide TS.

Melting point—About 186 °C (with decomposition).

Identification (1) To 0.2 g of Carbocisteine, add 1 mL of lead acetate TS and 3 mL of water, shake to mix, add 0.2 g of sodium hydroxide, and heat in direct fire for 1 minute; a dark brown to black precipitate forms.

(2) Determine the infrared spectra of Carbocisteine and carbocisteine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -33.5° and -36.5°. Weigh accurately 5 g of Carbocisteine, previously dried, dissolve in 20 mL of water and sodium hydroxide solution (13 in 100), add 1 mol/L hydrochloric acid TS and 0.1 mol/L hydrochloric acid TS to adjust pH to 6.0, and add water to make exactly 50 mL. Use this solution for measurement at the layer length of 100 mm.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Carbocisteine in 10 mL of sodium hydroxide TS; the resulting solution is colorless and clear.

(2) ***Chloride***—Dissolve 0.20 g of Carbocisteine in 10 mL of water and 20 mL of nitric acid, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 0.40 mL of 0.01 mol/L hydrochloric acid VS, 20 mL of nitric acid, and water to make 50 mL (NMT 0.071%).

(3) ***Ammonium***—Perform the test with 0.25 g of Carbocisteine. Prepare the control solution with 5.0 mL of ammonium standard solution (NMT 0.02%). However, perform the test as directed under the vacuum distillation.

(4) ***Heavy metals***—Mix 2.0 g of Carbocisteine and 0.5 g of magnesium oxide, and carbonize. After cooling, ignite at NMT 800 °C for 1 hour to incinerate. After cooling, dissolve the residue in 5 mL of a mixture of hydrochloric acid and water (1 : 1). Add 0.1 mL of phenolphthalein TS, and add an ammonia water(28) dropwise until the color of the solution turns pale red. After cooling, add acetic acid(100) until the color disappears, and add another 0.5 mL. Filter and wash, if necessary. Add water to make 20 mL, and use this solution as the test solution. Separately, proceed in the same manner as the preparation of the test solution using 2.0 mL of lead standard solution instead of Carbocisteine. To 10 mL of this solution, add 2 mL of the test solution, and use this solution as the control solution. Separately, add 2 mL of the test solution to 10 mL of water, and use this solution as the blank test solution. To 12 mL each of the test solution, the control solution, and the blank test solution, add 2 mL of pH 3.5 acetate buffer solution, mix, add 1.2 mL of thioacetamide TS, and mix immediately. Allow to stand for 2 minutes; the color of the test solution is not more intense than that of the control solution (NMT 10 ppm).

System suitability—The control solution shows a faint brown color compared to the blank test solution. Also, to the test solution, add 2.0 mL of lead standard solution. To 10 mL of this solution, add 2 mL of the test solution, and use this solution as the system suitability

solution. The system suitability solution is more intense than or has the same intensity as the control solution.

(5) ***Arsenic***—Prepare the test solution with 1.0 g of Carbocisteine, according to Method 3, and perform the test (NMT 2 ppm).

(6) ***Related substances***—Dissolve 0.30 g of Carbocisteine in 10 mL of 0.2 mol/L sodium hydroxide TS, and use this solution as the test solution. Pipet 2 mL of this solution, and add 0.2 mol/L sodium hydroxide TS to make exactly 100 mL. Pipet 1 mL of this solution, add 0.2 mol/L sodium hydroxide TS to make exactly 10 mL, and use it as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography in the starting line with a length of 15 mm. Next, develop the plate with a mixture of 1-butanol, water, and acetic acid(100) (3 : 1 : 1) as the developing solvent to a distance of about 10 cm, and dry the plate at 80 °C for 30 minutes. Spray evenly a solution of ninhydrin in acetone (1 in 50) on the plate and heat at 80 °C for 5 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.3% (1 g, 105 °C, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.25 g of Carbocisteine, previously dried, dissolve in exactly 20 mL of 0.1 mol/L perchloric acid, and add 50 mL of acetic acid(100), and titrate the excess perchloric acid with 0.1 mol/L sodium acetate VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 17.919 mg of $C_5H_9NO_4S$

Packaging and storage Preserve in tight containers.

Carbocisteine Capsules
카르보시스테인 캡슐

Carbocisteine Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of carbocisteine ($C_5H_9NO_4S$: 179.20).

Method of preparation Prepared as directed under Capsules, with Carbocisteine.

Identification (1) Suspend an amount of Carbocisteine Capsules equivalent to 0.1 g of carbocisteine according to the labeled amount in 2 mL of water, add 1% ninhydrin solution, and heat; it exhibits a purple color.

(2) Dissolve 30 mg of carbocisteine in Carbocisteine Capsules in 10 mL of water while shaking, filter this solution, and use the filtrate as the test solution. Weigh 30 mg of carbocisteine RS, dissolve in water, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on a thin-layer chromatographic plate made using silica gel for thin-layer chromatography. Develop the plate with a mixture of n-butanol, water and acetic acid(100) (3 : 1 : 1) as the developing solvent, and air-dry the plate. Spray Ninhydrin TS on the plate; the colors and the Rf values obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 capsule of Carbocisteine Capsules at 100 revolutions per minutes using a sinker according to Method 2 under the Dissolution, using 900 mL of water containing 0.5% sodium lauryl sulfate as the dissolution medium. Take the dissolved solution 60 minutes after starting the test, and filter. Use this solution as the test solution. Separately, weigh accurately about 20 mg of carbocisteine RS, dissolve in the dissolution solution to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of carbocisteine ($C_5H_9NO_4S$) in each solution. Meets the requirements if the amount dissolved of Carbocisteine Capsules in 60 minutes is NLT 80%.

Dissolution rate (%) of the labeled amount of Carbocisteine Capsules ($C_5H_9NO_4S$)
$$= \text{Amount (mg) of carbocisteine RS} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 900$$

C: Labeled amount (mg) of carbocisteine ($C_{15}H_{15}NO_4$) in 1 tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with 5 μm octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: phosphate buffer solution: acetonitrile (9 : 1).

Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area for carbocisteine is NMT 2.0%.

Phosphate buffer solution—Dissolve 23 g of phosphoric acid and 1.5 g of heptanesulfonate in water to make 1000 mL.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the contents of NLT 20 capsules of Carbocisteine Capsules, and weigh accurately an amount equivalent to about 0.4 g of carbocisteine ($C_5H_9NO_4S$). Add a small amount of ammonia water to make it alkaline, dissolve it with the mobile phase to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 200 mg of carbocisteine RS, dissolve it with the mobile phase to make exactly 50.0 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of carbocisteine in each solution.

Amount (mg) of carbocisteine ($C_5H_9NO_4S$)
= Amount (mg) of carbocisteine RS × (A_T /A_S) × 2

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with aminosilyl silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of acetonitrile and 0.05 mol/L potassium phosphate buffer solution (pH 4.5) (65 : 35).

Flow rate: 2 mL/min

Packaging and storage Preserve in tight containers.

Carbocisteine Syrup
카르보시스테인 시럽

Carbocisteine Syrup contains NLT 95.0% and NMT 105.0% of the labeled amount of carbocisteine ($C_5H_9NO_4S$: 179.20).

Method of preparation Prepare as directed under Syrups, with Carbocisteine.

Identification Take 5 mL of Carbocisteine Syrup, place in a test tube, and add 1% ninhydrin solution; the solution exhibits a violet color.

pH Between 5.0 and 7.0.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Pipet an amount of Carbocisteine Syrup equivalent to 0.4 g of carbocisteine ($C_5H_9NO_4S$: 179.20) according to the labeled amount, alkalify by adding a small amount of ammonia water, and dissolve in the mobile phase to make exactly 100.0 mL. Use this solution as the test solution. Separately, weigh accurately about 200 mg of carbocisteine RS, dissolve in the mobile phase to make exactly 50.0 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of carbocisteine from each solution.

Amount (mg) of carbocisteine ($C_5H_9NO_4S$)
= Amount (mg) of carbocisteine RS × A_T /A_S × 2

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with aminosilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of acetonitrile and 0.05 mol/L phosphate buffer solution (pH 4.5) (65 : 35).

Flow rate: 2 mL/min

Packaging and storage Preserve in tight containers.

Carbon Dioxide
이산화탄소

Carbonic Acid Gas CO_2 : 44.01
Carbon dioxide [*124-38-9*]

Carbon Dioxide contains NLT 99.5 vol% and NMT 101.0 vol% carbon dioxide (CO_2).

Description Carbon Dioxide occurs as a colorless and odorless gas at room temperature and under atmospheric pressure.
1 mL of Carbon Dioxide is soluble in 1 mL of water and is weakly acidic.
1000 mL of Carbon Dioxide is about 1.978 g at 0 °C and 101.3 kPa.

Identification (1) Put a flaming wood splinter into Carbon Dioxide; the flame is extinguished immediately.

(2) Pass Carbon Dioxide through potassium hydroxide TS; white precipitates are formed. Separately take the precipitates and add acetic acid to the precipitates; the precipitates are dissolved as bubbles are formed.

Purity The amount of Carbon Dioxide is taken after maintaining the container at between 18 and 22 ℃ 6 hours before performing the test, and converted to the volume at the pressure of 101.3 kPa at 20 ℃.

(1) ***Acid*—**Transfer 50 mL of freshly boiled and cooled water to a Nessler tube, position the top end of the gas injection tube with a diameter of about 1 mm at 2 mm from the bottom of the tube, pass 1000 mL of Carbon Dioxide over 15 minutes, and add 0.10 mL methyl orange TS; the red color of the resulting solution is not more intense than that of the following control solution.

Control solution—Transfer 50 mL of freshly boiled and cooled water to a Nessler tube and add 0.10 mL of methyl orange TS and 1.0 mL of 0.01 mol/L hydrochloric acid.

(2) ***Hydrogen phosphide, hydrogen sulfide and organic reducing substances*—**To 2 Nessler tubes A and B, add 25 mL of silver nitrate and ammonia TS and 3 mL of ammonia TS, respectively, and use these solutions as solution A and solution B. Pass 1000 mL of Carbon Dioxide through the solution A using the method of (1); the turbidity or staining of the solution A is the same as that of the solution B.

(3) ***Carbon monoxide*—**Take 5.0 mL of Carbon Dioxide directly from a pressure-resistant metal hermetic container with a pressure-reducing plug using a polyvinyl chloride injection tube in a gas measuring tube for gas chromatography or syringe, and perform the test with this solution as directed under the Gas Chromatography according to the following conditions; no peaks appear at the elution position of carbon monoxide.

Operating conditions

Detector: Thermal conductivity detector

Column: A column about 3 mm in internal diameter and about 3 m in length, packed with zeolite for gas chromatography (300 μm to 500 μm in particle diameter, pore diameter 0.5 nm).

Column temperature: A constant temperature of about 50 °C.

Carrier gas: Hydrogen or helium

Flow rate: Adjust the flow rate so that the retention time of carbon monoxide is about 20 minutes.

System suitability

Detection sensitivity: Adjust the sensitivity so that the peak height of carbon monoxide obtained from 5.0 mL of the mixed gas used in system performance is about 10 cm.

System performance: To a gas mixer, add 0.1 mL of carbon monoxide and 0.1 mL of air, add the carrier gas to make 100 mL, and shake to mix well. Proceed with 5.0 mL of the mixed gas according to the above conditions; oxygen, nitrogen and carbon monoxide are eluted in this order, and the individual peaks are completely separated.

(4) ***Oxygen and nitrogen*—**Take 1.0 mL of Carbon Dioxide directly from a pressure-resistant metal hermetic container with a pressure-reducing plug using a polyvinyl chloride collection tube into a gas measuring tube for gas chromatography or syringe and perform the test with this solution as directed under the Gas Chromatography according to the following conditions to determine the peak area A_T of air. Separately, take 0.50 mL of nitrogen in a gas mixer, add the carrier gas to make the total volume to exactly 100 mL, mix well, and use the mixed gas as the standard gas mixture. Proceed with 1.0 mL of the gas in the same manner as for Carbon Dioxide and determine the peak area A_S of nitrogen; A_T is not larger than A_S. Also, additional peaks do not appear.

Operating conditions

Detector: Thermal conductivity detector

Column: A column about 3 mm in internal diameter and about 3 m in length, packed with silica gel for gas chromatography (300 μm to 500 μm in particle diameter).

Column temperature: A constant temperature of about 50 °C.

Carrier gas: Hydrogen or helium

Flow rate: Adjust the flow rate so that the retention time of nitrogen is about 2 minutes.

System suitability

Detection sensitivity: Adjust the sensitivity so that the peak height of nitrogen obtained from 1.0 mL of the standard gas mixture is about 50% of full scale.

System performance: Take 0.5 mL of nitrogen in a gas mixer, add Carbon Dioxide to make 100 mL, and mix well. Proceed with 1.0 mL of the mixed gas according to the above conditions; nitrogen and carbon dioxide are eluted in this order, and the individual peaks are completely separated.

(5) ***Nitrogen monoxide*—**Proceed in the same manner as for (6) Nitrogen dioxide, passing 550 ± 50 mL of Carbon Dioxide in the form of vapor through a nitrogen monoxide-nitrogen dioxide detector tube at a constant rate, and determine the amount of nitrogen monoxide; it is NMT 2.5 ppm.

(6) ***Nitrogen dioxide*—**Connect a tube with a sufficient length to a container so that all liquid-phase contents are vaporized passing through the tube when opening the valve of the container, and prevent the inlet tube connected to the detector tube from frosting. Through the tube (previously replace the air in the apparatus with Carbon Dioxide) pass 550 ± 50 mL of Carbon Dioxide in the form of vapor through a nitrogen monoxide-nitrogen dioxide detector tube at an appropriate constant rate, and determine the amount of nitrogen dioxide; it is NMT 2.5 ppm. However, to prevent contamination, connect the gas volumetric apparatus to the bottom end of the detector tube for measurement.

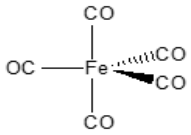
(7) ***Sulfur dioxide*—**Proceed in the same manner as for (6) Nitrogen dioxide, pass 1050 ± 50 mL of Carbon Dioxide in the form of vapor through a sulfur dioxide detector tube at an constant rate, and determine the amount of sulfur dioxide; it is NMT 5 ppm.

Assay Take a sample of Carbon Dioxide as directed under the Purity. Add 125 mL of potassium hydroxide solution (1 in 2) to a gas pipet of appropriate capacity. Next, take accurately about 100 mL of Carbon Dioxide in an about 100 mL of gas buret filled with water, transfer to a gas pipet, and mix by shaking for 5 minutes. Repeat this procedure, occasionally transferring the unabsorbed remaining gas to the gas buret and measuring the volume. When the volume of unabsorbed remaining gas becomes a constant mass, measure the volume, and use this volume as *V* (mL). Convert the amount collected of *V* to the volume at the pressure of 101.3 kPa at 20 ℃.

Amount (mL) of carbon dioxide (CO_2)
= Converted amount (mL) of amount of sample taken
− converted value (mL) of *V*

Packaging and storage Preserve in pressure-resistant metal hermetic containers at NMT 40 ℃.

Carbonyliron
카르보닐철



C_5FeO_5: 195.90

Pentacarbonyliron, [*73479-38-6*]

Carbonyliron is produced by thermally decomposing pentacarbonyliron, which is manufactured by carbonylating iron, to make fine iron.

Carbonyliron contains NLT 98.0% and NMT 101.0% of iron (Fe: 55.85).

Description Carbonyliron occurs as a light gray powder with micro-particles.
It is odorless and tasteless.
It is insoluble in water, acetone, chloroform and ether.
It is soluble in hot dilute hydrochloric acid or dilute nitric acid.
Average particle diameter: NMT 7 μm.

Identification (1) Transfer 0.5 g of Carbonyliron into a beaker, add 20 mL of dilute hydrochloric acid, dissolve on a steam bath until the solution becomes clear, and mix 50 mL of water. To this solution, add 1 mol/L sodium hydroxide TS; a grayish green gel-like precipitate forms, and when sodium sulfide solution is added, the color of the precipitate turns black.

(2) Transfer 0.5 g of Carbonyliron into a beaker, add 20 mL of dilute hydrochloric acid, dissolve on a steam bath until the solution becomes clear, and mix 50 mL of water. To this solution, add dropwise a solution of 1,10-phenanthroline in ethanol (1 in 50); the resulting solution exhibits an intense red color.

(3) To 50 mg of Carbonyliron, add 25 mL of 6 mol/L hydrochloric acid, warm on a steam bath to dissolve, and add water to make 100 mL. Take 5 mL of this solution, add water to make 100 mL, take 10 mL of this solution, and add 3 mL of 1,10-phenanthroline solution. Add 100 mL of water to make 100 mL. After allowing this solution to stand for 10 minutes, determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 507 nm and 511 nm.

Density Between 2 g/cm^3 and 3 g/cm^3.

Particle size distribution Pass 10 g of Carbonyliron through a sieve; it passes entirely through a No. 200 sieve and remains on a No. 330 sieve in an amount of NMT 5% of the total quantity.

Acid insolubles To 1 g of Carbonyliron, add 25 mL of dilute sulfuric acid, and dissolve by boiling for 5 minutes while shaking. Filter the insolubles using filter paper for quantitative analysis, wash the residue with water until it is not turbid when nitric acid solution is added, and dry the residue with the filter paper at 105 ℃ for 1 hour; the amount of residue is NMT 12.5 mg (NMT 1.25%).

Purity (1) ***Lead***—Proceed with 1.0 g of Carbonyliron and perform the test according to the Lead under the General tests of the United States Pharmacopeia (USP) (NMT 5 ppm).

(2) ***Mercury***—Proceed with 1.0 g of Carbonyliron and perform the test according to Method 2 under the Mercury of General tests of the United States Pharmacopeia (USP) (NMT 2 ppm).

(3) ***Arsenic***—Proceed with 0.75 g of Carbonyliron and perform the test according to Method 2 under the Arsenic of General tests of the United States Pharmacopeia (USP). (NMT 4 ppm).

Assay Weigh accurately about 0.5 g of Carbonyliron, add 50 mL of dilute sulfuric acid, heat on a steam bath to make a clear solution, and cool. Take 10.0 mL of this solution, add 20 mL of water, and titrate with 0.1 mol/L cerium(IV) tetraammonium sulfate VS (indicator: 2 drops of 1,10-phenanthroline TS). The endpoint of the titration is when the reddish orange color of the solution turns to yellowish green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L cerium (IV) tetraammonium sulfate VS
= 5.585 mg of Fe

Packaging and storage Preserve in tight containers.

Carbonyliron Tablets
카르보닐철 정

Carbonyliron Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of iron (Fe: 55.85)

Method of preparation Prepare as directed under Tablets, with Carbonyliron.

Identification (1) Weigh an amount of Carbonyliron Tablets, equivalent to 0.1 g of iron (Fe), add 20 mL of dilute hydrochloric acid, mix, boil for several minutes, cool and filter. With the filtrate, perform the test according to the Identification (1) for Carbonyliron (in the case of coated preparations, remove the coating and perform the test).

(2) Weigh an amount of Carbonyliron Tablets, equivalent to 0.1 g of iron (Fe), add 20 mL of dilute hydrochloric acid, mix, boil for several minutes, cool and filter. With the filtrate, perform the test according to the Identification (2) for Carbonyliron (in the case of coated preparations, remove the coating and perform the test).

(3) Weigh an amount of Carbonyliron Tablets, equivalent to 50 mg of carbonyliron, and perform the test according to the Identification (3) for Carbonyliron (in the case of coated preparations, remove the coating and then perform the test).

Disintegration Meets the requirements.

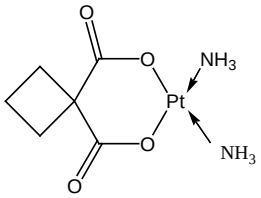
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Carbonyliron Tablets, and powder. Weigh accurately an amount of this powder, equivalent to about 0.1 g of iron (Fe), put it in a 200-mL beaker, add 50 mL of dilute sulfuric acid, heat on a steam bath to make a clear solution, add 20 mL of water, and titrate 0.1 mol/L cerium(IV) tetraammonium sulfate VS (indicator: 3 drops of 1,10-phenanthroline TS). The endpoint of the titration is when the color of the solution changes from reddish orange color to yellowish green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L cerium(IV) tetraammonium sulfate VS
= 5.585 mg of Fe

Packaging and storage Preserve in tight containers.

Carboplatin
카르보플라틴



$C_6H_{12}N_2O_4Pt$: 371.25

cis-Diammine(cyclobutane-1,1-dicarboxylate-*O*,*O*')platinum(II) [*41575-94-4*]

Carboplatin contains NLT 98.0% and NMT 102.0% of carboplatin ($C_6H_{12}N_2O_4Pt$), calculated on the anhydrous basis.

Description Carboplatin occurs as a white crystalline powder.
It is sparingly soluble in water and very slightly soluble in acetone or ethanol(95).

Melting point—About 200 °C (with decomposition).

Identification Determine the absorption spectra of Carboplatin and carboplatin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Crystallinity Meets the requirements.

pH Dissolve 0.25 g of Carboplatin in 25 mL of water; the pH of this solution is between 5.0 and 7.0.

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g of Carboplatin in water to make exactly 10 mL, perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance of the solution at the wavelength of 440 nm, using water as a control solution; it is NLT 97%.

(2) ***Platinum***—Weigh accurately about 0.25 g of Carboplatin, add 400 mL of water, shake occasionally, and dissolve by heating until boiling. After completely dissolving, boil for about 10 minutes, cool as it is for 1 minute, and filter with filter paper. Transfer the filtrate into a 600-mL beaker, wash the filter paper for quantitative analysis with hot water, and combine with the filtrate. Heat this solution to evaporate to about 300 mL, insert a stirring rod, heat to boiling, and slowly drop 10.0 mL of hydrazine monohydrate to the center of the beaker. Add 2 drops of 10 mol/L sodium hydroxide TS, boil for 10 minutes, cool, and coagulate the precipitate. Filter the solution using filter paper for quantitative analysis. Wash the beaker with hot water, filter the washings, and use a small piece of filter paper for quantitative analysis to wipe the beaker and stirring rod. Place all the filter papers in a porcelain crucible, cover it, carbonize by heating

slowly, and ignite at 800 ℃ for 1 hour. After cooling in a silica gel desiccator, weigh, and determine the amount of residue; Carboplatin contains NLT 52.0% and NMT 53.0% of dehydrated carboplatin, calculated on the anhydrous basis.

(3) ***Water-insoluble substances***—Weigh accurately about 1 g of Carboplatin, transfer into a beaker, add 100 mL of water, and dissolve for 30 minutes by stirring. Filter the solution using a glass filter, previously weighed, wash the beaker with water, and filter the washings. Dry the glass filter at 130 ± 10 ℃ to a constant mass; the amount of residue is NMT 0.5%.

(4) ***1,1-Cyclobutanedicarboxylic acid***—Weigh accurately about 50 mg of Carboplatin, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of 1,1-cyclobutanedicarboxylic acid, and dissolve in the mobile phase to make exactly 100 mL. Take 2.0 mL of this solution, add the mobile phase to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 100 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of 1,1-cyclobutanedicarboxylic acid, A_T and A_S, according to the automatic integration method; the amount of 1,1-cyclobutanedicarboxylic acid is NMT 0.5%.

$$\text{Content (\%) of 1,1-cyclobutanedicarboxylic acid} = 5\times\frac{C}{W}\times\frac{A_T}{A_S}$$

C: Concentration (μg/mL) of 1,1-cyclobutanedicarboxylic acid in the standard solution

W: Amount (mg) of Carboplatin taken in the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column, about 4.0 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: Dissolve 8.5 g of tetrabutylammonium hydrogen sulfate in 80 mL of water, add 3.4 mL of phosphoric acid, and add 10 mol/L sodium hydroxide TS to adjust the pH to 7.55. Transfer 20 mL of this solution into a mixture of 880 mL of water and 100 mL of acetonitrile, and mix.

Flow rate: 2 mL/min

System suitability

System performance: Mix 1.0 mL of the standard solution with 1.0 mL of the standard solution in Assay, and use this solution as the system suitability solution. Proceed with 100 μL of this solution under the above operating conditions; the relative retention times of the carboplatin peak and the 1,1-cyclobutanedicarboxylic acid peak are 0.65 and 1.0, respectively, the resolution between these peaks is NLT 2.5, and the number of theoretical plates obtained from the 1,1-cyclobutanedicarboxylic acid peak is NLT 1500.

System reproducibility: Repeat the test 6 times with each 20 μL of the system suitability solution under the above conditions; the relative standard deviation of the peak area of 1,1-cyclobutanedicarboxylic acid is NMT 10%.

(5) ***Related substances***—Dissolve 0.50 g of Carboplatin in water to make exactly 50 mL, and use this solution as the test solution. Separately, dissolve 25 mg of carboplatin RS in water to make exactly 100 mL, take 1.0 mL of this solution, add 1.0 mL of water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the sum of peak areas other than carboplatin and 1,1-cyclobutanedicarboxylic acid from the test solution according to the automatic integration method; it is NMT 2 times the peak area of the carboplatin obtained from the standard solution (0.5%), and each peak area is not larger than the peak area of the carboplatin obtained from the standard solution (0.25%).

Operating conditions

For detector, column, mobile phase, and system suitability, proceed as directed under the operating conditions as directed under the Assay.

Water NMT 0.5% (1 g, anhydrous formamide, volumetric titration, direct titration).

Assay Weigh accurately about 50 mg each of Carboplatin and carboplatin RS, dissolve in water to make exactly 50 mL each, and use these solutions as the test solution and the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas A_T and A_S of carboplatin according to the automatic integration method.

$$\text{Amount (mg) of carboplatin } (C_6H_{12}N_2O_4Pt) = \text{Amount (mg) of carboplatin RS}\times\frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with aminopropylsilyl silica gel for liquid chromatography (3 to 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and water (87 : 13).

Flow rate: 2 mL/min

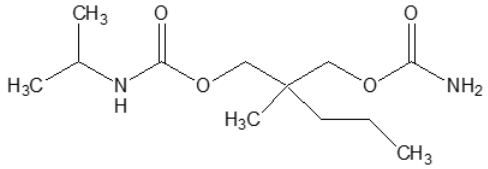
System suitability

System performance: Proceed with 10 μL of the standard solution under the above conditions; the mass distribution ratio for carboplatin is NLT 3.0, the number of theoretical plate for carboplatin is NLT 2500, and the symmetry factor for carboplatin peak is NMT 2.5.

System repeatability: Repeat the test 5 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of carboplatin is NMT 1.2%.

Packaging and storage Preserve in light-resistant, tight containers.

Carisoprodol
카리소프로돌



$C_{12}H_{24}N_2O_4$: 260.33

2-Methyl-2-({[(propan-2-yl)carbamoyl]oxy} methyl)pentyl carbamate [*78-44-4*]

Carisoprodol contains NLT 98.0% and NMT 102.0% of carisoprodol ($C_{12}H_{24}N_2O_4$), calculated on the dried basis.

Description Carisoprodol occurs as a white crystalline powder.
It has a characteristic odor and a bitter taste.
It is freely soluble in ethanol(95), acetone, or chloroform and very slightly soluble in water.

Identification (1) Determine the infrared spectra of Carisoprodol and Carisoprodol RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve 0.1 g each of Carisoprodol and Carisoprodol RS in 1.0 mL of chloroform, and use these solutions as the test solution and the standard solution. Perform the test with these solutions according to the Purity under Meprobamate; the R_f values of the principal spots obtained from the test solution and the standard solution are the same.

Melting point Between 91 and 94 ℃.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Carisoprodol according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Meprobamate***—Weigh 0.1 g of Carisoprodol, dissolve in 1.0 mL of chloroform, and use this solution as the test solution. Separately, weigh 10 mg of meprobamate RS, dissolve in 10 mL of chloroform, and use this solution as the standard solution. Spot 10 μL of the test solution and 5 μL of the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform and acetone (4 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray evenly antimony(III) chloride TS and a solution of 3% furfural in chloroform alternately on the plate until the black spot appears, and heat at 110 ℃ for 15 minutes; the meprobamate spot obtained from the test solution is not more intense than the spot obtained from the standard solution (NMT 0.5%).

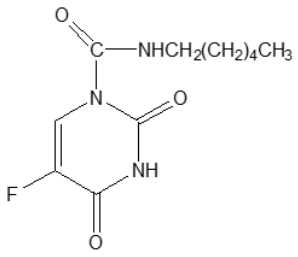
Loss on drying NMT 0.5% (1 g, in vacuum, 60 ℃, 3 hours).

Assay Weigh accurately about 0.4 g of Carisoprodol, add 10 mL of pyridine and 1 drop of phenolphthalein TS, and titrate with 0.1 mol/L sodium methoxide VS until the solution exhibits a pink color. To this solution, add 25.0 mL of 0.1 mol/L sodium methoxide VS, heat under a reflux condenser for 30 minutes, and cool. To this solution, add 40 mL of ethanol(95), and titrate with 0.1 mol/L hydrochloric acid VS (indicator: 7 drops of phenolphthalein TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium methoxide VS
= 26.033 mg of $C_{12}H_{24}N_2O_4$

Packaging and storage Preserve in tight containers.

Carmofur
카르모푸르



$C_{11}H_{16}FN_3O_3$: 257.26

5-Fluoro-N-hexyl-2,4-dioxopyrimidine-1-carboxamide [*61422-45-5*]

Carmofur, when dried, contains NLT 98.0% and NMT 101.0% of carmofur ($C_{11}H_{16}FN_3O_3$).

Description Carmofur occurs as a white crystalline powder.
It is very soluble in *N*,*N*-dimethylformamide, freely soluble in acetic acid(100), soluble in ether, sparingly soluble in ethanol(99.5), and practically insoluble in water.

Melting point—About 111 °C (with decomposition).

Identification (1) Proceed with 5 mg of Carmofur as directed under the Oxygen Flask Combustion, using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as an absorbent; the test solution responds to the Qualitative Analysis (2) for fluoride.

(2) Determine the absorption spectra of the solutions of Carmofur and Carmofur RS in a mixture of methanol, and phosphoric acid-acetic acid-boric acid buffer solution (pH 2.0) (9 : 1) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Carmofur and Carmofur RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Carmofur according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Dissolve 0.20 g of Carmofur in 10 mL of a mixture of methanol and acetic acid(100) (99 : 1), and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of methanol and acetic acid(100) (99 : 1) to make exactly 500 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin-layer chromatography. Spot 15 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (fluorescent indicator). Next, develop the plate with a mixture of toluene and acetone (5 : 3) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution. Spray bromine vapor on the plate for 30 seconds, and spray evenly a solution of fluorescein in ethanol(95) (1 in 2500); the spots other than the principal spot obtained from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, 50 °C, 3 hours).

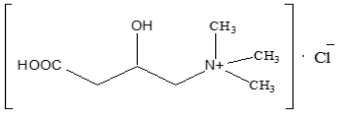
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Carmofur, previously dried, dissolve in 20 mL of *N*,*N*-dimethylformamide, and titrate the solution with 0.1 mol/L tetramethylammonium hydroxide-methanol VS (Indicator: 3 drops of thymol blue-dimethylformamide TS). However, the endpoint of the titration is when the yellow of this solution turns bluish green to blue.

Each mL of 0.1 mol/L tetramethylammonium hydroxide-methanol VS
= 25.726 mg of $C_{11}H_{16}FN_3O_3$

Packaging and storage Preserve in tight containers.

DL-Carnitine Hydrochloride
DL-카르니틴염산염



$C_7H_{16}ClNO_3$: 197.66
3-Carboxy-2-hydroxy-*N*,*N*,*N*-trimethyl-1-propanaminium chloride (1:1), [*461-05-2*]

DL-Carnitine Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of DL-carnitine hydrochloride ($C_7H_{16}ClNO_3$).

Description DL-Carnitine Hydrochloride occurs as white crystals or a crystalline powder.
It is odorless and has a sour taste.
It is very soluble in water, and practically insoluble in ethanol, acetic acid(100) or ether. DL-Carnitine Hydrochloride is deliquescent.
The pH of an aqueous solution of DL-Carnitine Hydrochloride (1 in 50) is between 2.3 and 2.6.
It has no optical rotation.

Melting point—About 198 °C (with decomposition).

Identification (1) To 3 mL of an aqueous solution of DL-Carnitine Hydrochloride, add 1 mL of Reinecke salt TS; a pale red precipitate forms.

(2) Determine the infrared absorption spectrum of DL-Carnitine Hydrochloride, previously dried, according to the potassium bromide disk method under the Mid-infrared Spectroscopy; it exhibits absorptions at the wavenumber of about 1733, 1486, 1407, 1177 and 1095 cm^{-1}.

(3) An aqueous solution of DL-Carnitine Hydrochloride responds to the Qualitative Analysis for chloride.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of DL-Carnitine Hydrochloride in 10 mL of water; the solution is clear and colorless.

(2) ***Ammonium***—Proceed with 0.3 g of DL-Carnitine Hydrochloride according to the Ammonium and perform the test. Prepare the control solution with 3.0 mL of ammonium standard solution (NMT 0.01%).

(3) ***Heavy metals***—Proceed with 1.0 g of DL-Carnitine Hydrochloride according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic***—Proceed with 2.0 g of DL-Carnitine Hydrochloride according to Method 1 under the Arsenic

(NMT 1 ppm).

(5) ***Related substances***—Dissolve 1.0 g of DL-Carnitine Hydrochloride in 50 mL of mobile phase, and use this solution as the test solution. Pipet 15.0 mL of this solution, add the mobile phase to make 100 mL, and use this solution as the standard solution. Perform the test with 1 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution as directed in the automatic integration method and calculate the amount of related substances; for the amount of related substances, the total area of peaks other than carnitine is not larger than the area of the carnitine peak in the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Dissolve 4.9 g of phosphoric acid and 2.45 g of sodium 1-pentanesulfonate in 1000 mL of water. To this solution, add sodium hydroxide TS to adjust the pH to 2.6.

Flow rate: Adjust the flow rate so that the retention time of carnitine is about 8 minutes.

Selection of column: Dissolve 0.50 g of DL-Carnitine Hydrochloride and 5 mg of L-histidine hydrochloride in 25 mL of the mobile phase. Proceed with 1 μL of this solution according to the operating conditions above; use a column with the resolution being NLT 2.5 between the two peaks.

Detection limit: Adjust the detection limit so that the peak height of DL-carnitine hydrochloride obtained from 1 μL of the standard solution is 6 to 15 mm.

Time span of measurement: About 2 times the retention time of DL-carnitine hydrochloride after the solvent peak.

Loss on drying NMT 1.0% (1 g, 105 °C, 5 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.3 g of DL-Carnitine Hydrochloride, previously dried, add 20 mL of acetic acid(100), dissolve by warming, and add 140 mL of acetic anhydride. Titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 19.766 mg of $C_7H_{16}ClNO_3$

Packaging and storage Preserve in tight containers.

β-Carotene Suspension 30%
β-카로틴 현탁액30%

β-Carotene Suspension 30% is oil where the microcrystalline β-carotene is dispersed in vegetable oil containing DL-α-tocopherol.

β-Carotene Suspension 30% contains NLT 30.0% of β-carotene ($C_{40}H_{56}$: 536.87).

Composition Each g of β-Carotene Suspension 30% contains 0.3 g of β-carotene, 7 mg of DL-α-tocopherol and 0.693 g of corn oil.

Description β-Carotene Suspension 30% occurs as viscous, reddish brown oil.

Identification Perform the test with β-Carotene Suspension 30% as directed under the Identification under β-Carotene in the US Pharmacopeia.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of β-Carotene Suspension 30% according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Peroxide value***—Perform the test with β-Carotene Suspension 30% as directed under the Peroxide value under General tests in the British Pharmacopoeia; the result is NMT 10 meq/g.

Assay Weigh accurately about 0.167 g of β-Carotene Suspension 30% and perform the test as directed under the Assay under β-Carotene in the US Pharmacopeia.

Packaging and storage Preserve in tight containers, in a cold and dark place.

Caroverine Hydrochloride Injection
카로베린염산염 주사액

Caroverine Hydrochloride Injection contains NLT 95.0% and NMT 105.0% of the labeled amount of caroverine hydrochloride hydrate ($C_{22}H_{27}N_3O_2 \cdot HCl \cdot H_2O$: 419.95).

Method of preparation Prepare as directed under Injections, with Caroverine Hydrochloride Hydrate.

Identification (1) Weigh an amount of Caroverine Hydrochloride Injection, equivalent to 0.1 g of caroverine hydrochloride hydrate, according to the labeled amount, dissolve in 5 mL of 95% ethanol and use this solution as the test solution. Separately, weigh accurately about 0.1 g of caroverine hydrochloride hydrate RS, dissolve in 5 mL of 95% ethanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each of the

test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Then, develop the plate with a mixture of 95% ethanol and 25% ammonia water (95 : 5) as the developing solvent and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm) or spray evenly Dragendorff's TS; the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

(2) Take 1.0 mL of Caroverine Hydrochloride Injection, add 0.1 mol/L hydrochloric acid, and use this solution as the test solution. Separately, take an appropriate amount of caroverine hydrochloride hydrate RS, add 0.1 mol/L hydrochloric acid to make it the same concentration as the test solution, and use this solution as the standard solution. Determine the absorption spectra of the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy using 0.1 mol/L hydrochloric acid as a control solution; both spectra exhibit similar intensities of absorption at the same wavelengths.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

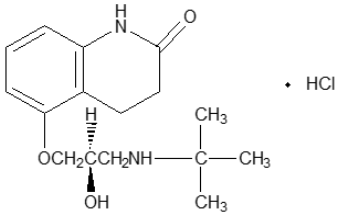
Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Caroverine Hydrochloride Injection, equivalent to 10 mg of caroverine hydrochloride hydrate ($C_{22}H_{27}N_3O_2 \cdot HCl \cdot H_2O$) according to the labeled amount, put into a 100-mL volumetric flask, and add 0.1 mol/L hydrochloric acid TS to make exactly 100 mL. Take 5 mL of this solution, add 0.1 mol/L hydrochloric acid TS to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of caroverine hydrochloride hydrate RS, proceed in the same manner as the test solution, and use this solution as the standard solution. With the test solution and the standard solution, perform the test as directed under the Ultraviolet-visible Spectroscopy using 0.1 mol/L hydrochloric acid TS as a control solution and determine absorbances, A_T and A_S, of caroverine hydrochloride hydrate at 335 nm.

$$\text{Amount (mg) of caroverine hydrochloride hydrate } (C_{22}H_{27}N_3O_2 \cdot HCl \cdot H_2O) = \text{Amount (mg) of caroverine hydrochloride hydrate RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in hermetic containers.

Carteolol Hydrochloride
카르테올롤염산염



and enantiomer

$C_{16}H_{24}N_2O_3 \cdot HCl$: 328.83

5-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-1,2,3,4-tetrahydroquinolin-2-one hydrochloride [*51781-21-6*]

Carteolol Hydrochloride, when dried, contains NLT 99.0% and NMT 101.0% of carteolol hydrochloride ($C_{16}H_{24}N_2O_3 \cdot HCl$).

Description Carteolol Hydrochloride occurs as white crystals or a crystalline powder.

It is soluble in water, sparingly soluble in methanol, very slightly soluble in ethanol(95) or acetic acid(100), and practically insoluble in ether.

An aqueous solution of Carteolol Hydrochloride (1 in 20) exhibits no optical rotation.

Dissolve 1.0 g of Carteolol Hydrochloride in 100 mL of water; the pH of this solution is between 5.0 and 6.0.

Melting point—About 277 °C (with decomposition).

Identification (1) Dissolve 0.1 g of Carteolol Hydrochloride in 5 mL of water, and add 5 drops of Reinecke salt TS; a pale red precipitate forms.

(2) Determine the absorption spectra of aqueous solutions of Carteolol Hydrochloride and carteolol hydrochloride RS solution (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Carteolol Hydrochloride and carteolol hydrochloride RS as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) An aqueous solution of Carteolol Hydrochloride (1 in 50) responds to the Qualitative Analysis for chloride.

pH The pH of an aqueous solution of Carteolol Hydrochloride (1 in 100) is between 5.0 and 6.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Carteolol Hydrochloride in 30 mL of water; the solution is colorless and clear.

(2) ***Heavy metals***—Proceed with 2.0 g of Carteolol Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Carteolol Hydrochloride according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.20 g of Carteolol Hydrochloride in 10 mL of methanol, and use this solution as the test solution. Pipet 2 mL of this solution and add methanol to make exactly 100 mL. Pipet 1 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, methanol, and ammonia water(28) (50 : 20 : 1) to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots obtained from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 °C, 3 hours).

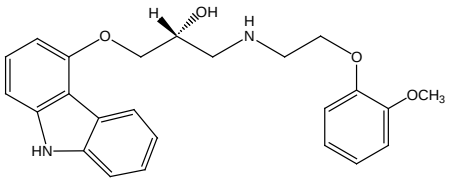
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Carteolol Hydrochloride, previously dried, and dissolve in 30 mL of acetic acid(100) by warming on a steam bath. After cooling, add 70 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 32.883 mg of $C_{16}H_{24}N_2O_3 \cdot HCl$

Packaging and storage Preserve in well-closed containers.

Carvedilol
카르베딜롤



and enantiomer

$C_{24}H_{26}N_2O_4$: 406.47

1-(9*H*-Carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)ethylamino]propan-2-ol [*72956-09-3*]

Carvedilol, when dried, contains NLT 99.0% and NMT 101.0% of carvedilol ($C_{24}H_{26}N_2O_4$).

Description Carvedilol occurs as a white crystalline powder.
It is slightly soluble in ethanol(95), soluble in dichloromethane, and practically insoluble in water.
It shows crystalline polymorphism.

Identification Determine the infrared spectra of Carvedilol and Carvedilol RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If there is any difference between the spectra, dissolve Carvedilol and Carvedilol RS each in 2-propanol, evaporate to dryness, and repeat the test with the residue.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Carvedilol according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Dissolve 25 mg of Carvedilol in the mobile phase to make exactly 25.0 mL, and use this solution as the test solution. To 1.0 mL of the test solution, add the mobile phase to make exactly 100 mL. To 1.0 mL of this solution, add the mobile phase to make exactly 10 mL, and use this solution as the standard solution (1). Separately, dissolve 5 mg of carvedilol related substance I RS {(2*RS*)-1-[Benzyl[2-(2-methoxyphenoxy)ethyl]amino]-3-(9*H*-carbazol-4-yloxy)propan-2-ol} in 5.0 mL of mobile phase, add the mobile phase to make exactly 100 mL, and use this solution as the standard stock solution. Take 4.0 mL of this solution, add the mobile phase to make exactly 100 mL, take 1.0 mL of this solution, and add the mobile phase to make exactly 10 mL. Use this solution as the standard solution (2). Perform the test with 20 μL each of the test solution, the standard solution (1), and the standard solution (2) as directed under the Liquid Chromatography according to the following conditions. To calculate the amount of related substance II, multiply the peak area by 2 as a correction factor. Related substance II obtained from the test solution is not larger than 0.2 times the major peak area obtained from standard solution (1) (0.2%), related substance III obtained from the test solution is not larger than 1.5 times the major peak area obtained from standard solution (1) (0.15%), related substance I is not larger than the peak area of related substance I obtained from standard solution (2) (0.02%), and peak areas of other related substances are not larger than the major peak area obtained from standard solution (1) (0.1%). The sum of the peak areas of related substances other than related substance I obtained from the test solution is not larger than 5 times the major peak area obtained from standard solution (1) (NMT 0.5%). However, exclude any peak having an area smaller than 0.5 times the area of the major peak obtained from the standard solution (1) (NMT 0.05%).

Operating conditions

Detector: An ultraviolet absorption photometer

(wavelength: 240 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 55 °C.

Mobile phase: Dissolve 1.77 g of potassium dihydrogen phosphate in water to make 650 mL, add phosphoric acid to adjust the pH to 2.0, and add 350 mL of acetonitrile to mix.

Flow rate: 1.0 mL/min

Relative retention time: The relative retention time of related substances II, I, and III to the retention time of carvedilol (about 4 minutes) is about 0.5, 2.9, and 3.8, respectively.

System suitability

System performance: Dissolve 5.0 mg of carvedilol related substance I RS {(2*RS*)-1-[Benzyl[2-(2-methoxyphenoxy)ethyl]amino]-3-(9*H*-carbazol-4-yloxy)propan-2-ol} in 5.0 mL of the test solution, add the mobile phase to make exactly 100.0 mL, and proceed with 20 μL of this resulting solution according to the above conditions; the resolution between the carvedilol peak and related substance I peak is NLT 17. Proceed with 20 μL of standard solution (2) according to the above conditions; the signal-to-noise ratio of the related substance I peak is NLT 10.

Time span of measurement: 6 times the retention time of carvedilol.

Loss on drying NMT 0.5% (1 g, 105 ℃, constant mass).

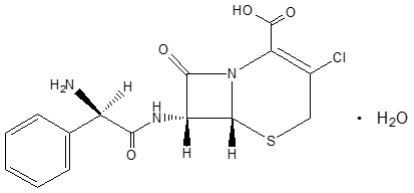
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.35 g of Carvedilol, previously dried, dissolve in 60 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Separately, perform a blank test, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 40.649 mg of $C_{24}H_{26}N_2O_4$

Packaging and storage Preserve in light-resistant, well-closed containers.

Cefaclor Hydrate
세파클러수화물



$C_{15}H_{14}ClN_3O_4S \cdot H_2O$: 385.82

(6*R*,7*R*)-7-[[(2*R*)-2-Amino-2-phenylacet]amido]-3-chloro-3,4-didehydrocepham-4-carboxylic acid monohydrate [*70356-03-5*]

Cefaclor Hydrate contains NLT 950 μg (potency) and NMT 1020 μg (potency) of cefaclor ($C_{15}H_{14}ClN_3O_4S$: 367.81) per mg, calculated on the anhydrous basis.

Description Cefaclor Hydrate occurs as a white to yellowish white crystalline powder.
It is odorless or has a slight characteristic odor, and has a slightly bitter taste.
It is soluble in water, sparingly soluble in methanol, very slightly soluble in ethanol(95) and practically insoluble in ether.

Identification (1) Determine the infrared spectra of Cefaclor Hydrate and cefaclor hydrate RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between +105° and +120° (0.1 g, calculated on the anhydrous basis, water, 25 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Cefaclor Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Prepare the test solution by suspending 1.0 g of Cefaclor Hydrate in 10 mL of *N*,*N*-dimethylformamide and perform the test (NMT 2 ppm).

(3) ***Related substances***—Weigh accurately about 50 mg of Cefaclor Hydrate, dissolve in sodium dihydrogen phosphate solution (pH 2.5) to make exactly 10 mL, and use this solution as the test solution. Weigh accurately a suitable amount of cefaclor RS, dissolve in sodium dihydrogen phosphate solution (pH 2.5) to a constant concentration of about 0.05 mg/mL, and use this solution as the standard solution. Perform the test with 20 μL each of the

test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, determine each peak area from each solution by the automatic integration method, and calculate the amount of each related substance; the amount of each related substance is NMT 0.5% and the total amount of related substances is NMT 2.0%. If necessary, proceed with 20 μL of sodium dihydrogen phosphate solution (pH 2.5) in the same manner as directed above to make a necessary correction.

$$\text{Content (\%) of each related substance} = \frac{C}{W} \times \frac{A_T}{A_S}$$

C: Concentration [μg (potency)/mL] of cefaclor in the standard solution

W: Weight [mg (potency)] of Cefaclor Hydrate taken

A_i: Peak area of each related substance obtained from the test solution

A_S: Peak area of cefaclor obtained from the standard solution

Sodium dihydrogen phosphate solution (pH 2.5)— Dissolve 2.4 g of sodium dihydrogen phosphate monohydrate in 1000 mL of water and adjust the pH to 2.5 with phosphoric acid.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: Dissolve 6.9 g of sodium dihydrogen phosphate monohydrate in 1000 mL of water and adjust the pH to 4.0 with phosphoric acid.

Mobile phase B: A mixture of the mobile phase A and acetonitrile (550 : 450).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0	95	5
0 - 30	95 → 75	5 → 25
30 - 45	75 → 0	25 → 100
45 - 55	0	100
55 - 60	0 → 95	100 → 5
60 - 70	95	5

Flow rate: 1.0 mL/minute

System suitability

Dissolve a suitable amount of cefaclor delta-3 isomer RS in the standard solution to obtain a solution having a known concentration of about 0.05 mg per mL, and use this solution as the system suitability solution. Proceed with the system suitability solution according to the above conditions; the peak of cefaclor is eluted between 23 minutes and 29 minutes, the resolution between the peaks of cefaclor delta-3 isomer and cefaclor is NLT 2.0, and the symmetry factor of the peak of cefaclor is NMT 1.2.

pH Dissolve 0.25 g of Cefaclor Hydrate in 10 mL of water; the pH of this solution is between 3.0 and 4.5.

Water Between 3.0% and 8.0% (0.2 g, volumetric titration, direct titration).

Assay Weigh accurately 15 mg (potency) each of Cefaclor Hydrate and cefaclor RS, dissolve each in the mobile phase to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography and determine the peak areas, A_T and A_S, of cefaclor from each solution.

$$\text{Potency (μg) of cefaclor } (C_{15}H_{14}ClN_3O_4S) = \text{Potency (μg) of cefaclor RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 265 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 1.0 g of sodium 1-pentanesulfonate in 780 mL of water, add 10 mL of triethylamine, mix, adjust the pH to 2.5 ± 1 with phosphoric acid, and add 220 mL of methanol.

Flow rate: 1.5 mL/min

System suitability

System performance: Proceed with the system suitability solution according to the above conditions; the relative retention times of cefaclor and cefaclor delta-3 isomer are about 0.8 and about 1.0, respectively, and the resolution between the peaks of cefaclor and cefaclor delta-3 isomer is NLT 2.5, and the symmetry factor of the peak of cefaclor is NMT 1.5.

System repeatability: Repeat the test 5 times with the system suitability solution according to the above conditions; the relative standard deviation of the peak area of cefaclor is NMT 2%.

System suitability solution—Weigh accurately a suitable amount of Cefaclor Hydrate and cefaclor delta-3 isomer RS, and dissolve in the mobile phase to obtain a solution having a known concentration of 0.3 mg per mL.

Packaging and storage Preserve in tight containers.

Cefaclor Capsules
세파클러 캡슐

Cefaclor Capsules contain NLT 90.0% and NMT 120.0% of the labeled amount of cefaclor ($C_{15}H_{14}ClN_3O_4S$: 367.81).

Method of preparation Prepare as directed under Capsules, with Cefaclor Hydrate.

Identification The retention times of the major peaks obtained from the test solution and the standard solution under the Assay are the same.

Water NMT 8.0% (0.2 g, volume titration, direct titration).

Purity ***Related substances***—Weigh accurately the mass of the contents of NLT 20 capsules of Cefaclor Capsules, weigh accurately an amount of the contents, equivalent to about 50 mg (potency) of cefaclor according to the labeled potency, dissolve in sodium dihydrogen phosphate, pH 2.5, and sonicate if necessary. Dilute with sodium dihydrogen phosphate, pH 2.5, to make exactly 10 mL, and use the filtrate as the test solution. Separately, prepare the standard solution as directed under the preparation of the standard solution for related substances under the Purity of cefaclor hydrate, and use this solution as the standard solution. Proceed with 20 μL each of the test solution and the standard solution as directed under the Related substances under the Purity of cefaclor hydrate, and calculate the content (%) of each related substance in each solution (each related substance content: NMT 0.5%, amount of total related substances: NMT 2.0%).

Dissolution Perform the test with 1 capsule of Cefaclor Capsules at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take the dissolved solution 30 minutes after starting the dissolution test, and filter. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 28 mg (potency) of cefaclor RS, dissolve in water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Assay of Cefaclor Hydrate, and determine the peak areas, A_T and A_S, of cefaclor in each solution. It meets the requirements when the dissolution rate in 30 minutes is NLT 80% (Q).

Dissolution rate (%) of the labeled amount of cefaclor ($C_{15}H_{14}ClN_3O_4S$)

$$= \text{Potency (mg) of cefaclor RS} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 900$$

C: Labeled amount (mg) of cefaclor ($C_{15}H_{14}ClN_3O_4S$) in 1 capsule

Uniformity of dosage units Meets the requirements of the mass variation test.

Assay Weigh accurately the mass of the contents of NLT 20 capsules of Cefaclor Capsules, weigh accurately about 75 mg (potency) of cefaclor according to the labeled potency, add the mobile phase to make exactly 250 mL, and shake well to mix. Then, filter, use the filtrate as the test solution, and perform the test as directed under the Assay of Cefaclor Hydrate.

$$\text{Potency (μg) of cefaclor } (C_{15}H_{14}ClN_3O_4S) = \text{Potency (μg) of cefaclor RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers.

Cefaclor for Syrup
시럽용 세파클러

Cefaclor for Syrup is a preparation for syrup, which is dissolved before use, and contains NLT 90.0% and NMT 120.0% of the labeled amount of cefaclor ($C_{15}H_{14}ClN_3O_4S$: 367.81).

Method of preparation Prepare as directed under Syrups, with Cefaclor Hydrate.

Identification The retention times of the major peaks obtained from the test solution and the standard solution are the same.

pH Dissolve Cefaclor for Syrup according to the label; the pH of the resulting solution is between 2.5 and 5.0.

Purity ***Related substances***—Weigh accurately an amount of Cefaclor for Syrup, equivalent to 50 mg (potency) of cefaclor according to the labeled amount, add sodium dihydrogen phosphate (pH 2.5) while shaking gently to avoid foaming to make exactly 50 mL, filter, and use the filtrate as the test solution. Use the test solution within 3 hours if stored at room temperature and use it within 20 hours if stored in a refrigerator. Separately, weigh accurately 10 mg (potency) of cefaclor RS, dissolve in sodium dihydrogen phosphate (pH 2.5) to make 20 mL, pipet 1 mL of this solution, and add sodium dihydrogen phosphate (pH 2.5) to make 10 mL so that each mL contains 0.05 mg. Use this solution as the standard solution. Perform the test with each 20 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak area of each so-

lution according to the automatic integration method. Calculate the amount of each related substance according to the following formula; the amount of each related substance is NMT 1.0%, and the total amount of related substances is NMT 3.0%. Exclude any related substances with an amount less than 0.1%.

$$\text{Content (\%) of related substances} = 100 \times \frac{C_S}{C_T} \times \frac{A_i}{A_S}$$

C_S: Concentration [mg (potency)/mL] of cefaclor in the standard solution

C_T: Concentration [mg (potency)/mL] of cefaclor in the test

A_i: Peak area of each related substance from the test solution

A_s: Peak area of cefaclor from the standard solution

Sodium dihydrogen phosphate (pH 2.5)—Dissolve 2.5 g of sodium dihydrogen phosphate monohydrate in 1000 mL of water and adjust the pH to 2.5 with phosphoric acid.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (1.5 μm to 10 μm in particle diameter).

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: Dissolve 6.9 g of sodium dihydrogen phosphate monohydrate in 1000 mL of water and adjust the pH to 4.0 with phosphoric acid.

Mobile phase B: A mixture of mobile phase A and acetonitrile (550 : 450).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0	95	5
0 - 30	95 → 75	5 → 25
30 - 45	75 → 0	25 → 100
45 - 55	0	100
55 - 60	0 → 95	100 → 5
60 - 70	95	5

Flow rate: 1.0 mL/min

System suitability

System performance: Weigh accurately a suitable amount of cefaclor delta-3-isomer, dissolve in the standard solution so that Each mL of the resulting solution contains 0.05 mg, and use this solution as the system suitability solution. Proceed with the system suitability solution according to the above operating conditions; the retention time of the cefaclor peak is between 23 and 29 minutes, the resolution between the peaks of cefaclor delta-3-isomer and cefaclor is NLT 2.0, and the symmetry factor of the cefaclor is NMT 1.2.

Water 2.0% (0.5 g, volumetric titration, direct titration).

Uniformity of dosage units (distribution) Meets the requirements.

Assay Proceed as directed under the Assay under Cefaclor Hydrate. Weigh accurately an amount of Cefaclor for Syrup, equivalent to about 50 mg (potency) according to the labeled potency, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg (potency) of cefaclor RS, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the standard solution.

Packaging and storage Preserve in tight containers.

Cefaclor Extended-Release Tablets
세파클러 서방정

Cefaclor Extended-Release Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of cefaclor ($C_{15}H_{14}ClN_3O_4S$: 367.81).

Method of preparation Prepare as directed under Tablets, with Cefaclor Hydrate.

Identification Perform the test as directed under the Assay; the retention time of the major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard solution.

Water NMT 6.5% (0.2 g, volumetric titration, direct titration).

Dissolution Perform the test with 1 tablet of Cefaclor Extended-Release Tablets at 100 revolutions per minute according to Method 1 under the Dissolution, using 900 mL of 0.1 mol/L hydrochloric acid TS as the dissolution medium. Take exactly a volume of the dissolved solution after 30 minutes from the start of the test, and carefully add the same volume of the dissolution medium, previously warmed to 37 ± 0.5 °C. Filter the dissolved solution taken through a membrane filter with a pore size not exceeding 0.5 μm, pipet an amount of the filtrate, dilute it with 0.1 mol/L hydrochloric acid TS so that each mL contains about 20 to 30 μg (potency) of cefaclor, and use this solution as the test solution (30 minutes). Repeat this procedure after 60 minutes and after 240 minutes from the start of the test, and use the solutions thus obtained as the test solutions (60 minutes and 240 minutes, respectively). Separately, weigh accurately about 0.11 g (poten-

cy) of cefaclor RS, dissolve in 0.1 mol/L hydrochloric acid TS, dilute with 0.1 mol/L hydrochloric acid TS so that each mL contains about 20 to 30 μg (potency) of cefaclor, and use this solution as the standard solution. Determine the absorbances of the test solutions and the standard solution at 265 nm as directed under the Ultraviolet-visible Spectroscopy, using 0.1 mol/L hydrochloric acid TS as the blank test solution, and calculate the dissolution rate; the acceptable dissolution criterion is 5% to 30% of Cefaclor Extended-Release Tablets dissolved in 30 minutes, 20% to 50% of Cefaclor Extended-Release Tablets dissolved in 60 minutes and NLT 80% of Cefaclor Extended-Release Tablets dissolved in 240 minutes.

Uniformity of dosage units It meets the requirements when the Content uniformity test is performed according to the following procedure. Take 10 tablets of Cefaclor Extended-Release Tablets, dissolve in a volume of methanol equivalent to 25 mL per each tablet, and add the mobile phase so that each mL contains about 1.5 mg (potency) of cefaclor. Pipet 10 mL of this solution, add the internal standard solution to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 15 mg (potency) of cefaclor RS, dissolve in the internal standard solution to make exactly 50 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Assay.

Assay Weigh accurately the mass of NLT 20 tablets of Cefaclor Extended-Release Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 75 mg (potency) of the labeled potency, dissolve in 150 mL of the internal standard solution, add the mobile phase to make 250 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 15 mg (potency) of cefaclor RS, add 30 mL of the internal standard solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of cefaclor to the internal standard, respectively.

$$\text{Potency (μg) of cefaclor } (C_{15}H_{14}N_3O_4S) = \text{Potency (μg) of cefaclor RS} \times \frac{Q_T}{Q_S} \times 5$$

Internal standard solution—Dissolve 0.45 g of sodium 2-naphthalenesulfonate in the mobile phase to make 1000 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 265 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 250 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 1.0 g of sodium 1-pentanesulfonate in 780 mL of water, add 10 mL of triethylamine, mix, adjust the pH to 2.5 with phosphoric acid, and add 220 mL of methanol.

Flow rate: 1.5 mL/min

Packaging and storage Preserve in tight containers.

Cefaclor Tablets for Oral Suspension
세파클러 현탁용 정

Cefaclor Tablets for Oral Suspension contain NLT 90.0% and NMT 120.0% of the labeled amount of cefaclor ($C_{15}H_{14}ClN_3O_4S$: 367.81).

Method of preparation Prepare as directed under Tablets, with Cefaclor.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Dissolution Perform the test with 1 tablet of Cefaclor Tablets for Oral Suspension at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of 0.1 mol/L hydrochloric acid TS as the dissolution medium. Take exactly a volume of the dissolved solution after 15 minutes from the start of the test, filter through a membrane filter with a pore size not exceeding 0.5 μm, and use 10 mL of the filtrate as the test solution. Separately, weigh accurately about 70 mg (potency) of cefaclor RS, dissolve in 0.1 mol/L hydrochloric acid TS to make 100 mL. To 10 mL of this solution, add 0.1 mol/L hydrochloric acid TS to make 100 mL. Then, to 4 mL of this solution, add 0.1 mol/L hydrochloric acid TS to make 10 mL and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at 265 nm as directed under the Ultraviolet-visible Spectroscopy, and calculate the dissolution rate according to the following equation; the acceptable dissolution criteria is NLT 80% of the labeled potency of Cefaclor Tablets for Oral Suspension dissolved in 15 minutes.

$$\text{Dissolution rate (\%)} = \frac{\text{Potency (mg) of cefaclor RS}}{\text{Labled amount of 1 tablet of Cefaclor Tablets for Oral Suspension}} \times \frac{A_T}{A_S} \times 36$$

Uniformity of dosage units It meets the requirements when tested according to the Mass variation test.

Water NMT 6.5% (0.2 g, volumetric titration, direct

titration).

Assay Weigh accurately the mass of NLT 20 tablets of Cefaclor Tablets for Oral Suspension, and powder. Weigh accurately a portion of the powder, equivalent to about 65 mg (potency) of the labeled potency, and dissolve in the mobile phase to make exactly 100 mL. Pipet 10 mL of this solution, add the mobile phase to make 25 mL, and use this solution as the test solution. Separately, weigh accurately about 65 mg (potency) of cefaclor RS and dissolve in the mobile phase to make exactly 100 mL. Pipet 10 mL of this solution, add the mobile phase to make 25 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak areas, A_T and A_S, of cefaclor from the test solution and the standard solution, respectively.

$$\text{Potency (μg) of cefaclor } (C_{15}H_{14}ClN_3O_4S) = \text{Potency (μg) of cefaclor RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 265 nm).

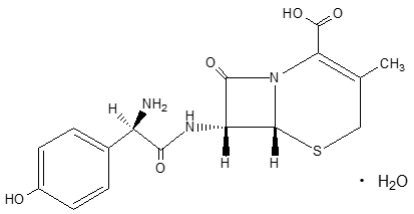
Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 1.0 g of sodium 1-pentanesulfonate in 780 mL of water, add 10 mL of triethylamine, mix, adjust the pH to 2.5 with phosphoric acid, and add 220 mL of methanol.

Flow rate: 1.5 mL/min

Packaging and storage Preserve in tight containers.

Cefadroxil Hydrate
세파드록실수화물



$C_{16}H_{17}N_3O_5S \cdot H_2O$: 381.40

(6*R*,7*R*)-7-[[(2*R*)-2-amino-2-(4-hydroxyphenyl)acet]amido]-3-methyl-3,4-didehydrocepham-4-carboxylic acid monohydrate [*66592-87-8*]

Cefadroxil Hydrate contains NLT 950 μg and NMT 1020 μg (potency) of cefadroxil ($C_{16}H_{17}N_3O_5S$: 363.39) per mg, calculated on the anhydrous basis.

Description Cefadroxil Hydrate occurs as a white to pale yellowish white powder.

It is sparingly soluble in water, slightly soluble in methanol and very slightly soluble in ethanol(99.5).

Identification (1) Determine the absorption spectra of solutions of Cefadroxil Hydrate and cefadroxil RS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cefadroxil Hydrate and cefadroxil RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Determine the ^1H spectrum of a solution of Cefadroxil Hydrate in a mixture of heavy water for nuclear magnetic resonance spectroscopy and hydrochloric acid for nuclear magnetic resonance spectroscopy (3 : 1) (1 in 10), using sodium 3-(trimethylsilyl)propionic acid-d_4 sodium salt for nuclear magnetic resonance spectroscopy as the internal standard, as directed under the Nuclear Magnetic Resonance Spectroscopy; it exhibits signal A of a single line at about δ 2.1 ppm, signal B of double lines at around δ 7.0 ppm and signal C of double lines at about δ 7.5 ppm, and the integrated intensity ratio of signals A, B and C is 3 : 2 : 2.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{25}$: Between +164 ° and +182° (0.6 g, calculated on the anhydrous basis, water, 100 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Cefadroxil Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 0.1 g of Cefadroxil Hydrate in 4 mL of a mixture of ethanol(99.5), water and diluted hydrochloric acid (1 in 5) (75 : 22: 3) and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of ethanol(99.5), water and diluted hydrochloric acid (1 in 5) (75 : 22: 3) to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel (with a fluorescent indicator) for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, water, ethanol(99.5) and formic acid (14 : 5 : 5 : 1) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Spray evenly ninhydrin-citric acid-acetic acid TS on the plate and heat at 100 °C for 10 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

(3) ***Dimethylaniline***—Weigh accurately about 1.0 g of Cefadroxil Hydrate, add 5 mL of 1 mol/L sodium hydroxide TS and 1 mL of the internal standard solution, centrifuge, if necessary, and use the clear supernatant as the test solution. Separately, weigh accurately about 50 mg of dimethylaniline, add 2.0 mL of hydrochloric acid, and add water to make 50 mL. Pipet 5.0 mL of this solution and add water to make exactly 250 mL. Pipet 1.0 mL of this solution, add 5.0 mL of 1 mol/L sodium hydroxide TS, add 1.0 mL of the internal standard solution, centrifuge, if necessary, and use the supernatant as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the peak area ratio, Q_T and Q_S, of dimethylaniline to the internal standard from the test solution and the standard solution, respectively (NMT 20 ppm).

$$\text{Content (ppm) of dimethylaniline} = \text{Amount (mg) of dimethylaniline taken} \times \frac{Q_T}{Q_S} \times \frac{Purity\ (\%) of\ dimethylaniline}{Amount\ (mg)\ of\ Cefadroxil\ Hydrate\ taken} \times 4$$

Internal standard solution—Dissolve 50.0 mg of naphthalene in cyclohexane to make 50 mL. To 5.0 mL of this solution, add cyclohexane to make 100 mL, and use this solution as the internal standard solution.

Operating conditions

Detector: A flame ionization detector

Column: A column about 2 mm in internal diameter and about 2 m in length, packed with diatomaceous earth for gas chromatography, which is coated with 50% phenyl-50% methylpolysiloxane for gas chromatography, equivalent to 3% of the mass of the diatomaceous earth.

Column temperature: 120 ℃

Temperatures of the sample injection port and the detector: 150 ℃

Carrier gas: Nitrogen

Flow rate: 30 mL/min

pH Dissolve 1.0 g of Cefadroxil Hydrate in 200 mL of water; the pH of this solution is between 4.0 and 6.0.

Water Between 4.2% and 6.0% (0.2 g, volumetric titration, direct titration).

Assay Weigh accurately 50 mg (potency) each of Cefadroxil Hydrate and cefadroxil RS, dissolve each in water to make exactly 500 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with exactly 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculated the peak areas, A_T and A_S, of cefadroxil, respectively, from each solution.

$$\text{Potency (μg) of cefadroxil } (C_{16}H_{17}N3O_5S) = \text{Potency (μg) of cefadroxil RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 262 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 250 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of a solution of potassium dihydrogen phosphate (17 in 12500) and methanol (17 : 3).

Flow rate: Adjust the flow rate so that the retention time of cefadroxil is about 5 minutes.

System suitability

System performance: Dissolve about 5 mg (potency) of cefadroxil and about 10 mg (potency) of cefatrizine propylene glycol in 50 mL of water. Proceed with 10 μL of this solution according to the above conditions; cefadroxil and cefatrizine propylene glycol are eluted in this order with the resolution between these peaks being NLT 4.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of cefadroxil is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Cefadroxil Capsules
세파드록실 캡슐

Cefadroxil Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of cefadroxil ($C_{16}H_{17}N_3O_5S$: 363.39).

Method of preparation Prepare as directed under Capsules, with Cefadroxil Hydrate.

Identification Take an amount of Cefadroxil Capsules, equivalent to 10 mg (potency) of cefadroxil according to the labeled amount, add water to make 500 mL, and then filter. Determine the absorption spectrum of the filtrate as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 228 nm and 232 nm and between 261 nm and 265 nm.

Water NMT 7.0% (0.15 g, volumetric titration, direct titration).

Dissolution Perform the test with 1 capsule of Cefadroxil Capsules at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of 0.05 mol/L acetic acid-sodium acetate buffer solution, pH 4.0,

as the dissolution medium. Take 20 mL or more of the dissolved solution 90 minutes after starting the dissolution test, and filter through a membrane filter with a pore size of NMT 0.45 μm. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add water to make exactly *V'* mL of a solution containing about 22 μg (potency) of cefadroxil per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately an amount equivalent to about 22 mg (potency) of cefadroxil RS, and dissolve in water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 50 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution at the wavelength of 263 nm as directed under the Ultraviolet-visible Spectroscopy, using water as a control solution. Meets the requirements if the dissolution rate of Cefadroxil Capsules in 90 minutes is NLT 80%.

Dissolution rate (%) of the labeled amount of cefadroxil ($C_{16}H_{17}N_3O_5S$)

$$= \text{Potency (mg) of cefadroxil RS} \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 90$$

C: Labeled amount [mg (potency)] of cefadroxil ($C_{16}H_{17}N_3O_5S$) in 1 capsule

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following procedure. Take 1 capsule of Cefadroxil Capsules, add 300 mL of water, sonicate for 30 minutes to disperse, and then add water to make exactly 500 mL. Pipet 5 mL of this solution, and add water to make a solution containing 0.1 mg (potency) of cefadroxil per mL. Filter, discard the first 10 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately an amount equivalent to about 20 mg (potency) of cefadroxil RS, add water to make exactly 200 mL, and use this solution as the standard solution. Perform the test as directed under the Assay of Cefadroxil Hydrate.

Assay Weigh accurately the mass of NLT 20 Sodium Chondroitin Sulfate Capsules. Weigh accurately an amount of the contents, equivalent to about 50 mg (potency) of cefadroxil, add 30 mL of water, shake for 30 minutes to mix, and add water to make exactly 500 mL. Then, filter. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 20 mg (potency) of cefadroxil RS, add water to make exactly 200 mL, and use this solution as the standard solution. Perform the test as directed under the Assay of Cefadroxil Hydrate.

Potency (μg) of cefadroxil ($C_{16}H_{17}N_3O_5S$)

$$= \text{Potency (μg) of cefadroxil RS} \times \frac{A_T}{A_S} \times \frac{5}{2}$$

Packaging and storage Preserve in tight containers.

Cefadroxil for Syrup
시럽용 세파드록실

Cefadroxil for Syrup is a preparation for syrup, which is dissolved before use, and contains NLT 95.0% and NMT 110.0% of the labeled amount of cefadroxil ($C_{16}H_{17}N_3O_5S$: 363.39).

Method of preparation Prepare as directed under Syrups, with Cefadroxil Hydrate.

Identification Weigh an amount of Cefadroxil for Syrup, equivalent to 10 mg (potency) of cefadroxil according to the labeled amount, and dissolve in water to make 500 mL. Determine the absorption spectrum of the solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 228 nm and 232 nm and between 261 nm and 265 nm.

pH Dissolve Cefadroxil for Syrup according to the label; the pH of the resulting solution is between 4.5 and 6.0.

Water NMT 2.0% (0.5 g, volumetric titration, direct titration).

Dissolution Weigh accurately an amount of Cefadroxil for Syrup, equivalent to about 0.1 g (potency) of cefadroxil according to the labeled amount, and perform the test at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium (add the sample to be dispersed in the dissolution medium). Take NLT 20 mL of the dissolved solution 15 minutes after starting the test and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 10 mL of the filtrate, take exactly 4 mL of the subsequent filtrate, add water to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately 22 mg (potency) of cefadroxil RS and add water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 50 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution at the wavelength of 263 nm as directed under the Ultraviolet-visible Spectroscopy, using water as a control solution. Meets the requirements if the dissolution rate of Cefadroxil for Syrup in 15 minutes is NLT 85%.

Dissolution rate (%) with respect to the labeled amount of cefadroxil ($C_{16}H_{17}N_3O_5S$)

$$= \frac{Potency\ (mg)\ of\ \text{cefadroxil RS}}{Amount\ (g)\ of\ \text{Cefadroxil for Syrup taken}} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 450$$

C: Labeled amount [mg (potency)]of cefadroxil ($C_{16}H_{17}N_3O_5S$) per g

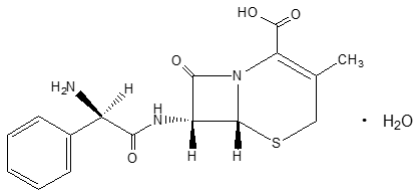
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately an amount of Cefadroxil for Syrup, equivalent to about 50 mg (potency) of cefadroxil according to the labeled amount, dissolve in water to make exactly 500 mL, and use this solution as the test solution. Separately, weigh accurately 20 mg (potency) of cefadroxil RS, add water to make exactly 200 mL, and use the solution as the standard solution. Perform the test with each 10 μL of the test solution and the standard solution as directed under the Assay under Cefadroxil Hydrate.

Potency (μg) of cefadroxil ($C_{16}H_{17}N_3O_5S$)
= Potency (μg) of cefadroxil RS × A_T / A_S × 5 / 2

Packaging and storage Preserve in tight containers.

Cefalexin Hydrate
세팔렉신수화물



$C_{16}H_{17}N_3O_4S \cdot H_2O$: 365.40
(6*R*,7*R*)-7-[(2*R*)-2-Amino-2-phenylacetamido]-3-methyl-3,4-didehydrocepham-4-carboxylic acid monohydrate [*23325-78-2*]

Cefalexin Hydrate contains NLT 950 μg (potency) and NMT 1030 μg (potency) of cefalexin ($C_{16}H_{17}N_3O_4S$: 347.39) per mg, calculated on the anhydrous basis.

Description Cefalexin Hydrate occurs as white to light yellowish white crystals or a crystalline powder.
It is sparingly soluble in water, slightly soluble in methanol and practically insoluble in ethanol(95) or in *N*,*N*-dimethylformamide.
It is hygroscopic.

Identification (1) Determine the absorption spectra of solutions of Cefalexin Hydrate and cefalexin hydrate RS (3 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cefalexin Hydrate and cefalexin hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Determine the ^1H spectrum of a solution of Cefalexin Hydrate in heavy water for nuclear magnetic resonance spectroscopy (1 in 200), using 3-(trimethylsilyl)propanesulfonic acid sodium salt for nuclear magnetic resonance spectroscopy as the internal standard, as directed under the Nuclear Magnetic Resonance Spectroscopy; it exhibits signal A of a single line at around δ 1.8 ppm and signal B of a single line or multiple lines at the tip at around δ 7.5 ppm. The integrated intensity ratio of signals A and B is 3 : 5.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between +144° and +158° (0.125 g, calculated on the anhydrous basis, water, 25 mL, 100 mm).

pH Dissolve 0.5 g of Cefalexin Hydrate in 10 mL of water; the pH of this solution is between 3.0 and 5.5.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Cefalexin Hydrate according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Prepare the test solution by suspending 1.0 g of Cefalexin Hydrate in 10 mL of *N*,*N*-dimethylformamide and perform the test (NMT 2 ppm).

(3) ***Dimethylaniline***—Weigh accurately about 1.0 g of Cefalexin Hydrate, add 5 mL of 1 mol/L sodium hydroxide TS and 1 mL of the internal standard solution, centrifuge, if necessary, and use the clear supernatant as the test solution. Separately, weigh accurately about 50 mg of dimethylaniline, add 2.0 mL of hydrochloric acid, and add water to make 50 mL. Pipet 5.0 mL of this solution and add water to make exactly 250 mL. Pipet 1.0 mL of this solution, add 5.0 mL of 1 mol/L sodium hydroxide TS, add 1.0 mL of the internal standard solution, centrifuge, if necessary, and use the clear supernatant as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of dimethylaniline to the peak area of the internal standard from the test solution and the standard solution, respectively (NMT 20 ppm).

$$\text{Content (ppm) of dimethylaniline} = \text{Amount (mg) of dimethylaniline taken} \times \frac{Q_T}{Q_S} \times \frac{Purity\ (\%)\ of\ \text{dimethylaniline}}{Amount\ (\text{mg})\ of\ Cefalexin\ Hydrate\ taken} \times 4$$

Internal standard solution—Dissolve 50.0 mg of naphthalene in cyclohexane to make 50 mL. To 5.0 mL of this solution, add cyclohexane to make 100 mL, and use this solution as the internal standard solution.

Operating conditions

Detector: A flame ionization detector

Column: A column about 2 mm in internal diameter and about 2 m in length, packed with diatomaceous earth

for gas chromatography, which is coated with 50% phenyl-50% methylpolysiloxane for gas chromatography equivalent to 3% of the mass of the diatomaceous earth for gas chromatography.

Column temperature: 120 °C

Temperatures of the sample injection port and the detector: 150 °C

Carrier gas: Nitrogen

Flow rate: 30 mL/min

(4) ***Related substances***—Weigh accurately about 25 mg of Cefalexin Hydrate, dissolve in a solution of potassium dihydrogen phosphate (9 in 500) to make 5 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add a solution of potassium dihydrogen phosphate (9 in 500) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Calculate the peak area from each solution according to the automatic integration method. If necessary, perform the test with 20 μL of the potassium dihydrogen phosphate solution (9 in 500) in the same manner as directed above to correct the variation of the baseline; the area of any peak other than the peak of cefalexin obtained from the test solution is not larger than the peak of cefalexin from the standard solution. Also, the sum of the areas of peaks other than the peak of cefalexin obtained from the test solution that is larger than 1/50 of the peak area of cefalexin obtained from the standard solution is not larger than 5 times the peak area of cefalexin from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: Dissolve 1.0 g of sodium 1-pentanesulfonate in a mixture of 1000 mL of water and 15 mL of triethylamine, and add phosphoric acid to adjust the pH to 2.5.

Mobile phase B: Dissolve 1.0 g of sodium 1-pentanesulfonate in a mixture of 300 mL of water and 15 mL of triethylamine, and add phosphoric acid to adjust the pH to 2.5. To this solution, add 350 mL of acetonitrile and 350 mL of methanol.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0	100	0
0 - 1	100	0
1 - 34.5	100 → 0	0 → 100
34.5 - 35.5	0	100

Flow rate: 1.0 mL/min

System suitability

Detection sensitivity: Pipet 2 mL of the standard solution and add the potassium dihydrogen phosphate solution (9 in 500) to make exactly 100 mL. Proceed with 20 μL of this solution according to the above conditions; the peak area of cefalexin is equivalent to 1.8% to 2.2% of the peak area of cefalexin obtained from 20 μL of the standard solution.

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the number of theoretical plates and the symmetry factor of the peak of cefalexin are NLT 150000 and between.0.8 and 1.3, respectively.

System repeatability: Repeat the test 3 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviations of the retention time and the peak area of cefalexin are NMT 2.0%.

Time span of measurement: About 2 times the retention time of cefalexin beginning after the solvent peak.

Water Between 4.0% and 8.0% (0.2 g, volumetric titration, direct titration).

Assay Weigh accurately about 0.1 g (potency) each of Cefalexin Hydrate and cefalexin RS, dissolve each in 0.1 mol/L phosphate buffer solution (pH 4.5), and add water to make exactly 100 mL. Pipet 10 mL each of these solutions, add exactly 5.0 mL each of the internal standard solutions, add 0.1 mol/L phosphate buffer solution (pH 4.5) to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of cefalexin to that of the internal standard, respectively.

$$\text{Potency (μg) of cefalexin } (C_{16}H_{17}N_3O_4S) = \text{Potency (μg) of cefalexin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of *m*-hydroxyacetophenone in 0.1 mol/L phosphate buffer solution (pH 4.5) (1 in 1500).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with

octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 6.8 g of potassium dihydrogen phosphate in 1000 mL of water and add diluted phosphoric acid (3 in 500) to adjust the pH to 3.0. To 800 mL of this solution, add 200 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of cefalexin is about 7 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; cefalexin and the internal standard are eluted in this order with the resolution between these peaks being NLT 6.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area ratio of cefalexin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Cefalexin Capsules
세팔렉신 캡슐

Cefalexin Capsules contain NLT 93.0% and NMT 107.0% of the labeled amount of cefalexin ($C_{16}H_{17}N_3O_4S$: 347.39).

Method of preparation Prepare as directed under Capsules, with Cefalexin Hydrate.

Identification Weigh an amount of Cefalexin Capsules, equivalent to 70 mg (potency) of cefalexin, according to the labeled amount, add 25 mL of water, shake vigorously for 5 minutes to mix, and then filter. Pipet 1 mL of the filtrate, and add water to make 100 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 260 nm and 264 nm.

Water NMT 10.0% (0.1 g, volumetric titration, direct titration).

Dissolution Perform the test with 1 capsule of Cefalexin Capsule at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take NLT 20 mL of the dissolved solution 60 minutes after starting the test, and filter through a membrane filter with a pore size of NMT 0.5 μm. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add water to make *V'* mL of a solution containing about 22 μg (potency) of cefalexin ($C_{16}H_{17}N_3O_4S$) according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 22 mg (potency) of cefalexin RS, and dissolve in water to make exactly 50 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength at about 262 nm as directed under Ultraviolet-visible Spectrophotometry. It meets the requirements when the dissolution rate of Cefalexin Capsules in 60 minutes is NLT 80%.

Dissolution rate (%) of the labeled amount of cefalexin ($C_{16}H_{17}N_3O_4S$)

$$= \text{Potency (mg) of cefalexin RS} \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 90$$

C: Labeled amount (mg) of cefalexin ($C_{16}H_{17}N_3O_4S$) in 1 capsule

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following procedure.

Take 1 capsule of Cefalexin Capsule, add 3*V*/5 mL of 0.1 mol/L phosphate buffer solution (pH 4.5), shake vigorously to mix, then add 0.1 mol/L phosphate buffer solution (pH 4.5) to make exactly *V* mL of a solution containing about 1.25 mg (potency) of cefalexin per mL. Then, centrifuge this solution, pipet 2 mL of the supernatant, add exactly 10 mL of the internal standard solution, and add 0.1 mol/L phosphate buffer solution (pH 4.5) to make exactly 100 mL. Use this solution as the test solution. Separately, weigh accurately about 25 mg (potency) of cefalexin RS, and dissolve in 0.1 mol/L phosphate buffer solution (pH 4.5) to make exactly 100 mL. Pipet 10 mL of this solution, add exactly 10 mL of the internal standard solution, add 0.1 mol/L phosphate buffer solution to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, of cefalexin to the peak area of the internal standard, respectively.

Amount [mg (potency)] of cefalexin ($C_{16}H_{17}N_3O_4S$)

$$= W_S \times \frac{Q_T}{Q_S} \times \frac{V}{20}$$

W_S: Amount [mg (potency)] of cefalexin RS

Assay Weigh accurately the mass of NLT 20 Cefalexin Capsules, weigh accurately an amount equivalent to about 0.1 g of cefalexin, previously powdered, add 60 mL of 0.1 mol/L phosphate buffer solution (pH 4.5), and shake vigorously for 10 minutes. Then, add 0.1 mol/L phosphate buffer solution (pH 4.5) to make exactly 100 mL, and centrifuge. Pipet 2 mL of the supernatant, add exactly 10 mL of the internal standard solution, add 0.1 mol/L phosphate buffer solution (pH 4.5) to make exactly 100 mL, and use this solution as the test solution. Per-

form the test as directed under the Assay of Cefalexin for Syrup.

Packaging and storage Preserve in tight containers.

Cefalexin for Syrup
시럽용 세팔렉신

Cefalexin for Syrup is a preparation for syrup, which is dissolved or suspended before use, and contains NLT 90.0% and NMT 110.0% of the labeled amount of cefalexin ($C_{16}H_{17}N_3O_4S$: 347.39).

Method of preparation Prepare as directed under Syrups, with Cefalexin Hydrate.

Identification Weigh an amount of Cefalexin for Syrup, equivalent to 3 mg (potency) of cefalexin according to the labeled amount, and dissolve in water to make 100 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 260 nm and 264 nm.

pH Dissolve Cefalexin for Syrup according to the label; the pH of the resulting solution is between 3.0 and 6.0.

Water NMT 5.0% (0.4 g, volumetric titration, direct titration).

Uniformity of dosage units (distribution) Perform the procedure for content uniformity according to the following procedure; it meets the requirements. Take the entire content of 1 pack of Cefalexin for Syrup, add 3*V*/5 mL of 0.1 mol/L phosphate buffer solution (pH 4.5), and mix vigorously for 10 minutes. Add 0.1 mol/L phosphate buffer solution (pH 4.5) to make exactly *V* mL of a solution containing about 1 mg (potency) of cefalexin per mL, and centrifuge. Pipet 2 mL of the supernatant, add exactly 10 mL of the internal standard solution, add 0.1 mol/L phosphate buffer solution (pH 4.5) to make 100 mL, and use this solution as the test solution. Proceed as directed under the Assay and perform the test.

Amount [mg (potency)] of cefalexin ($C_{16}H_{17}N_3O_4S$)
$$= W_S \times \frac{Q_T}{Q_S} \times \frac{V}{20}$$

W_S: Amount [mg (potency)] of cefalexin RS

Internal standard solution—A solution of *m*-hydroxyacetophenone in 0.1 mol/L phosphate buffer solution (pH 4.5) (1 in 15000).

Dissolution Weigh accurately an amount of Cefalexin for Syrup, equivalent to about 0.25 g (potency) of cefalexin according to the labeled amount, and perform the test at 50 revolutions per minute according to Method 2, using 900 mL of water as the dissolution medium. Take NLT 20 mL of the dissolved solution 15 minutes after starting the test and filter through a membrane filter with a pore size not exceeding 0.5 μm. Discard the first 10 mL of the filtrate, pipet 2 mL of the subsequent filtrate, add water to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately an amount of cefalexin RS, equivalent to about 22 mg (potency), and dissolve in water to make exactly 50 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution at the absorbance maximum wavelength of around 262 nm, as directed under the Ultraviolet-visible Spectroscopy. It meets the requirements if the dissolution rate of Cefalexin for Syrup in 15 minutes is NLT 80%.

Dissolution rate (%) with respect to the labeled amount cefalexin ($C_{16}H_{17}N_3O_4S$)
$$= \frac{W_S}{W_T} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 1125$$

W_S: Amount [mg (potency)] of cefalexin RS
W_T: Amount (g) of Cefadroxil for Syrup taken
C: Labeled amount [mg (potency)] of cefalexin ($C_{16}H_{17}N_3O_4S$) per g

Assay Powder Cefalexin for Syrup, if necessary, and weigh accurately a portion of the powder, equivalent to about 0.1 g (potency) of cefalexin, add 60 mL of 0.1 mol/L phosphate buffer solution (pH 4.5), and shake vigorously for 10 minutes. Add 0.1 mol/L phosphate buffer solution (pH 4.5) to make exactly 100 mL and centrifuge. Pipet 2 mL of the supernatant, add exactly 10 mL of the internal standard solution, add 0.1 mol/L phosphate buffer solution (pH 4.5) to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg (potency) of cefalexin RS and add 0.1 mol/L phosphate buffer solution (pH 4.5) to make exactly 100 mL. Take exactly 10 mL of this solution, add exactly 10 mL of the internal standard solution, add 0.1 mol/L of phosphate buffer solution (pH 4.5) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with each 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the ratios, Q_T and Q_S, of the peak area of cefalexin to that of the internal standard.

Potency (μg) of cefalexin ($C_{16}H_{17}N_3O_4S$)
$$= \text{Potency (μg) of cefalexin RS} \times \frac{Q_T}{Q_S} \times 5$$

Internal standard solution—A solution of *m*-hydroxyacetophenone in 0.1 mol/L phosphate buffer solution (pH 4.5) (1 in 15000).

Operating conditions

Detector: An ultraviolet absorption photometer

(wavelength: 254 nm).

Column: A stainless steel column, about 3.0 mm in internal diameter and 75 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dilution 2.72 g of potassium dihydrogen phosphate in 1000 mL of water and adjust the pH to 3.0 with diluted phosphoric acid (3 in 500). Add 200 mL of methanol to 800 mL of this solution.

Flow rate: Adjust the flow rate so that the retention time of cefalexin is about 6 minutes.

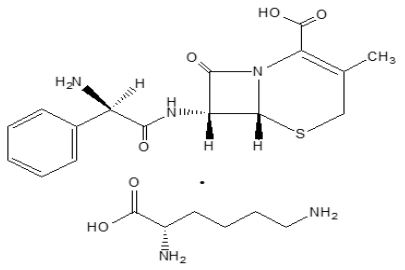
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; cefalexin and the internal standard are eluted in this order, with the resolution being NLT 8.

System repeatability: Repeat the test 6 times with each 10 μL of the standard solution according to the above operating conditions; the relative standard deviation of the ratios of the peaks of cefalexin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Cefalexin Lysinate
세팔렉신리시네이트



$C_{16}H_{17}N_3O_4S \cdot C_6H_{14}N_2O_2$: 493.58

L-Lysine (6*R*,7*R*)-7-[[(2*R*)-2-amino-2-phenylacetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (1:1), [*53950-14-4*]

Cefalexin Lysinate contains NLT 634 μg (potency) and NMT 715 μg (potency) of cefalexin ($C_{16}H_{17}N_3O_4S$: 347.39) per mg.

Description Cefalexin Lysinate occurs as a white to pale yellow crystalline powder.
It is freely soluble in water.

Identification (1) Determine the infrared spectra of Cefalexin Lysinate and cefalexin lysinate RS as directed in the potassium bromide disk method under the Mid-infrared spectroscopy; both spectra exhibit same intensities of absorption at the same wavenumbers.

(2) Weigh a suitable amount each of Cefalexin Lysinate and cefalexin lysinate RS, dissolve each in water to obtain solutions having known concentrations of 20% (potency), and use these solutions as the test solution and the standard solutions, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of acetonitrile-water (3 : 1) as the developing solvent. Spray evenly ninhydrin TS on the thin-layer chromatographic plate; the R_f values of the spots obtained from the test solution and the standard solution are the same.

Optical rotation $[\alpha]_D^{20}$: Between +98° and +107° (2.5 g, calculated on the anhydrous basis, potassium hydrogen phthalate buffer solution (pH 4.4), 25 mL).

Melting point Between 168 and 174 °C.

pH Dissolve Cefalexin Lysinate in water to obtain a solution having known concentration of 0.1 g/mL. the pH of this solution is between 7.5 and 8.5.

Water NMT 0.8% (1.0 g, volumetric titration, direct titration).

Absorbance $E_{1cm}^{1\%}$ (260 nm): Between 145 and 170 (2 mg, water, 100 mL).

Sterility It meets the requirements when Cefalexin Lysinate is used for manufacturing sterile preparations. However, it is excluded when there is a terminal sterilization process in the manufacturing process of sterile preparations.

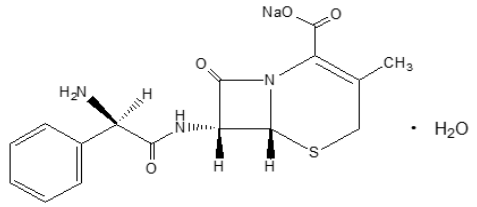
Pyrogen It meets the requirements when Cefalexin Lysinate is used for manufacturing sterile preparations. However, perform the test by injecting 1 mL of a solution prepared by adding physiological saline injection to obtain a solution having known concentration of 7 mg (potency) per mL of Cefalexin Lysinate per kg of the body weight of a rabbit.

Assay Weigh accurately about 0.15 g (potency) of Cefalexin Lysinate, dissolve in water to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.15 g (potency) of cefalexin RS, dissolve in water to make exactly 100 mL, and use this solution as the standard solution. Pipet 10 mL each of the test solution and the standard solution, put them into a 100-mL glass-stoppered flask, add 5 mL each of 1 mol/L sodium hydroxide TS, and allow to stand for 20 minutes. Then, add exactly 20 mL of a freshly prepared buffer solution (containing 5.44 w/v%) of sodium acetate and 2.4 w/v% of acetic acid(100)), exactly 5 mL of 1 mol/L hydrochloric acid and exactly 25 mL of 0.01 mol/L io-

dine solution, close the stopper, and allow to stand in the dark for 20 minutes. Titrate the excess iodine with 0.02 mol/L sodium thiosulfate VS (Indicator: 0.2 ~ 0.5 mL of starch solution). Separately, pipet 10 mL each of the test solution and the standard solution, add exactly 20 mL of a freshly prepared buffer solution (containing 5.44 w/v% of sodium acetate and 2.4 w/v% of acetic acid(100)) and exactly 25 mL of 0.01 mol/L iodine solution, and perform a blank test in the same manner as directed above to make any necessary correction.

Packaging and storage Preserve in tight containers.

Cefalexin Sodium Hydrate
세팔렉신나트륨수화물



$C_{16}H_{16}N_3NaO_4S \cdot H_2O$: 387.39

(6*R*,7*R*)-7-[[(2*R*)-2-Amino-2-phenylacetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1) monohydrate, [*15686-71-2, calculated on the anhydrous basis*]

Cefalexin Sodium Hydrate contains NLT 845 μg (potency) of cefalexin ($C_{16}H_{17}N_3O_4S$: 347.39) per mg, calculated on the anhydrous basis.

Description Cefalexin Sodium Hydrate occurs as a white to almost white crystalline powder and is odorless. It is freely soluble in water.

Identification (1) Determine the infrared spectra of Cefalexin Sodium Hydrate and cefalexin sodium hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Cefalexin Sodium Hydrate responds to the Qualitative Analysis 1) for sodium salt.

Crystallinity It meets the requirements as directed under the Crystallinity.

pH Dissolve Cefalexin Sodium Hydrate in water to obtain a solution having known concentration of 10 mg/mL; the pH of this solution is between 7.5 and 10.0.

Water NMT 5.5% (0.2 g, volumetric titration, direct titration).

Sterility It meets the requirements when Cefalexin Sodium Hydrate is used for manufacturing sterile preparations. However, it is excluded when there is a terminal sterilization process in the manufacturing process of sterile preparations.

Pyrogen It meets the requirements when Cefalexin Sodium Hydrate is used for manufacturing sterile preparations. In this case, perform the test by injecting 1 mL of a solution prepared by adding Isotonic Sodium Chloride Injection to obtain a solution having known concentration of 20 mg (potency) per mL of Cefalexin Sodium Hydrate per kg of the body weight of a rabbit.

Assay Weigh accurately about 50 mg (potency) each of Cefalexin Sodium Hydrate and cefalexin sodium hydrate RS and dissolve each in water to make exactly 50 mL. Pipet 5 mL each of these solutions, add 5.0 mL of the internal standard solution and water to make exactly 50 mL and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and calculate the peak area ratios, Q_T and Q_S, of cefalexin to the peak area of the internal standard, respectively.

$$\text{Potency (μg) of cefalexin } (C_{16}H_{17}N_3O_4S) = \text{Potency (μg) of cefalexin RS} \times (Q_T/Q_S)$$

Internal standard solution—A solution of *m*-hydroxyacetophenone in 0.1 mol/L phosphate buffer solution (pH 4.5) (1 in 1500).

Operating conditions

Detector: An ultraviolet-visible spectrometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 - 10 μm in particle diameter).

Mobile phase: Adjust the pH of 0.05 mol/L potassium dihydrogen phosphate solution to 3.0 with phosphoric acid. To 800 mL of this solution, add 200 mL of methanol.

Packaging and storage Preserve in tight containers.

Cefalexin Sodium for Injection
주사용 세팔렉신나트륨

Cefalexin Sodium for Injection, as an injection that is dissolved upon use, contains NLT 90.0% and NMT 120.0% of the labeled amount of cefalexin ($C_{16}H_{17}N_3O_4S$: 347.39).

Method of preparation Prepare as directed under Injections, with Cefalexin Sodium Hydrate.

Description Cefalexin Sodium for Injection occurs as a white crystalline powder or a powder.

Identification Perform the test as directed under the Identification (1) under Cefalexin Sodium Hydrate.

pH Dissolve Cefalexin Sodium for Injection in water to make 10 mg/mL; the pH of the solution is between 7.5 and 10.0.

Water NMT 5.5% (0.2 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Pyrogen It meets the requirements when performing the test by injecting 1 mL per kg of the body weight of a rabbit as directed under the Pyrogen.

Particulate contamination: Visible particles Meets the requirements.

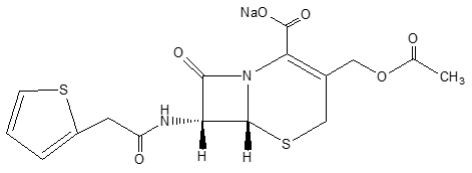
Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay under Cefalexin Sodium Hydrate. However, weigh accurately about 0.1 g (potency) according to the labeled potency of Cefalexin Sodium for Injection, dissolve in water, add water to make exactly 100 mL, then filter. Pipet 5 mL of the filtrate, add 5 mL of the internal standard solution and water to make exactly 50 mL, and use this solution as the test solution.

Packaging and storage Preserve in hermetic containers.

Cefalotin Sodium
세팔로틴나트륨



$C_{16}H_{15}N_2NaO_6S_2$: 418.42

Sodium (6*R*,7*R*)-7-[2-(thiophen-2yl)acetamido]-3-acetyloxymethyl-3,4-didehydrocepham-4-carboxylate [*58-71-9*]

Cefalotin Sodium contains NLT 920 μg (potency) and NMT 980 μg (potency) of cefalotin ($C_{16}H_{16}N_2O_6S_2$: 396.44) per mg, calculated on the anhydrous basis.

Description Cefalotin Sodium occurs as white to light yellowish white crystals or a crystalline powder.
It is freely soluble in water, slightly soluble in methanol, very slightly soluble in ethanol(95) and practically insoluble in ether.

Identification (1) Determine the absorption spectra of solutions of Cefalotin Sodium and cefalotin sodium RS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cefalotin Sodium and cefalotin sodium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Determine the ^1H spectrum of a solution of Cefalotin Sodium in heavy water for nuclear magnetic resonance spectroscopy (1 in 10), using 3-(trimethylsilyl)propanesulfonic acid sodium salt for nuclear magnetic resonance spectroscopy as the internal standard, as directed under the Nuclear Magnetic Resonance Spectroscopy; it exhibits signal A of a single line at around δ 2.1 ppm, signal B of a single line or different lines at the tip at around δ 3.9 ppm and signal C of multiple lines at around δ 7.0 ppm. The integrated intensity ratio of signals A, B and C is 3 : 2. : 2.

(4) Cefalotin Sodium responds to the Qualitative Analysis (1) for sodium salt.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between +124 ° and +134° (5.0 g, calculated on the anhydrous basis, water, 100 mL, 100 mm).

pH Dissolve 1.0 g of Cefalotin Sodium in 10 mL of water; the pH of this solution is between 4.5 and 7.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Cefalotin Sodium in 10 mL of water; the resulting solution is clear. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at 450 nm is NMT 0.20.

(2) ***Heavy metals***—Proceed with 1.0 g of Cefalotin Sodium according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Prepare the test solution with 1.0 g of Cefalotin Sodium according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Pipet 1 mL of the standard solution obtained in the Assay, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate each peak area by the automatic integration method; the area of any peak other than the peak of cefalotin obtained from the test solution is not

larger than the peak area of cefalotin from the standard solution, and the total area of the peaks other than the peak of cefalotin obtained from the test solution is not larger than 3 times the peak area of cefalotin from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

Detection sensitivity: Pipet 1 mL of the standard solution and add the mobile phase to make exactly 10 mL. Proceed with 10 μL of this solution according to the above conditions; the peak area of cefalexin is equivalent to 7% to 13% of the peak area of cefalexin obtained from 10 μL of the standard solution.

System performance: Heat the standard solution at 90 °C for about 10 minutes. After cooling, pipet 2.5 mL of this solution and add the mobile solution to make exactly 100 mL. Proceed with 10 μL of this solution according to the above conditions; the resolution between the peak of cefalotin and the peak of the related substance having a relative retention time of about 0.5 with respect to cefalotin is NLT 9, and the symmetry factor of the peak of cefalotin is NMT 1.8.

System repeatability: Repeat the test 3 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of cefalotin is NMT 2.0%.

Time span of measurement: About 4 times the retention time of cefalotin.

Water NMT 1.0% (0.5 g, volumetric titration, direct titration).

Sterility It meets the requirements when Cefalotin Sodium is used for manufacturing sterile preparations. However, it is excluded when there is a terminal sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins Less than 0.13 EU/mg (potency) of cefalotin when used for manufacturing sterile preparations.

Assay Weigh accurately 25 mg (potency) each of Cefalotin Sodium and cefalotin sodium RS, dissolve each in the mobile phase to make exactly 25 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography and determine the peak areas, A_T and A_S, of cefalotin.

$$\text{Potency (μg) of cefalotin } (C_{16}H_{16}N_2O_6S_2) = \text{Potency (μg) of cefalotin sodium RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: Dissolve 17 g of sodium acetate trihydrate in 790 mL of water and add 0.6 mL of acetic acid(100). If necessary, adjust the pH to 5.9 with 0.1 mol/L sodium hydroxide TS or acetic acid(100). To this solution, add 150 mL of acetonitrile and 70 mL of ethanol(95).

Flow rate: Adjust the flow rate so that the retention time of cefalotin is about 12 minutes.

System suitability

System performance: Heat the standard solution on a steam bath at 90 ℃ for 10 minutes. After cooling, take 2.5 mL of this solution and add the mobile phase to make exactly 100 mL. Proceed with 10 μL of this solution under the above conditions; the resolution between the peak of cefalotin and the peak having the relative retention time of 0.5 with respect to cefalotin is NLT 9, and the symmetry factor of the peak of cefalotin is NMT 1.8.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of cefalotin is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Cefalotin Sodium for Injection
주사용 세팔로틴나트륨

Cefalotin Sodium for Injection, as an injection that is dissolved upon use, contains NLT 90.0% and NMT 120.0% of the labeled amount of cefalotin ($C_{16}H_{16}N_2O_6S_2$: 396.44)

Method of preparation Prepare as directed under Injections, with Cefalotin Sodium.

Description Cefalotin Sodium for Injection occurs as a white to pale yellowish white powder.

Identification Determine the absorption spectra of 0.0025% aqueous solutions of Cefalotin Sodium for Injection and cefalotin sodium RS as directed under the Ultraviolet-visible Spectroscopy at the wavelength of between 220 nm and 310 nm; both spectra exhibit maxima and minima at the same wavelengths.

pH Dissolve an amount of Cefalotin Sodium for Injection equivalent to 0.25 g (potency) of cefalotin in 1 mL of

water; the pH of this solution is between 5.0 and 7.5.

Water NMT 1.5% (1.0 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.13 EU per mg (potency) of cefalotin.

Particulate contamination: Visible particles Meets the requirements.

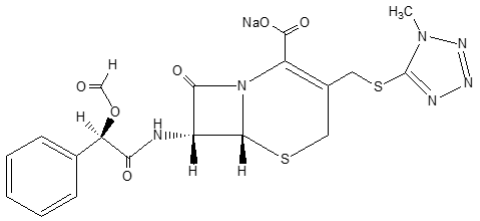
Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay under Cefalotin Sodium. Weigh accurately an appropriate amount according to the labeled potency of Cefalotin Sodium for Injection, dissolve in the mobile phase to obtain a solution having a known concentration of 1 mg (potency) per mL, and use this solution as the test solution.

Packaging and storage Preserve in hermetic containers.

Cefamandole Nafate
세파만돌나페이트



$C_{19}H_{17}N_6NaO_6S_2$: 512.50

Sodium (6*R*,7*R*)-7-[[(2*R*)-2-formyloxy-2-phenylacet]amido]-3-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanylmethyl]-3,4-didehydrocepham-4-carboxylate [*42540-40-9*]

Cefamandole Nafate contains NLT 810 μg and NMT 1000 μg (potency) of cefamandole ($C_{18}H_{18}N_6O_5S_2$: 462.51) per mg, calculated on the anhydrous basis.

Description Cefamandole Nafate occurs as a white powder.
It is soluble in water or in ethanol and very slightly soluble in ethyl acetate, in chloroform, in ether or in benzene.

Identification Dissolve 10 mg each of Cefamandole Nafate and cefamandole nafate RS in the developing solution to make 1 mL and use these solutions as the test solution and the standard solution, respectively. Use these solutions promptly after preparation. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solutions and the standard solutions on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, acetone, acetic acid(100) and water (5 : 2 : 1 : 1) to a distance of about three-fourths of the length of the plate, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values of the spots obtained from the test solution and the standard solution are the same.

pH Dissolve 1 g of Cefamandole Nafate in 10 mL of water; the pH of this solution is between 3.5 and 7.0.

Purity ***Heavy metals***—Proceed with 1.0 g of Cefamandole Nafate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Water NMT 2.0% (0.5 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins Less than 0.15 EU/mg (potency) of cefamandole, when used in the manufacturing sterile preparations.

Assay Weigh accurately 50 mg each of Cefamandole Nafate and cefamandole nafate RS, dissolve each in the mobile phase to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Prepare these solutions before use. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the sums of peak areas, S_T and S_S, of cefamandole and cefamandole nafate from the test solution and the standard solution, respectively.

$$\text{Potency (μg) of cefamandole } (C_{18}H_{18}N_6O_5S_2) = \text{Potency (μg) of cefamandole nafate RS} \times \frac{S_T}{S_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: To 350 mL of acetonitrile, add 600

mL of water and 100 μL of triethylamine, adjust the pH to 2.5 with phosphoric acid, and add water to make exactly 1000 mL.

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 20 μL of the system suitability solution according to the above conditions; cefamandole and cefamandole nafate are eluted in this order with the resolution between these peaks being NLT 7.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of cefamandole is NMT 1.0%.

System suitability solution—The standard solution heated at 60 ℃ for 30 minutes.

Packaging and storage Preserve in tight containers.

Cefamandole Nafate for Injection
주사용 세파만돌나페이트

Cefamandole Nafate for Injection, as an injection that is dissolved upon use, contains NLT 90.0% and NMT 120.0% of the labeled amount of cefamandole ($C_{18}H_{18}N_6O_5S_2$: 462.51).

Method of preparation Prepare as directed under Injections, with Cefamandole Nafate.

Description Cefamandole Nafate for Injection occurs as a white powder.

Identification Perform the test as directed under the Identification under Cefamandole Nafate.

pH Dissolve an amount of Cefamandole Nafate for Injection equivalent to 0.1 g (potency) of cefomandole in 1 mL of water and allow to stand for 30 minutes; the pH of this solution is between 6.0 and 8.0.

Water NMT 3.0% (0.2 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.15 EU per mg (potency) of cefamandole.

Particulate contamination: Visible particles Meets the requirements.

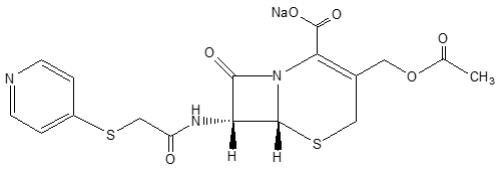
Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Perform the test according to the Assay under Cefamandole Nafate. However, weigh accurately an amount of Cefamandole Nafate for Injection equivalent to about 50 mg (potency) of cefamandole nafate, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately an amount equivalent to about 50 mg (potency) of cefamandole nafate RS, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Prepare before use.

Packaging and storage Preserve in hermetic containers.

Cefapirin Sodium
세파피린나트륨



$C_{17}H_{16}N_3NaO_6S_2$: 445.45

Sodium (6*R*,7*R*)-7-[2-(pyridin-4-yl)sulfanyl-acetamido]-3-acetyloxymethyl-3,4-didehydro-cepham-4-carboxylate [*24356-60-3*]

Cefapirin Sodium contains NLT 865 μg (potency) of cefapirin ($C_{17}H_{17}N_3O_6S_2$: 423.46) per mg, calculated on the anhydrous basis.

Description Cefapirin Sodium occurs as a white to yellowish white powder.

It is freely soluble in water, sparingly soluble in methanol, slightly soluble in ethanol(95) and practically insoluble in acetone.

Identification (1) Determine the absorption spectra of solutions of Cefapirin Sodium and cefapirin sodium RS (3 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cefapirin Sodium and cefapirin sodium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Determine the ^1H spectrum of a solution of Cefapirin Sodium in heavy water for nuclear magnetic resonance spectroscopy (1 in 10), using 3-(trimethylsilyl)propionic acid-d_4 sodium salt for nuclear magnetic resonance spectroscopy as the internal standard, as directed under the Nuclear Magnetic Resonance Spectroscopy; it exhibits signal A of a single line at around δ 2.2 ppm and signals B and C of multiple lines at around δ 7.3 ppm and δ 8.3 ppm, respectively. The integrated area

ratio of signals A, B and C is about 3 : 2 : 2.

(4) Cefapirin Sodium responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between +157° and +175° (2 g, calculated on the anhydrous basis, water, 100 mL, 100 mm).

pH Dissolve 0.1 of Cefapirin Sodium in 10 mL of water; the pH of this solution is between 6.5 and 8.5.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Cefapirin Sodium according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Prepare the test solution with 1.0 g of Cefapirin Sodium according to Method 3 and perform the test. Use a solution of magnesium nitrate in ethanol(95) (1 in 25) (NMT 2 ppm).

(3) ***Related substances***—Dissolve 0.1g of Cefapirin Sodium in a mixture of acetone and water (3 : 1) to make exactly 5 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of acetone and water (3 : 1) to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solutions and the standard solutions on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, acetone, water and acetic acid(100) (5 : 2 : 1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot and the spot of the starting point obtained from the test solution are not more intense than the spots from the standard solutions.

Water NMT 2.0% (0.7 g, volumetric titration, direct titration).

Sterility It meets the requirements when Cefapirin Sodium is used for manufacturing sterile preparations. However, it is excluded when there is a terminal sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins Less than 0.17 EU/mg (potency) of cefapirin when used for manufacturing sterile preparations.

Assay Weigh accurately about 0.1 g (potency) each of Cefapirin Sodium and cefapirin sodium RS, and dissolve each in 1% phosphate buffer solution (pH 6.0) to make exactly 100 mL. Then, pipet 5 mL of each solution, add exactly 5 mL each of the internal standard solution and 1% phosphate buffer solution (pH 6.0) to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratio, Q_T and Q_S, of cefapirin to the internal standard, respectively.

$$\text{Potency (μg) of cefapirin } (C_{17}H_{17}N_3O_6S_2) = \text{Potency (μg) of cefapirin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of vanillin (1 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of 0.05 mol/L sodium dihydrogen phosphate TS (pH 2.6) and acetonitrile (93 : 7).

Flow rate: Adjust the flow rate so that the retention time of cefapirin is about 7 minutes.

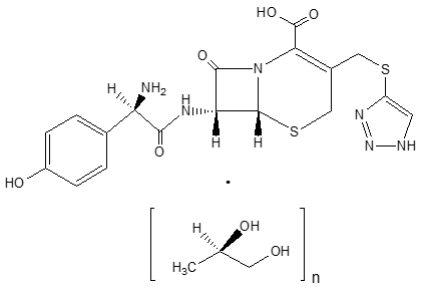
System suitability

System performance: Proceed with 20 μL of the standard solution under the above conditions; cefapirin and the internal standard are eluted in this order with the resolution between these peaks being NLT 10.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area ratio of cefapirin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in hermetic containers.

Cefatrizine Propylene Glycol
세파트리진프로필렌글리콜



$C_{18}H_{18}N_6O_5S_2 \cdot (C_3H_8O_2)n$

(6*R*,7*R*)-7-[[(2*R*)-2-Amino-2-(4-hydroxyphenyl)acet]amido]-3-[(2H-triazol-4-yl)sulfanylmethyl]-3,4-didehydrocepham-4-carboxylic acid (2*R*)-propane-1,2-diol [*51627-14-6*, cefatrizine]

Cefatrizine Propylene Glycol contains NLT 816 μg (potency) and NMT 876 μg (potency) of cefatrizine ($C_{18}H_{18}N_6O_5S_2$: 462.50) per mg, calculated on the anhydrous basis.

Description Cefatrizine Propylene Glycol occurs as a white to yellowish white powder.
It is sparingly soluble in water and practically insoluble in methanol or ethanol(95).

Identification (1) Determine the absorption spectra of solutions of Cefatrizine Propylene Glycol and cefatrizine propylene glycol RS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cefatrizine Propylene Glycol and cefatrizine propylene glycol RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Determine the ^1H spectrum of a solution of Cefatrzine Propylene Glycol in a mixture of heavy water for nuclear magnetic resonance spectroscopy and deuterated hydrochloric acid for nuclear magnetic resonance spectroscopy (3 : 1) (1 in 10), using 3-(trimethylsilyl)propionic acid-d_4 sodium salt for nuclear magnetic resonance spectroscopy as the internal standard, as directed under the Nuclear Magnetic Resonance Spectroscopy; it exhibits signal A of double lines at about δ 1.2 ppm, signal B of double lines at around δ 7.0 ppm, signal C of double lines at about δ 7.5 ppm and signal D of a single line at δ 8.3 ppm. The integrated intensity ratio of signals A : B : C : D is about 3 : 2 : 2 : 1.

Optical rotation $[\alpha]_D^{20}$: Between +52° and +58° (2.5 g, calculated on the anhydrous basis, 1 mol/L hydrochloric acid TS, 50 mL, 100 mm).

pH Dissolve 1 g of Cefatrzine Propylene Glycol in 10 mL of water; the pH of this solution is between 3.5 and 6.0.

Absorbance $E_{1cm}^{1\%}$ (270 nm): Between 190 and 220 (40 mg, water, 2000 mL).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Cefatrzine Propylene Glycol according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Prepare the test solution with 1.0 g of Cefatrzine Propylene Glycol according to Method 3 and perform the test (NMT 2 ppm). Use a solution of magnesium nitrate hexahydrate in ethanol(95) (1 in 25).

(3) ***Related substances***—Dissolve 25 mg of Cefatrzine Propylene Glycol in 5 mL of water and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solutions and the standard solutions on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate using a mixture of 1-butanol, water and acetic acid(100) (3 : 1 : 1) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Spray evenly ninhydrin-citric acid-acetic acid TS on the plate and heat at 100 °C for 10 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Water NMT 2.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g, platinum crucible).

Assay Weigh accurately 20 mg (potency) each of Cefatrizine Propylene Glycol and cefatrizine propylene glycol RS, dissolve each in water to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak areas, A_T and A_S, of cefatrizine from each solution.

$$\text{Potency (μg) of cefatrizine } (C_{18}H_{18}N_6O_5S_2) = \text{Potency (μg) of cefatrizine propylene glycol RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of a solution prepared by dissolving 1.36 g of potassium dihydrogen phosphate in water to make 1000 mL and methanol (17 : 3).

Flow rate: 1.0 mL/min

System suitability

System performance: Weigh accurately about 5 mg (potency) of cefadroxil and about 10 μL (potency) of Cefatrizine Propylene Glycol and dissolve in 50 mL of water. Proceed with 10 μL of this solution under the above conditions; cefadroxil and cefatrizine are eluted in this order with the resolution between these peaks being NLT 4.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of cefatrizine is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Cefatrizine Propylene Glycol Capsules
세파트리진프로필렌글리콜 캡슐

Cefatrizine Propylene Glycol Capsules contain NLT 90.0% and NMT 120.0% of the labeled amount of cefatrizine ($C_{18}H_{18}N_6O_5S_2$: 462.51).

Method of preparation Prepared as directed under Capsules, with Cefatrizine Propylene Glycol.

Identification Dissolve 3 mg (potency) of Cefatrizine Propylene Glycol Capsules in 2 mL of water, add 2 mL of dilute sodium hydroxide TS, mix, and allow to stand for 30 minutes. Then, add 1 mL of 1 mol/L hydrochloric acid TS; the resulting solution exhibits a yellow color.

Disintegration Meets the requirements.

Water NMT 4.0% (0.2 g, volumetric titration, direct titration).

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the contents of NLT 20 capsules of Cefatrizine Propylene Glycol Capsules, weigh accurately about 20 mg (potency) according to the labeled potency, dissolve in water to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg (potency) of cefatrizine propylene glycol RS, dissolve in water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak areas, A_T and A_S, of cefatrizine from each solution.

$$\text{Potency (μg) of cefatrizine } (C_{18}H_{18}N_6O_5S_2) = \text{Potency (μg) of cefatrizine propylene glycol RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of a solution prepared by dissolving 1.36 g of potassium dihydrogen phosphate in water to make 1000 mL and methanol (17 : 3).

Flow rate: 1.0 mL/min

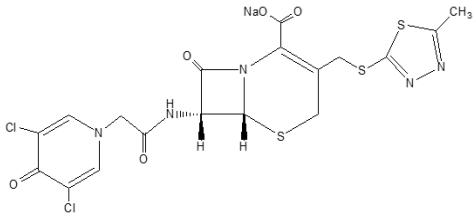
System suitability

System performance: Weigh accurately about 5 mg (potency) of cefadroxil and about 10 mg (potency) of Cefatrizine Propylene Glycol and dissolve in 50 mL of water. Proceed with 10 μL of this solution under the above conditions; cefadroxil and cefatrizine are eluted in this order with the resolution between these peaks being NLT 4.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of cefatrizine is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Cefazedone Sodium
세파제돈나트륨



$C_{18}H_{15}Cl_2N_5NaO_5S_3$: 570.43

(6*R*,7*R*)-7-[[2-(3,5-Dichloro-4-oxo-1(4*H*)-pyridinyl)acetyl]amino]-3-[[(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1), [*63521-15-3*]

Cefazedone Sodium contains NLT 865 μg (potency) of cefazedone ($C_{18}H_{15}Cl_2N_5O_5S_3$: 548.45) per mg, calculated on the anhydrous basis.

Description Cefazedone Sodium occurs as a white to yellowish white powder and is odorless.
It is very soluble in water, slightly soluble in ethanol, very slightly soluble in chloroform and practically insoluble in diethyl ether.
It is slightly hygroscopic.
It is easily changed by light.

Identification (1) Determine the infrared spectra of Cefazedone Sodium and cefazedone sodium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Cefazedone Sodium responds to the Qualitative Analysis for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between -3° and +4° (1% aqueous solution, 100 mm).

pH The pH of 1% aqueous solution of Cefazedone Sodium is between 4.5 and 6.5.

Absorption $E_{1cm}^{1\%}$ (278 nm): Between 490 and 570 (2.0 mg, calculated as an anhydrous basis, water, 100 mL).

Purity ***Heavy metals***—Proceed with 1.0 g of

Cefazedone Sodium according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, it is excluded in cases where there is a final sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins Less than 0.016 EU/mg (potency) of cefazedone, when used in the manufacturing of sterile preparations.

Water NMT 7.0% (0.1 g, volumetric titration, direct titration).

Residue on ignition Between 12.0% and 12.8% (calculated on the anhydrous basis).

Assay Weigh accurately about 50 mg (potency) each of Cefazedone Sodium and cefazedone sodium RS and dissolve each in the mobile phase to make exactly 50 mL. Pipet 1 mL each of these solutions, add the mobile phase to make exactly 50 mL, and use these solutions as the test solution and the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and calculate the peak areas, A_T and A_S, of cefazedone, respectively, from each solution.

Potency (μg) of cefazedone ($C_{18}H_{15}Cl_2N_5O_5S_3$)
= Potency (μg) of cefazedone sodium RS× $\frac{A_T}{A_S}$ ×0.96

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 278 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of 0.02 mol/L ammonium phosphate buffer (pH 5.0) and acetonitrile (17 : 3).

Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of Cefazedone Sodium is NMT 1.0%.

0.02 mol/L ammonium phosphate buffer (pH 5.0)— Dissolve 2.3 g of ammonium dihydrogen phosphate in 980 mL of water, adjust the pH to 5.0 with 0.1 mol/L sodium hydroxide solution, and add water to make 1000 mL.

Packaging and storage Preserve in light-resistant, tight containers.

Cefazedone Sodium for Injection
주사용 세파제돈나트륨

Cefazedone Sodium for Injection, as an injection that is dissolved upon use, contains NLT 90.0% and NMT 120.0% of the labeled amount of cefazedone ($C_{18}H_{15}Cl_2N_5O_5S_3$: 548.45).

Method of preparation Prepare as directed under Injections, with Cefazedone Sodium.

Description Cefazedone Sodium for Injection occurs as a white to yellowish white powder.

Identification Perform the test as directed under the Identification (2) under Cefazedone Sodium.

Optical rotation $[\alpha]_D^{20}$: Between -3° and +10° (1% aqueous solution, 100 mm).

pH Dissolve Cefazedone Sodium for Injection according to the labeled amount; the pH of this solution is between 4.5 and 6.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.1 EU per mg of cefazedone sodium.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

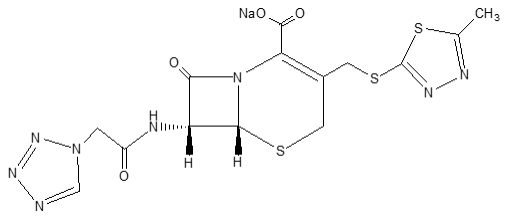
Uniformity of dosage units Meets the requirements.

Water NMT 2.5% (0.5 g, volumetric titration, direct titration)

Assay Perform the test as directed under the Assay under Cefazedone Sodium. However, weigh accurately each 50 mg (potency) of Cefazedone Sodium for Injection and cefazedone sodium RS, and add each the mobile phase to make exactly 100 mL. Take 5 mL each of these solutions, add each the mobile phase to make exactly 100 mL, and use these solution as the test solution and the standard solution.

Packaging and storage Preserve in light-resistant, hermetic containers.

Cefazolin Sodium
세파졸린나트륨



$C_{14}H_{13}N_8NaO_4S_3$: 476.49
Sodium (6*R*,7*R*)-3-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanylmethyl]-7-[[2-(tetrazol-1-yl)acet] amido]-3,4-didehydrocepham-4-carboxylate [*27164-46-1*]

Cefazolin Sodium contains NLT 900 μg and NMT 975 μg (potency) of cefazolin ($C_{14}H_{14}N_8O_4S_3$: 454.51) per mg, calculated on the anhydrous basis.

Description Cefazolin Sodium occurs as white to light yellowish white crystals or a crystalline powder.
It is freely soluble in water or in formamide, slightly soluble in methanol and practically insoluble in ethanol(95).

Identification (1) Determine the absorption spectra of solutions of Cefazolin Sodium and cefazolin sodium RS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cefazolin Sodium and cefazolin sodium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Determine the ^1H spectrum of a solution of Cefazolin Sodium in heavy water for nuclear magnetic resonance spectroscopy (1 in 10), using sodium 3-(trimethylsilyl)propionic acid-d_4 sodium salt for nuclear magnetic resonance spectroscopy as the internal standard, as directed under the Nuclear Magnetic Resonance Spectroscopy; it exhibits signals A and B of single lines at around δ 2.7 ppm and around δ 9.3 ppm, respectively. The ratio of integrated intensity of signals A and B is about 3 : 1.

(4) Cefazolin Sodium responds to the Qualitative Analysis for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between -19° and -23° (2.5 g, calculated on the anhydrous basis, water, 25 mL, 100 mm).

pH Dissolve 1 g of Cefazolin Sodium in 10 mL of water; the pH of this solution is between 4.8 and 6.5.

Absorption $E_{1cm}^{1\%}$ (272 nm): Between 264 and 292 (1.6 mg, water 100 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Cefazolin Sodium in 10 mL of water; the resulting solution is colorless to pale yellow and clear. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at 420 nm is NMT 0.35. The test should be performed within 10 minutes after preparing the solution.

(2) ***Heavy metals***—Proceed with 2.0 g of Cefazolin Sodium according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Prepare the test solution with 2.0 g of Cefazolin Sodium according to Method 3 and perform the test. When preparing the test solution, add 10 mL of a solution of magnesium nitrate in ethanol(95) (1 in 50) and then 1.5 mL of strong hydrogen peroxide, and ignite (NMT 1 ppm).

(4) ***Related substances***—Dissolve 0.10 g of Cefazolin Sodium in 20.0 mL of 0.1 mol/L phosphate buffer (pH 7.0) and use this solution as the test solution. Prepare the test solution immediately before use. Take 5 μL of the test solution and perform the test as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of the test solution by the automatic integration method and calculate the amount of related substances by the percentage peak area method; the amount of the related substance having a relative retention time of about 0.2 with respect to cefazolin and of each related substance other than cefazolin is NMT 1.5%, and the total amount of related substances other than cefazolin is NMT 2.5%. For the area of the peak having the relative retention time of about 0.2 with respect to the retention time of cefazolin, multiply the area obtained by the automatic integration method by the correction factor,1.43.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

Detection sensitivity: Dissolve about 80 mg of cefazolin RS in 0.1 mol/L phosphate buffer solution (pH 7.0) to make 100 mL, and use this solution as the system suitability solution. Pipet 1 mL of this solution and add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 20 mL. Confirm that the peak area of cefazolin obtained from 5 μL of this solution is equivalent to 3 to 7% of the peak area of cefazolin obtained from the system suitability solution.

System performance: Proceed as directed under the system suitability under the Assay.

System repeatability: Repeat the test 6 times with 5 μL each of the system suitability solutions according to the above conditions; the relative standard deviation of the peak area of cefazolin is NMT 1.0%.

Time span of measurement: About 3 times the retention time of cefazolin beginning after the solvent peak.

(5) ***Dimethylaniline***—Weigh accurately about 1.0 g

of Cefazolin Sodium, add 5 mL of 1 mol/L sodium hydroxide TS and 1 mL of the internal standard solution, centrifuge, if necessary, and use the supernatant as the test solution. Separately, weigh accurately about 50 mg of dimethylaniline, add 2.0 mL of hydrochloric acid, and add water to make 50 mL. Pipet 5.0 mL of this solution and add water to make exactly 250 mL. Pipet 1.0 mL of this solution, add 5.0 mL of 1 mol/L sodium hydroxide TS, add 1.0 mL of the internal standard solution, centrifuge, if necessary, and use the supernatant as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of dimethylaniline to the internal standard, respectively (NMT 20 ppm).

$$\text{Content (ppm) of dimethylaniline} = \text{Amount (mg) of dimethylaniline taken} \times \frac{Q_T}{Q_S} \times \frac{Purity\ (\%) of\ dimethylaniline}{Amount\ (mg)\ of\ Cefazolin\ Sodium\ taken} \times 4$$

Internal standard solution—Dissolve 50.0 mg of naphthalene in cyclohexane to make 50 mL. To 5.0 mL of this solution, add cyclohexane to make 100 mL, and use this solution as the internal standard solution.

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A column about 2 mm in internal diameter and about 2 m in length, packed with diatomaceous earth for gas chromatography, which is coated with 50% phenyl-50% methylpolysiloxane for gas chromatography equivalent to 3% of the mass of the diatomaceous earth.

Column temperature: 120 ℃

Temperatures of the sample injection port and the detector: 150 ℃

Carrier gas: Nitrogen

Flow rate: 30 mL/min

Water NMT 2.5% (1 g, volumetric titration, direct titration). Use a mixture of formamide for water determination and methanol for water determination (2 : 1) instead of methanol for water determination.

Sterility It should meet the requirement when used in the manufacturing of sterile preparations. However, it is excluded when there is a terminal sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins Less than 0.10 EU/mg (potency) of cefazolin when used in the manufacturing of sterile preparations.

Assay Weigh accurately about 0.1 g (potency) each of Cefazolin Sodium and cefazolin sodium RS, dissolve each in the internal standard solution to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of cefazolin to the internal standard, respectively.

$$\text{Potency (μg) of cefazolin } (C_{14}H_{14}N_8O_4S_3) = \text{Potency (μg) of cefazolin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of *p*-acetoanisidide in 0.1 mol/L phosphate buffer solution (pH 7.0) (11 in 20000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: Dissolve 2.27 g of disodium hydrogen phosphate dodecahydrate and 0.47 g of citric acid monohydrate in water to make 935 mL, and add 65 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of cefazolin is about 8 minutes.

System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; cefazolin and *p*-acetoanisidide are eluted in this order with the resolution between these peaks being NLT 4.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area ratio of cefazolin to the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Cefazolin Sodium for Injection
주사용 세파졸린나트륨

Cefazolin Sodium for Injection, as an injection that is dissolved upon use, contains NLT 90.0% and NMT 110.0% of the labeled amount of cefazolin ($C_{14}H_{14}N_8O_4S_3$: 454.51).

Method of preparation Prepare as directed under Injections, with Cefazolin Sodium.

Description Cefazolin Sodium for Injection occurs as white to yellowish white crystals, a crystalline powder or a mass.

Identification (1) Determine the absorption spectrum of

a solution of Cefazolin Sodium for Injection (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelength of between 270 nm and 274 nm.

(2) Cefazolin Sodium for Injection responds to the Qualitative Analysis (1) for sodium salt.

pH Dissolve an amount of Cefazolin Sodium for Injection equivalent to 1.0 g (potency) of cefazolin in 10 mL of water; the pH of this solution is between 4.5 and 6.5.

Purity (1) ***Clarity and color of solution***—Perform the test within 10 minutes after preparing the solution. Dissolve an amount of Cefazolin Sodium for Injectionequivalent to 1.0 g (potency) of cefazolin sodium according to the labeled amount, in 10 mL of water; the resulting solution is clear. Determine the absorbance of this solution at the wavelength of 400 nm as directed under the Ultraviolet-visible Spectroscopy; it is NMT 0.35.

(2) ***Related substances***—Take an amount of Cefazolin Sodium for Injection, equivalent to 0.10 g (potency) of cefazolin sodium according to the labeled amount, dissolve in 20 mL of 0.1 mol/L phosphate buffer solution, pH 7.0, and use this solution as the test solution. Prepare the test solution before use. Perform the test with 5 μL of the test solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the area percentage of individual peak by the automatic integration method. The peak of individual related substance other than cefazolin is NMT 1.5%, and the sum of the peaks of total related substances other than cefazolin is NMT 2.5%. Determine the peak area of the related substances having a relative retention time of about 0.2 to cefazolin by multiplying the correction factor of 1.43.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed according to the operating conditions as directed under the Assay under Cefazolin Sodium.

System suitability

Test for required detectability: Pipet 8 mL of the test solution, add 0.1 mol/L phosphate buffer solution, pH 7.0, to make exactly 50 mL, and use this solution as the system suitability solution. To 1 mL of this solution, add 0.1 mol/L phosphate buffer solution, pH 7.0, to make exactly 20 mL. Confirm that the peak area of cefazolin sodium obtained from 5 μL of this solution is between 3% and 7% of the peak area of cefazolin sodium obtained from 5 μL of the system suitability solution.

System performance: Proceed as directed under the system suitability in the Assay under the Cefazolin Sodium.

System repeatability: Repeat the test 6 times with 5 μL of the system suitability solution according to the above operating conditions; the relative standard deviation of peak areas of cefazolin is NMT 1.0%.

Time span of measurement: About 3 times the retention time of cefazolin after the solvent peak.

Water NMT 3.0% (0.5 g, volumetric titration, direct titration). Use a mixture of formamide for water determination and methanol for water determination (2:1) instead of methanol for water determination.

Sterility Meets the requirements.

Bacterial endotoxin NMT 0.05 EU per mg (potency) of cefazolin sodium.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

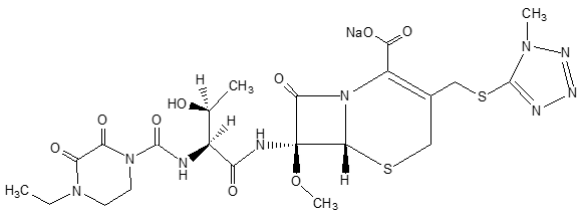
Assay Weigh accurately the mass of the contents of NLT 10 containers of Cefazolin Sodium for Injection. Weigh accurately an amount of Cefazolin Sodium for Injection equivalent to 50 mg (potency), dissolve in the internal standard solution to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg (potency) of cefazolin RS, dissolve it in the internal standard solution to make 50 mL, and use this solution as the standard solution. Perform the test as directed under the Assay under Cefazolin Sodium.

$$\text{Potency (μg) of cefazolin } (C_{14}H_{14}N_8O_4S_3) = \text{Potency (μg) of cefazolin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of *p*-acetanisidide in 0.1 mol/L phosphate buffer solution, pH 7.0, (11 in 20000).

Packaging and storage Preserve in hermetic containers.

Cefbuperazone Sodium
세프부페라존나트륨



$C_{22}H_{28}N_9NaO_9S_2$: 649.63

Sodium (6*R*,7*S*)-7-[[(2*S*,3*R*)-2-[(4-ethyl-2,3-dioxopiperazine-1-carbonyl)amido]-3-hydroxybutanamido]-7-methoxy-3-[(1-methyltetrazol-5-yl)sulfanyl-methyl]-3,4-didehydrocepham-4-carboxylate [*76648-01-6*]

Cefbuperazone Sodium contains NLT 870 μg (potency) of cefbuperazone ($C_{22}H_{29}N_9O_9S_2$: 627.65) per mg, calculated on the anhydrous basis.

Description Cefbuperazone Sodium occurs as a white to pale yellowish white powder or a mass.
It is very soluble in water, freely soluble in methanol or pyridine, sparingly soluble in ethanol(95), and very slightly soluble in acetonitrile.

Identification (1) Determine the absorption spectra of respective aqueous solutions of Cefbuperazone Sodium and cefbuperazone sodium RS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine ^1H of a solution prepared by adding 0.5 mL of deuterated pyridine for nuclear magnetic resonance spectroscopy and 1 drop of deuterium oxide for nuclear magnetic resonance spectroscopy to 0.1 g of Cefbuperazone Sodium, as directed under the Nuclear Magnetic Resonance Spectroscopy, using tetramethylsilane for nuclear magnetic resonance spectroscopy as the internal standard; it exhibits the triplet signal A at about δ 1.1 ppm and doublet signals B and C at about δ 1.6 ppm and δ 5.1 ppm, respectively, with the ratio of area strength of the signals A : B : C being about 3 : 3 : 1.

(3) Cefbuperazone Sodium responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between +48° and +56° (0.4 g, calculated on the anhydrous basis, water, 20 mL, 100 mm).

pH Dissolve 1.0 g of Cefprozil Hydrate in 4 mL of water; the pH of this solution is between 4.0 and 6.0.

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Cefuroxime Sodium in 4 mL of water; the solution is pale yellow and clear.

(2) ***Heavy metals*—**Proceed with 2.0 g of Cefbuperazone Sodium as directed under Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic*—**Prepare the test solution with 1.0 g of Cefbuperazone Sodium, according to Method 4 and perform the test (NMT 2 ppm).

(4) ***Related substances*—**Dissolve 0.10 g of Cefbuperazone Sodium in 100 mL of the mobile phase, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to it make exactly 50 mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, determine individual peak areas in each of the respective solutions according to the automatic integration method, and obtain the percentage of the peak area of each related substance in the test solution compared to 50 times the peak area of cefbuperazone in the standard solution; the related substance with the relative retention time with respect to cefbuperazone of about 0.2 is NMT 2.0%, the related substance with the relative retention time with respect to cefbuperazone of about 0.6 is NMT 4.5%, the related substance with the relative retention time with respect to cefbuperazone of about 1.6 is NMT 1.0%. Also, the sum of peak areas of related substances is NMT 6.0%. The peak areas of the related substances with relative retention times of about 0.2 and 1.6 are the results of multiplying the correction factors 0.72 and 0.69 by the areas obtained according to the automatic integration method, respectively.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution and add the mobile phase to make exactly 10 mL. Confirm that the peak area of cefbuperazone obtained from 25 mL of this solution is within the range between 7% and 13% of the peak area of cefbuperazone obtained from the standard solution.

System performance: Proceed with 25 μL of the standard solution according to the above conditions; the number of theoretical plates of the cefbuperazone peak is NLT 5000, and the symmetry factor is NMT 1.5.

System repeatability: Repeat the test 6 times with 25 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of cefbuperazone is NMT 2.0%.

Time span of measurement: About 2 times the retention time of cefbuperazone.

Water NMT 1.0% (3 g, volumetric titration, direct titration).

Sterility It meets the requirements when Cefbuperazone Sodium is used in a sterile preparation. However, it is exempt from the requirements when there is a final sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins It is less than 0.1 EU per mg (potency) of cefbuperazone when used in a sterile preparation.

Assay Weigh accurately about 0.1 g (potency) each of Cefbuperazone Sodium and cefbuperazone RS, and add the mobile phase to each to make exactly 100 mL. Pipet 10 mL each of these solutions, add exactly 10 mL of the internal standard solution to each, add the mobile phase to each to make 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following operating conditions, and calculate the peak area

ratios, Q_T and Q_S, of cefbuperazone to the internal standard, respectively.

$$\text{Potency (μg) of cefbuperazone } (C_{22}H_{29}N_9O_9S_2) = \text{Potency (μg) of cefbuperazone RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of acetanilide in the mobile phase (1 in 4000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: In 1000 mL of a mixture of water, acetonitrile, and acetic acid (pH 5.0)-sodium acetate buffer (83 : 13 : 4), dissolve 2.0 g of tetra n-propylammonium bromide.

Flow rate: 1.4 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the internal standard and cefbuperazone are eluted in this order with the resolution being NLT 3.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area ratio of cefbuperazone to the internal standard is NMT 1.0%.

Packaging and storage Preserve in hermetic containers in a cold place.

Cefbuperazone Sodium for Injection
주사용 세프부페라존나트륨

Cefbuperazone Sodium for Injection, as an injection that is dissolved before use, contains NLT 90.0% and NMT 120.0% of the labeled amount of cefbuperazone ($C_{22}H_{29}N_9O_9S_2$: 627.65).

Method of preparation Prepare as directed under Injections, with Cefbuperazone Sodium.

Description Cefbuperazone Sodium for Injection occurs as a white to pale yellow powder or a mass.

Identification (1) Weigh 20 mg (potency) of Cefbuperazone Sodium for Injection, dissolve in 1 mL of hydroxylamine hydrochloride-ethanol TS, and allow it to stand for 3 minutes. Add 1 mL of acidic ammonium iron(III) sulfate TS, and shake to mix; the resulting solution exhibits a reddish brown color.

(2) Weigh 0.1 g (potency) of Cefbuperazone Sodium for Injection, dissolve in 4 mL of 1 mol/L sodium hydroxide TS, and heat on a steam bath for 20 minutes. After cooling, neutralize with 6 mol/L hydrochloric acid TS. Heat again on a steam bath for 2 to 3 minutes, add 1 mL of calcium chloride TS, and allow it to stand for 30 minutes. Filter the formed precipitate through a glass filter (G4), wash the precipitate 4 times with 5 mL of water, and dissolve in 1 mL of 2 mol/L sulfuric acid TS. Dissolve in about 10 mg of magnesium. Take 3 drops of this solution, add 2 mL of 2,7-dihydroxynaphthalene TS, and heat on a steam bath for 10 minutes; the resulting solution exhibits a violet red color.

(3) Determine the absorption spectrum of a solution of Cefbuperazone Sodium for Injection (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima absorbance at 226 nm to 230 nm and 267 nm to 271 nm.

pH Dissolve 2.5 g of Cefbuperazone Sodium for Injection in 10 mL of water; the pH of this solution is 4.0 to 6.0.

Water NMT 1.0% (1.0 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.1 EU per mg (potency) of cefbuperazone.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately an amount of Cefbuperazone Sodium for Injection, equivalent to about 0.5 g (potency), according to the labeled potency, and dissolve in the mobile phase to make exactly 100 mL. Pipet an appropriate amount of this solution to obtain 1 mg (potency) in 1 mL. Pipet 10 mL of this solution, add 10 mL of the internal standard solution, add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g (potency) of cefbuperazone RS, and dissolve in the mobile phase to make exactly 100 mL. Pipet 10 mL of this solution, add exactly 10 mL of the internal standard solution, add the mobile phase to make 50 mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of cefbuperazone to that of the internal standard in each solution.

Potency (μg) of cefbuperazone ($C_{22}H_{29}N_9O_9S_2$)
= Potency (μg) of cefbuperazone RS× $\frac{Q_T}{Q_S}$ × 5

Internal standard solution—Weigh accurately 0.1 g of acetanilide, dissolve in the mobile phase to make 200 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (8 μm to 10 μm in particle diameter).

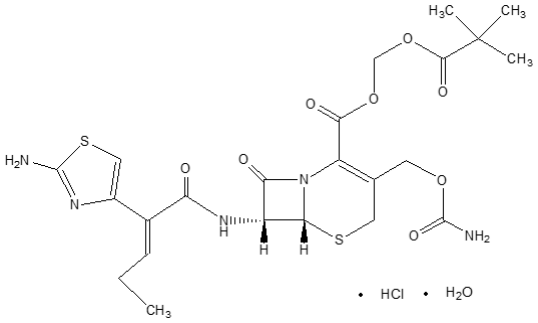
Mobile phase: Weigh 60.1 g of acetic acid(100) and 101.1 g of triethylamine, dissolve in water to make 1000 mL. Add 2 mL of dilute acetic acid and 120 mL of acetonitrile to 4.0 mL of this solution, and add water to make 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of cefbuperazone is about 5 minutes.

Selection of column: Proceed with the standard solution according to the above conditions; cefbuperazone and the internal standard are eluted in this order with the resolution being NLT 10.0.

Packaging and storage Preserve in hermetic containers.

Cefcapene Pivoxil Hydrochloride Hydrate
세프카펜피복실염산염수화물



Cefcapene pivoxil hydrochloride
$C_{23}H_{29}N_5O_8S_2 \cdot HCl \cdot H_2O$: 622.11
2,2-Dimethylpropanoyloxymethyl (6*R*,7*R*)-7-[(2*E*)-2-(2-amino-1,3-thiazol-4-yl)pent-2-enamido]-3-(carbamoyloxymethyl)-3,4-didehydrocepham-4-carboxylate hydrate hydrochloride [*147816-24-8*]

Cefcapene Pivoxil Hydrochloride Hydrate contains NLT 722 μg (potency) and NMT 764 μg (potency) of cefcapene ($C_{17}H_{19}N_5O_6S_2$: 453.49) per mg, calculated on the anhydrous basis.

Description Cefcapene Pivoxil Hydrochloride Hydrate occurs as a white to pale yellowish white crystalline powder or a mass.
It has a slightly characteristic odor.
It is freely soluble in *N,N*-dimethylformamide or methanol, soluble in ethanol(99.5), slightly soluble in water, and practically insoluble in ether.

Identification (1) Determine the infrared spectra of Cefcapene Pivoxil Hydrochloride Hydrate and cefcapene pivoxil hydrochloride RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Determine ^1H of a solution of Cefcapene Pivoxil Hydrochloride Hydrate in deuterated methanol for nuclear magnetic resonance spectroscopy (1 in 50) as directed under the Nuclear Magnetic Resonance Spectroscopy, using tetramethylsilane for nuclear magnetic resonance spectroscopy as the internal standard; it exhibits the triplet signal A at about δ 6.3 ppm and singlet signal B at about δ 6.7 ppm, with the ratio of area strength of the signals A : B being about 1 : 1.

(3) Dissolve 10 mg of Cefcapene Pivoxil Hydrochloride Hydrate in 2 mL of a mixture of water and methanol (1 in 1) and add 1 drop of silver nitrate TS; a white precipitate is formed.

Optical rotation $[\alpha]_D^{20}$: Between +51° and +54° (0.1 g, calculated on the anhydrous basis, methanol, 10 mL, 100 mm).

Absorbance $E_{1cm}^{1\%}$ (265 nm): Between 255 and 285 (30 mg, calculated on the anhydrous basis, 2000 mL of a mixture of acetate buffer (pH 5.5) and methanol (1 in 1)).

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Carvedilol according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 10 ppm).

(2) ***Related substance I***—Dissolve an amount equivalent to about 10 mg (potency) of Cefcapene Pivoxil Hydrochloride Hydrate in 2 mL of methanol, add a mixture of water and methanol (1 in 1) to make 50 mL, and use this solution as the test solution. Perform the test with 30 μL of the test solution as directed under the Liquid Chromatography according to the following conditions, and determine individual peak areas according to the automatic integration method. If necessary, proceed with 30 μL of a mixture of water and methanol (1 : 1) in the same manner to make corrections for baseline variability. Obtain the amount of peaks other than cefcapene pivoxil according to the percentage peak area method; the peaks with the relative retention times with respect to cefcapene pivoxil of about 1.5 and 1.7 are NMT 0.2%, respectively, each of other peaks is NMT 0.1%, and the sum of peaks is NMT 1.5%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 265 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and 15 to 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 20 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: Dissolve 5.99 g of potassium dihydrogen phosphate in water to make 1100 mL. To this solution, add a solution prepared to 1000 mL by dissolving 1.89 g of tetra *n*-pentylammonium bromide in methanol.

Mobile phase B: A mixture of methanol and water (22 : 3).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 20	98	2
20 - 40	98 → 50	2 → 50
40 - 50	50	50

Flow rate: 0.8 mL/min

System suitability

Test for required detectability: Pipet 1 mL of the test solution, add a mixture of water and methanol (1 : 1) to make exactly 100 mL, and use this solution as the system suitability solution. Pipet 1 mL of this solution, and add a mixture of water and methanol (1 : 1) to make exactly 10 mL. Confirm that the peak area of cefcapene pivoxil obtained from 30 μL of this solution is within the range between 7% and 13% of the peak area of cefcapene pivoxil obtained from the system suitability solution.

System performance: Dissolve 10 mg of Cefcapene Pivoxil Hydrochloride Hydrate and 10 mg of propyl p-hydroxybenzoate in 25 mL of methanol, and add water to make 50 mL. To 5 mL of this solution, add a mixture of water and methanol (1 : 1) to make 50 mL. Proceed with 30 μL of this solution according to the above conditions; cefcapene pivoxil and propyl p-hydroxybenzoate are eluted in this order with the resolution being NLT 7.

System repeatability: Repeat the test 3 times with 30 μL each of the system suitability solutions according to the above conditions; the relative standard deviation of the peak area of cefcapene pivoxil is NMT 4.0%.

Time span of measurement: About 2.5 times the retention time of cefcapene pivoxil.

(3) ***Related substance II***—Dissolve an amount equivalent to about 2 mg (potency) of Cefcapene Pivoxil Hydrochloride Hydrate in *N*,*N*-dimethylformamide for liquid chromatography to make 20 mL, and use this solution as the test solution. Perform the test with 20 L of the test solution as directed under the Liquid Chromatography according to the following operating conditions. Determine individual peak areas in the test solution according to the automatic integration method; the sum of areas of peaks eluted before cefcapene pivoxil is NMT 1.7% of the sum of areas of peaks other than the solvent-derived peak.

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 280 nm).

Column: A stainless steel column, about 7.8 mm in internal diameter and about 30 cm in length, packed with styrene-divinylbenzene copolymer for liquid chromatography.

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A solution of lithium bromide in *N*,*N*-dimethylformamide for liquid chromatography (13 in 5000).

Flow rate: Adjust the flow rate so that the retention time of cefcapene pivoxil is about 22 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the test solution, add *N*,*N*-dimethylformamide for liquid chromatography to make exactly 100 mL, and use this solution as the system suitability solution. Pipet 3 mL of this solution, and add *N*,*N*-dimethylformamide for liquid chromatography to make exactly 10 mL. Confirm that the peak area of cefcapene pivoxil obtained from 20 μL of this solution is within the range between 20% and 40% of the peak area of cefcapene pivoxil obtained from the system suitability solution.

System performance: Proceed with 20 μL of the test solution according to the above conditions; the number of theoretical plates of the cefcapene pivoxil peak is NLT 12000.

System repeatability: Repeat the test 6 times with 20 μL each of the system suitability solution according to the above conditions; the relative standard deviation of the peak area of cefcapene pivoxil is NMT 4.0%.

Time span of measurement: About 1.8 times the retention time of cefcapene pivoxil.

Water Between 2.8% and 3.7% (0.5 g, volumetric titration, back titration).

Assay Weigh accurately about 20 mg (potency) each of Cefcapene Pivoxil Hydrochloride Hydrate and cefcapene pivoxil hydrochloride RS, and dissolve each in a respective mixture of water and methanol (1 : 1) to make exactly 50 mL. To 10 mL each of these solutions, add exactly 10 mL of the internal standard solution. Add a mixture of water and methanol (1 : 1) to each to make 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following operating conditions, and calculate the peak area ratios, Q_T and Q_S, of cefcapene pivoxil to the internal standard, respectively.

Potency (μg) of cefcapene ($C_{17}H_{19}N_5O_6S_2$)
= Potency (μg) of cefcapene pivoxil hydrochloride RS
$$\times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of *p*-benzylphenol in a mixture of water and methanol (1 : 1) (7 in 4000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 265 nm).

Column: A stainless steel column about 3.0 mm in internal diameter and 7.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 1.56 g of sodium dihydrogen phosphate dihydrate and 1.22 g of sodium 1-decanesulfonate in water to make 1000 mL. To 700 mL of this solution, add 300 mL of acetonitrile and 100 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of cefcapene pivoxil is about 5 minutes.

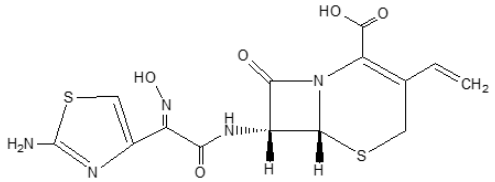
System suitability

System performance: Dissolve 0.2 g of Cefcapene Pivoxil Hydrochloride Hydrate in 10 mL of methanol, and warm in a 60 ℃ water bath for 20 minutes. After cooling, pipet 1 mL of this solution, add exactly 10 mL of the internal standard solution, and add a mixture of water and methanol (1 : 1) to make 50 mL. Proceed with 10 μL of this solution according to the above conditions; cefcapene pivoxil, cefcapene pivoxil substituent, and the internal standard are eluted in this order, the retention time ratios of cefcapene pivoxil substituent and the internal standard to cefcapene pivoxil are about 1.7 and 2.0, respectively, and the resolution between cefcapene pivoxil substituent and the internal standard is NLT 1.5.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio of cefcapene pivoxil to the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers at below 5 ℃.

Cefdinir
세프디니르



$C_{14}H_{13}N_5O_5S_2$: 395.41

(6*R*,7*R*)-7-[(2*E*)-2-(2-Amino-1,3-thiazol-4-yl)-2-methoxyiminoacetamido]-3-ethenyl-3,4-didehydrocepham-4-carboxylic acid [*91832-40-5*]

Cefdinir contains NLT 930 μg (potency) and NMT 1020 μg (potency) of cefdinir ($C_{14}H_{13}N_5O_5S_2$: 395.41) per mg.

Description Cefdinir occurs as a white to pale yellow crystalline powder.
It is sparingly soluble in water, ethanol(95) or ether.
It dissolves in 0.1 mol/L phosphate buffer (pH 7.0).

Identification (1) Determine the absorption spectra of respective solutions of Cefdinir and cefdinir RS in 0.1 mol/L phosphate buffer (pH 7.0) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cefdinir and cefdinir RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Determine ^1H of a solution of Cefdinir in a mixture of deuterated dimethylsulfoxide for nuclear magnetic resonance spectroscopy and deuterium oxide for nuclear magnetic resonance spectroscopy (4 : 1) (1 in 10) as directed under the Nuclear Magnetic Resonance Spectroscopy, using tetramethylsilane for nuclear magnetic resonance spectroscopy as the internal standard; it exhibits the multiplet signals A and B at about δ 5.0 to 6.1 ppm and at about δ 6.4 to 7.5 ppm, respectively, with the ratio of area strength of the signals A : B being about 2 : 1.

Optical rotation $[\alpha]_D^{20}$: Between -58° and -66° (0.25 g, 0.1 mol/L phosphate buffer (pH 7.0) 25 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Cefdinir as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Dissolve 0.1 g of Cefdinir in 10 mL of 0.1 mol/L phosphate buffer (pH 7.0). Pipet 3 mL of this solution, add tetramethylammonium hydroxide TS (pH 5.5) to make exactly 20 mL, and use this solution as the test solution. With 10 μL of the test solution, perform the test as directed under the Liquid

Chromatography according to the following conditions. Determine each peak area in the test solution according to the automatic integration method; the peak area of *E*-isomer with the relative retention time with respect to the cefdinir peak of 1.5 under the percentage peak area method is NMT 0.8% and the sum of peak areas other than cefdinir is NMT 3.0%.

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature at about 40 °C.

Delivery of mobile phase: Control the mobile phases A and B stepwise or based on the gradient elution as follows.

Mobile phase A: To 1000 mL of tetramethylammonium hydroxide TS (pH 5.5), add 0.4 mL of 0.1 mol/L disodium dihydrogen ethylenediaminetetraacetate TS.

Mobile phase B: To 500 mL of tetramethylammonium hydroxide TS (pH 5.5), add 300 mL of acetonitrile for liquid chromatography and 200 mL of methanol, and add 0.4 mL of 0.1 mol/L disodium dihydrogen ethylenediaminetetraacetate TS.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 2	95	5
2 - 22	95 → 75	5 → 25
22 - 32	75 → 50	25 → 50
32 - 37	50	50
37 - 38	50 → 95	50 → 5
38 - 58	95	5

Flow rate: 1.0 mL/min. Under this condition, the retention time of cefdinir is about 22 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the test solution, add tetramethylammonium hydroxide TS (pH 5.5) to make exactly 100 mL, and use this solution as the system suitability solution. To 1 mL of this solution, add tetramethylammonium hydroxide TS (pH 5.5) to make exactly 10 mL. Confirm that the peak area of cefdinir obtained from 10 μL of this solution is within the range between 7% and 13% of the peak area of cefdinir obtained from the system suitability solution.

System performance: Dissolve 0.03 g of cefdinir RS and 2 mg of cefdinir lactam ring-cleavage lactones in 3 mL of 0.1 mol/L phosphate buffer (pH 7.0), and add tetramethylammonium hydroxide TS (pH 5.5) to make 20 mL. Proceed with 10 μL of this solution according to the above conditions; the peak 1 and peak 2 of the cefdinir lactam ring-cleavage lactones (split into 4), cefdinir, and the peak 3 and peak 4 of the cefdinir lactam ring-cleavage lactones are eluted in this order, the relative retention time of the peak 3 of the cefdinir lactam ring-cleavage lactones with respect to cefdinir is NLT 1.09, the number of theoretical plates of the cefdinir peak is NLT 7000, and the symmetry factor is NMT 3.0.

System repeatability: Repeat the test 3 times with 10 μL each of the system suitability solutions according to the above conditions; the relative standard deviation of the peak area of cefdinir is NMT 2.0%.

Time span of measurement: 40 minutes after injecting the test solution.

Water NMT 2.0% (1 g, volumetric titration, direct titration. Use a mixture of formamide for water determination and methanol for water determination (2 : 1) instead of methanol for water determination.

Assay Weigh accurately about 20 mg (potency) each of Cefdinir and cefdinir RS, dissolve each in respective 0.1 mol/L phosphate buffer (pH 7.0) to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 5 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of cefdinir, respectively.

$$\text{Potency (μg) of cefdinir } (C_{14}H_{13}N_5O_5S_2) = \text{Potency (μg) of cefdinir RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: To 1000 mL of tetramethylammonium hydroxide TS (pH 5.5), add 0.4 mL of 0.1 mol/L disodium dihydrogen ethylenediaminetetraacetate TS. To 900 mL of this solution, add 60 mL of acetonitrile for liquid chromatography and 40 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of cefdinir is about 8 minutes.

System suitability

System performance: Dissolve 2 mg of cefdinir RS and 5 mg of cefdinir lactam ring-cleavage lactones in 10 mL of 0.1 mol/L phosphate buffer (pH 7.0). Proceed with 5 μL of this solution according to the above conditions; the peak 1 and peak 2 of the cefdinir lactam ring-cleavage lactones (split into 4), cefdinir, and the peak 3 and peak 4 of the cefdinir lactam ring-cleavage lactones are eluted in this order, the resolution between the peak 2 of the cefdinir lactam ring-cleavage lactones and cefdinir

is NLT 1.2, the number of theoretical plates of the cefdinir peak is NLT 2000, and the symmetry factor is NMT 1.5.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of cefdinir is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Cefdinir Capsules
세프디니르 캡슐

Cefdinir Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of cefdinir ($C_{14}H_{13}N_5O_5S_2$: 395.41).

Method of preparation Prepare as directed under Capsules, with Cefdinir.

Identification Weigh an amount of Cefalexin Capsules, equivalent to 10 mg (potency) of cefdinir according to the labeled amount, add 100 mL of 0.1 mol/L phosphate buffer solution (pH 7.0), sonicate for 1 minute, and then filter. To 2 mL of the filtrate, add 0.1 mol/L phosphate buffer solution (pH 7.0) to make 20 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 221 and 225 nm and 285 and 289 nm.

Dissolution Perform the test with 1 capsule of Cefdinir Capsules at 50 revolutions per minute according to Method 2 under the Dissolution with a sinker, using 900 mL of Solution 2 in the Dissolution as the dissolution solution. Take NLT 20 mL of the dissolved solution 45 minutes after starting the test, and filter through a membrane filter with a pore size of NMT 0.5 μm. Discard the first 10 mL of the filtrate, take exactly *V* mL of the subsequent filtrate, add Solution 2 in the Dissolution to obtain exactly *V′* mL of a solution containing about 56 μg (potency) of cefdinir per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately an amount equivalent to about 28 mg (potency) of cefdinir RS, and dissolve in Solution 2 in the Dissolution to make exactly 100 mL. Pipet 4 mL of this solution, add Solution 2 in the Dissolution to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, respectively. The acceptable dissolution criterion is NLT 75% of Cefdinir Capsules dissolved in 45 minutes.

Dissolution rate (%) of the labeled amount of cefdinir ($C_{14}H_{13}N_5O_5S_2$)

$$= \text{Potency (mg) of cefdinir RS} \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 180$$

C: Labeled amount (mg) of cefalexin ($C_{14}H_{13}N_5O_5S_2$) in 1 capsule

Operating conditions

Perform the test according to the operating conditions of the Assay under Cefdinir.

System suitability

System performance: Proceed with 20 μL of the standard solution under the above operating conditions; the number of theoretical plates of the cefdinir peak is NLT 2,000 plates with the symmetry factor being NMT 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of cefdinir is NMT 1.0%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Cefdinir Capsules. Weigh accurately an amount of Cefdinir Capsules, equivalent to about 0.1 g (potency) of cefdinir according to the labeled potency, add 70 mL of 0.1 mol/L phosphate buffer solution (pH 7.0), shake for 30 minutes to mix, and then add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 100 mL. Then, centrifuge this solution at 3000 rpm for 10 minutes, pipet 4 mL of the clear supernatant, add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg (potency) of cefdinir RS, dissolve in 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 100 mL, and use this solution as the standard stock solution. Perform the test as directed under the Assay of Cefdinir.

Potency (mg) of cefdinir ($C_{14}H_{13}N_5O_5S_2$)

$$= \text{Potency (mg) of cefdinir RS} \times \frac{A_T}{A_S} \times 5$$

Packaging and storage Preserve in tight containers.

Cefdinir Fine Granules
세프디니르 세립

Cefdinir Fine Granules contain NLT 93.0% and NMT 107.0% of the labeled amount of cefdinir ($C_{14}H_{13}N_5O_5S_2$: 395.41).

Method of preparation Prepare as directed under Powders, with Cefdinir.

Identification Weigh an amount of Cefdinir Fine Granules equivalent to 10 mg (potency) of cefdinir according

to the labeled amount, add 100 mL 0.1 mol/L phosphate buffer solution (pH 7.0), sonicate for 1 minute, and filter. To 2 mL of the filtrate, add 0.1 mol/L phosphate buffer solution (pH 7.0) to make 20 mL. Determine the absorption spectra of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima 221 to 225 nm and 285 to 289 nm.

Particle size distribution estimation by analytical sieving Meets the requirements.

Dissolution Weigh accurately an amount of Cefdinir Fine Granules equivalent to about 0.1 g (potency) according to the labeled potency, and perform the test at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of Solution 2 as the dissolution medium. Take NLT 20 mL of the dissolved solution 30 minutes after starting the test, and filter through a membrane filter with a pore size of NMT 0.5 μm. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately an amount equivalent to about 28 mg (potency) of cefdinir RS, and dissolve in Solution 2 in the Dissolution to make exactly 50 mL. Pipet 4 mL of this solution, add Solution 2 in the Dissolution to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas A_T and A_S of cefdinir. Meets the requirements if the dissolution rate of Cefdinir Fine Granules in 30 minutes is NLT 75%.

Dissolution rate (%) with respect to the labeled amount of cefdinir ($C_{14}H_{13}N_5O_5S_2$)

$$= \frac{Potency\ (mg)\ of\ cefdinir\ RS}{W_T} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 360$$

W_T: Taken amount (g) of Cefdinir Fine Granules

C: Labeled amount [mg (potency)] of cefdinir ($C_{14}H_{13}N_5O_5S_2$) in 1 g

Operating conditions

Perform the test according to the operating conditions as directed under the Assay of Cefdinir.

System suitability

System performance: Proceed with 20 μL of the standard solution under the above operating conditions; the number of theoretical plates of the cefdinir peak is NLT 2,000 plates, and the symmetry factor is NMT 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of cefdinir is NMT 1.0%.

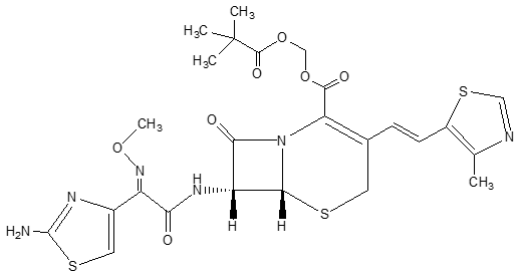
Uniformity of dosage units (distribution) Meets the requirements.

Assay Perform the test as directed under the Assay of Cefdinir. If necessary, weigh accurately an amount of powdered Cefdinir Fine Granules equivalent to 0.1 g (potency) of cefdinir according to the labeled amount, add 70 mL of 0.1 mol/L phosphate buffer solution (pH 7.0), shake for 30 minutes to mix, and add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 100 mL. Centrifuge this solution at 3000 rpm for 10 minutes, pipet 4 mL of the clear supernatant, add 0.1 mol/L phosphate buffer solution (pH 7.0), shake for 30 minutes to mix, and add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg (potency) of cefdinir RS, dissolve in 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 100 mL, and use this solution as the standard solution.

Potency (mg) of cefdinir ($C_{14}H_{13}N_5O_5S_2$)
= Potency (mg) of cefdinir RS× $\frac{A_T}{A_S}$ ×5

Packaging and storage Preserve in light-resistant, tight containers.

Cefditoren Pivoxil
세프디토렌피복실



$C_{25}H_{28}N_6O_7S_3$: 620.72

2,2-Dimethylpropanoyloxymethyl (6*R*,7*R*)-7-[(2*E*)-2-(2-amino-1,3-thiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(4-methyl-1,3-thiazol-5-yl)ethen-1-yl]-3,4-didehydrocepham-4-carboxylate [*117467-28-4*]

Cefditoren Pivoxil contains NLT 770 μg (potency) and NMT 820 μg (potency) of cefditoren ($C_{19}H_{18}N_6O_5S_3$: 506.58) per mg, calculated on the anhydrous basis.

Description Cefditoren Pivoxil occurs as a pale yellowish white to pale yellow crystalline powder.
It is sparingly soluble in methanol, slightly soluble in acetonitrile or ethanol(95), very slightly soluble in ether, and practically insoluble in water.
It dissolves in dilute hydrochloric acid.

Identification (1) Dissolve 5 mg of Cefditoren Pivoxil in 3 mL of hydroxyammonium hydrochloride-ethanol TS, allow to stand for 5 minutes, add 1 mL of acidic ammonium iron(III) sulfate TS, and shake to mix; the resulting

solution exhibits a reddish brown color.

(2) Dissolve 1 mg of Cefditoren Pivoxil in 1 mL of dilute hydrochloric acid and 4 mL of water. While cooling, add 3 drops of sodium nitrite TS, shake to mix, and allow to stand for 2 minutes. Add 1 mL of ammonium amidosulfate TS, shake well to mix, and allow to stand for 1 minute. To this, add 1 mL of a solution prepared by dissolving 1.0 g of *N*,*N*-diethyl-*N*′-1-naphthylethylenediamine oxalate in 100 mL of a mixture of acetone and water (1 : 1); the resulting solution exhibits a violet color. Prepare the mixture of acetone and water (1 : 1) just before the use.

(3) Determine the absorption spectra of respective solutions of Cefditoren Pivoxil and cefditoren pivoxil RS in methanol (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine ^{1}H of a solution of Cefditoren Pivoxil in deuterated chloroform for nuclear magnetic resonance spectroscopy (1 in 50) as directed under the Nuclear Magnetic Resonance Spectroscopy, using tetramethylsilane for nuclear magnetic resonance spectroscopy as the internal standard; it exhibits the singlet signals A, B and C at about δ 1.1 ppm, δ 2.4 ppm and δ 4.0 ppm, respectively, doublet signals D and E at about δ 6.4 ppm and δ 6.7 ppm, respectively, and singlet signal F at about δ 8.6 ppm, with the ratio of area strength of the signals A : B : C : D : E : F being about 9 : 3 : 3 : 1 : 1 : 1.

Optical rotation $[\alpha]_D^{20}$: Between -45° and -52° (50 mg, methanol, 10 mL, 100 mm).

Absorbance $E_{1cm}^{1\%}$ (231 nm): Between 340 and 360 (50 mg, methanol, 2500 mL).

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Cefditoren Pivoxil as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Perform this test using a light-resistant container, protected from direct sunlight. Weigh accurately about 20 mg (potency) of Cefditoren Pivoxil, add exactly 5 mL of the internal standard solution, add acetonitrile to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg (potency) of cefditoren pivoxil RS and add acetonitrile to make exactly 100 mL. Pipet 1 mL of this solution, add exactly 5 mL of the internal standard solution, add acetonitrile to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_{TI}, Q_{TII} and Q_{TIII}, of the related substances I, II and III to that of the internal standard in the test solution, respectively, and the peak area ratio Q_S of cefditoren pivoxil to that of the internal standard. (related substance I NMT 1.5%, related substance II NMT 2.0%, and related substance III NMT 1.0%) The peak areas of related substances I, II and III are the results of multiplying the correction factors 1.25, 0.97 and 1.17 by the areas obtained according to the automatic integration method, respectively.

$$\text{Content (\%) of related substances} = \frac{Q_T}{Q_S} \times \frac{W_S}{W_T}$$

W_S: $\dfrac{\text{Taken amount (mg) of cefditoren pivoxil RS}}{\dfrac{\textit{Potency } (\mu g/mg) \textit{ of } \text{cefditoren pivoxil RS}}{816}}$

W_T: Taken amount (mg) of Cefditoren Pivoxil

Internal standard solution—A solution of acetonitrile in propyl p-hydroxybenzoate (1 in 40000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 250 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 1.58 g of ammonium formate in 900 mL of water, adjust the pH to about 6.0 with diluted formic acid (1 in 250), and add water to make exactly 1000 mL. To 450 mL of this solution, add 275 mL of acetonitrile and 275 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of cefditoren pivoxil is about 15 minutes. Under this condition, the related substance I is eluted in about 6 minutes, the related substance II is eluted in about 17 minutes, and the related substance III is eluted in about 22 minutes.

Selection of column: Dissolve 20 mg of cefditoren pivoxil RS and 5 mg of propyl p-hydroxybenzoate in 20 mL of acetonitrile, and proceed with 10 μL of this solution according to the above conditions. Use a column with which propyl p-hydroxybenzoate and cefditoren pivoxil are eluted in this order with the resolution being NLT 5.0.

(3) ***Other related substances***—Perform this test using a light-resistant container, protected from direct sunlight. Weigh accurately about 20 mg (potency) of Cefditoren Pivoxil, add acetonitrile to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg (potency) of cefditoren pivoxil RS, and dissolve in acetonitrile to make exactly 100 mL. Pipet 1 mL of this solution, add acetonitrile to make exactly 20 mL, and use it as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the conditions of (2); each peak area, other than cefditoren pivoxil and related substances I, II and III, obtained from the test so-

lution is not larger than the peak area of cefditoren pivoxil from the standard solution (NMT 1.0%), and the sum of peak areas obtained from the test solution is not larger than 2 times the peak area of cefditoren pivoxil from the standard solution (NMT 2.0%). For detection sensitivity and time span of measurement, proceed as below.

Detection sensitivity: Adjust the sensitivity so that the peak height of cefditoren pivoxil from 10 μL of the standard solution is between 5% and 10% of the full scale.

Time span of measurement: About 2 times the retention time of cefditoren pivoxil after the solvent peak

Water NMT 1.5% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Perform this test using a light-resistant container, protected from direct sunlight. Weigh accurately about 40 mg (potency) each of Cefditoren Pivoxil and cefditoren pivoxil RS, dissolve each in respective 40 mL of acetonitrile, add exactly 10 mL of the internal standard solution to each, and add acetonitrile to each to make 100 mL. Use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of cefditoren pivoxil to that of the internal standard, respectively.

$$\text{Potency (μg) of cefditoren } (C_{19}H_{18}N_6O_5S_3) = \text{Potency (μg) of cefditoren pivoxil RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of acetonitrile in propyl p-hydroxybenzoate (1 in 200).

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 230 nm).

Column: A stainless steel column about 4.6 mm internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 1.58 g of ammonium formate in 900 mL of water, adjust the pH to 6.0 with diluted formic acid (1 in 250), and add water to make 1000 mL. To 450 mL of this solution, add 275 mL of acetonitrile and 275 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of cefditoren pivoxil is about 15 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the internal standard and cefditoren pivoxil are eluted in this order with the resolution being NLT 5.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area ratio of cefditoren pivoxil to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers

Cefditoren Pivoxil Fine Granules
세프디토렌피복실 세립

Cefditoren Pivoxil Granules

Cefditoren Pivoxil Fine Granules contain NLT 90.0% and NMT 110.0% of labeled amount of cefditoren ($C_{19}H_{18}N_6O_5S_3$: 506.58).

Method of preparation Prepare as directed under Powders, with Cefditoren Pivoxil.

Identification (1) Powder Cefditoren Pivoxil Fine Granules, weigh an appropriate amount of Cefditoren Pivoxil Fine Granules equivalent to 0.1 g (potency) of cefditoren pivoxil, according to the labeled amount, add 10 mL of acetonitrile, shake vigorously to mix, and filter. To 1 mL of the filtrate, add acetonitrile to make 50 mL. To 1 mL of this solution, add acetonitrile to make 20 mL, and determine the absorption spectrum of the resulting solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum 230 nm to 234 nm.

(2) Proceed as directed under the Assay; the test solution and the standard solution exhibit peaks at the same retention time.

Purity (1) ***Related substances***—Perform the test as directed under the Purity (2) Cefditoren Pivoxil. Weigh accurately about 16 mg (potency) of pulverized Cefditoren Pivoxil Fine Granules according to the labeled potency, add 10 mL of diluted acetonitrile (3 in 4), shake to mix, add exactly 5 mL of the internal standard solution and diluted acetonitrile (3 in 4) to make exactly 20 mL, and filter. Centrifuge the filtrate, and use this solution as the test solution (NMT 2.0% for related substance I, NMT 3.5% for related substance II, and NMT 1.0% for related substance III).

(2) ***Other related substances***—Perform the test as directed under the Purity (3) of Cefditoren Pivoxil. Weigh accurately about 16 mg (potency) of pulverized Cefditoren Pivoxil Fine Granules according to the labeled potency, add 10 mL of diluted acetonitrile (3 in 4), shake to mix, add diluted acetonitrile (3 in 4) to make exactly 20 mL, filter, centrifuge, and use the solution as the test solution. Each peak area, other than cefditoren pivoxil, related substances I, II and III from the test solution is NMT that of cefditoren pivoxil from the standard solution

(NMT 1.0%), and the sum of peak areas obtained from the test solution is NMT 2 times the peak area of cefditoren pivoxil from the standard solution (NMT 2.0%).

Loss on drying NMT 4.5% (0.5 g, in vacuum at the pressure not exceeding·0.67 kPa, 60 ℃, 3 hours).

Dissolution Perform the test as directed under the Dissolution of Cefditoren Pivoxil Tablets Weigh accurately an amount of Cefditoren Pivoxil Fine Granules equivalent to about 0.1 g (potency) according to the labeled potency, and perform the test at 50 revolutions per minute according to Method 2, using 900 mL of Solution 1 for the Disintegration as the dissolution medium. Take NLT 20 mL of the dissolved solution 20 minutes after starting the test, and filter. Discard the first 10 mL of the filtrate, pipet 2 mL of the subsequent filtrate, add water to make exactly 20 mL, and use this solution as the test solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy using the dissolution medium as a control solution; it meets the requirements if the dissolution rate of Cefditoren Pivoxil Fine Granules in 30 minutes is NLT 80%.

Particle size distribution estimation by analytical sieving Meets the requirements.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Perform the test using a light-resistant container protected from direct sunlight. Weigh accurately an amount of powdered Cefditoren Pivoxil Fine Granules, equivalent to about 40 mg (potency) of cefditoren pivoxil according to the labeled amount, add 70 mL of diluted acetonitrile (3 in 4), and shake vigorously to mix. To this solution, add exactly 10 mL of the internal standard solution and acetonitrile to make 100 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 20 mg (potency) of cefditoren pivoxil RS, dissolve in 20 mL of acetonitrile, add exactly 5 mL of the internal standard solution, add acetonitrile to make 50 mL, and use this solution as the standard solution. Perform the test as directed under the Assay of Cefditoren Pivoxil.

$$\text{Potency (μg) of cefditoren } (C_{19}H_{18}N_6O_5S_3) = \text{Potency (μg) of cefditoren pivoxil RS} \times \frac{Q_T}{Q_S} \times 2$$

Internal standard solution—An acetonitrile solution of propyl *p*-hydroxybenzoate (1 in 200).

Packaging and storage Preserve in light-resistant, tight containers.

Cefditoren Pivoxil Tablets
세프디토렌피복실 정

Cefditoren Pivoxil Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of cefditoren ($C_{19}H_{18}N_6O_5S_3$: 506.58).

Method of preparation Prepare as directed under Tablets, with Cefditoren Pivoxil.

Identification (1) Powder Cefditoren Pivoxil Tablets, weigh a portion of the powder equivalent to 35 mg (potency) of cefditoren pivoxil according to the labeled amount, add 100 mL of methanol, shake to mix, and filter. To 5 mL of the filtrate, add methanol to make 100 mL, and determine the absorption spectrum of the resulting solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 229 nm and 233 nm.

(2) Perform the test as directed under the Assay; the test solution and the standard solution exhibit peaks at the same retention time.

Loss on drying NMT 4.0% (0.5 g, in vacuum at the pressure not exceeding·0.67 kPa, 60 ℃, 3 hours).

Dissolution Perform the test with 1 tablet of Cefditoren Pivoxil Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of Solution 1 for dissolution test as the dissolution medium. Take NLT 20 mL of the dissolved solution after 20 minutes from the beginning of the dissolution test, and filter through a membrane filter with a pore size of NMT 0.45 μm. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add water to make exactly *V'* mL of a solution containing about 11 μg (potency) of cefditoren pivoxil per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 22 mg (potency) of cefditoren pivoxil RS, dissolve in 20 mL of diluted acetonitrile (3 in 4), and add Solution 1 for dissolution test to make exactly 200 mL. Pipet 2 mL of this solution, add water to make exactly 20 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution at the wavelength of 272 nm as directed under the Ultraviolet-visible Spectroscopy, using water as a control solution. Meets the requirements if the dissolution rate of Cefditoren Pivoxil Tablets in 20 minutes is NLT 85%.

$$\text{Dissolution rate (\%) with respect to the labeled amount of cefditoren pivoxil } (C_{25}H_{28}N_6O_7S_3) = \text{Potency (mg) of cefditoren pivoxil RS} \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 45$$

C: Labeled amount [mg (potency)] of cefditoren

pivoxil ($C_{25}H_{28}N_6O_7S_3$) in 1 tablet

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following method. Perform the test using light-resistant containers away from direct sunlight. To 1 tablet of Cefditoren Pivoxil Tablets, add exactly 12.5 mL of Solution 1 for dissolution test, and shake vigorously to mix. Add about 25 mL of acetonitrile, shake to mix again, and add acetonitrile to make exactly 50 mL. Weigh accurately V mL of this solution, equivalent to about 20 mg (potency) of cefditoren pivoxil according to the labeled amount, add exactly 5 mL of the internal standard solution, then add diluted acetonitrile (3 in 4) to make exactly 50 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 20 mg (potency) of cefditoren pivoxil RS, add exactly 2.5 mL of Solution 1 for dissolution test, shake vigorously to mix, dissolve in 20 mL of diluted acetonitrile (3 in 4), add 5 mL of internal standard solution, and then add diluted acetonitrile (3 in 4) again to make exactly 50 mL, and use this solution as the standard solution. Perform the test as directed under the Assay of Cefditoren Pivoxil.

Potency (μg) of cefditoren ($C_{19}H_{18}N_6O_5S_3$)
= Potency (μg) of cefditoren pivoxil RS
× Q_T / Q_S × 50 / V

Internal standard solution—A solution of propyl p-hydroxybenzoate in acetonitrile (1 in 200).

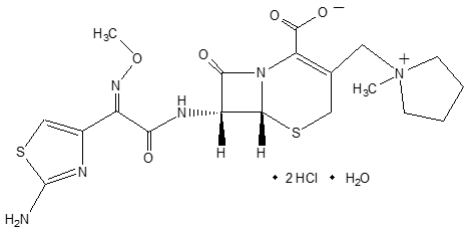
Assay Perform this test using light-resistant containers, protected from direct sunlight. Weigh accurately an amount of Cefditoren Pivoxil Tablets, equivalent to 0.5 g (potency) of cefditoren pivoxil according to the labeled amount, add 63 mL of Solution 1 for dissolution test, shake vigorously to mix, add 125 mL of acetonitrile, shake to mix again, and add acetonitrile to make exactly 250 mL. Pipet 10 mL of this solution, add exactly 5 mL of the internal standard solution, add diluted acetonitrile (3 in 4) to make exactly 50 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 20 mg (potency) of cefditoren pivoxil RS, add 2.5 mL of the Solution 1 for dissolution test, shake vigorously to mix, dissolve in 20 mL of diluted acetonitrile (3 in 4), add 5 mL of internal standard solution, then add diluted acetonitrile (3 in 4) to make exactly 50 mL, and use this solution as the standard solution. Perform the test as directed under the Assay of Cefditoren Pivoxil.

Potency (μg) of cefditoren ($C_{19}H_{18}N_6O_5S_3$)
= Amount (μg) of cefditoren pivoxil RS × Q_T / Q_S × 25

Internal standard solution—A solution of propyl p-hydroxybenzoate in acetonitrile (1 in 200).

Packaging and storage Preserve in tight containers.

Cefepime Dihydrochloride Hydrate
세페핌염산염수화물



$C_{19}H_{24}N_6O_5S_2 \cdot 2HCl \cdot H_2O$: 571.50

(6R,7R)-7-{2-[(2Z)-2-(2-Amino-1,3-thiazol-4-yl)-2-methoxyimino]acetamido}-3-(1-methyl-pyrrolidin-1-ium-1-yl)methyl-3,4-didehydrocepham-4-carboxylate hydrate dihydrochloride [*123171-59-5*]

Cefepime Dihydrochloride Hydrate contains NLT 835 μg and NMT 886 μg (potency) of cefepime ($C_{19}H_{24}N_6O_5S_2$: 480.56) per mg, calculated on the anhydrous basis.

Description Cefepime Dihydrochloride Hydrate occurs as white to yellow crystals or a crystalline powder.
It is freely soluble in water or methanol, slightly soluble in ethanol(95) and practically insoluble in ether.

Identification (1) Weigh 20 mg (potency) of Cefepime Dihydrochloride Hydrate, dissolve in 2 mL of water, add 1 mL of hydroxylamine hydrochloride solution (1 in 10) and 2 mL of sodium hydroxide TS, and allow to stand for 5 minutes. Then, add 3 mL of 1 mol/L hydrochloric acid TS, and 3 drops of Iron(III) chloride TS; the solution exhibits a reddish brown color.

(2) Weigh about 15 mg (potency) of Cefepime Dihydrochloride Hydrate, dissolve in 5 mL of water, and add 2 drops of silver nitrate TS; the solution becomes turbid in white.

(3) Determine the absorption spectra of aqueous solutions of Cefepime Dihydrochloride Hydrate and cefepime hydrochloride RS (1 in 20000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared spectra of Cefepime Dihydrochloride Hydrate and cefepime hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(5) Weigh 50 mg (potency) of Cefepime Dihydrochloride Hydrate, dissolve in 5 mL of deuterium water, and determine the nuclear magnetic resonance spectrum as directed under the Nuclear Magnetic Resonance Spectroscopy (^{1}H); it exhibits a single line signal at around 3.1 ppm and around 7.2 ppm, respectively, and the area ratio strength of each signal is 3 : 1.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between +39° and +47° (60 mg calculated on the anhydrous basis, water, 20 mL, 100 mm).

Absorbance $E_{1cm}^{1\%}$ (259 nm): Between 310 and 340 (60 mg calculated on the anhydrous basis, water, 1 mL).

pH Dissolve 0.1 g (potency) of Cefepime Dihydrochloride Hydratein in 10 mL of water; the pH is between 1.6 and 2.1.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Cefepime Dihydrochloride Hydrate in 50 mL of an arginine solution; the solution is clear and the color of the solution is not more intense than the Matching Fluid for Color H.

(2) ***Heavy metals***—Proceed with 1.0 g of Cefepime Dihydrochloride Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 20 ppm).

(3) ***Related substances***—(i) *N*-Methylpyrrolidone: Weigh accurately about 80 mg (potency) of Cefepime Dihydrochloride Hydrate, dissolve in dilute nitric acid (2 in 3125) to make exactly 10 mL, and use this solution as the test solution. Separately, add 30 mL of water to a 100-mL volumetric flask and weigh accurately the mass. Spot about 0.125 g of *N*-methylpyrrolidone RS into this solution, weigh accurately the mass, and add water to this solution to make 100 mL. Take exactly 4 mL of this solution, add diluted nitric acid (2 in 3125) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 100 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak areas, A_T and A_S, of *N*-Methylpyrrolidone in the test solution and in the standard solution.

$$\text{Content (\%) of } N\text{-methylpyrrolidone} = \frac{Amount\ (mg)\ of\ N\text{-methylpyrrolidone RS} \times f}{Amount\ (mg)\ of\ Cefepime\ Dihydrochloride\ Hydrate\ taken} \times \frac{A_T}{A_S} \times \frac{1}{250}$$

f: Purity (%) of *N*-methylpyrrolidone RS

Operating conditions

Detector: An electrical conductivity detector

Column: A plastic tube about 4.6 mm in internal diameter and about 5 cm in length, packed with 5 μm of hydrophilic silica gel for liquid chromatography, was introduced with sulfonic acid groups with an exchange capacity of about 0.3 meq/g.

Column temperature: A constant temperature of about 35 °C.

Mobile phase: Add 10 mL of acetonitrile to 990 mL of diluted nitric acid (2 in 3125).

Flow rate: 1.0 mL/min

System suitability

System performance: Add about 0.125 g of *N*-methylpyrrolidone RS to 20 mL of a sodium chloride solution (3 in 1000). Take exactly 4 ml of the solution prepared by adding water to make 100 mL, and add diluted nitric acid (2 in 3125) to make 100 mL. Proceed with 100 μL of this solution under the above operating conditions; sodium and *N*-methylpyrrolidone are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 5 times with 100 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area of *N*-methylpyrrolidone is NMT 4.0%.

(ii) Other related substances: Weigh accurately about 0.1 g (potency) of Cefepime Dihydrochloride Hydrate, dissolve in the mobile phase A to make exactly 50 mL, and use this solution as the test solution. Take 5 μL of the test solution and perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the peak area in the test solution and calculate the amount of related substances as directed under the percentage peak area method (NMT 0.5%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Mix the mobile phase A with the mobile phase B from 0% to 25% at a rate of 1% per minute.

Mobile phase A: Dissolve 0.57 g of ammonium dihydrogen phosphate in 1000 mL of water.

Mobile phase B: Acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of cefepime is about 9.5 minutes.

System suitability

Test for required detectability: Pipet 1.0 mL of the test solution, add the mobile phase A to make exactly 10 mL, and use this solution as the system suitability solution. Pipet 1 mL of the system suitability solution, add the mobile phase A to make 10 mL, and use this solution as the detection confirmation solution. Pipet 1 mL of the detection confirmation solution and add the mobile phase A to make 10 mL. Confirm that the peak area of cefepime obtained from 5 μL of this solution is 7 to 13% of the peak area of cefepime obtained from 5 μL of the detection confirmation solution.

System performance: Proceed with 5 μL of the system suitability solution under the above operating conditions; the number of theoretical plates of the peak of cefepime is NMT 6000.

System repeatability: Repeat the test 3 times with 5 mL of the system suitability solution under the above operating conditions; the relative standard deviation of the peak area for cefepime is NMT 2.0%.

Time span of measurement: About 2.5 times of the retention time of cefepime.

Water Between 3.0% and 4.5%. However, weigh accurately about 50 mg of Cefepime Dihydrochloride Hydrate, and dissolve in 2 mL of methanol for water determination. Pipet 0.5 mL of this solution and perform the test (volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Sterility It meets the requirements when used in sterility preparations. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins It is less than 0.04 EU per mg of cefepime (potency) when used in the manufacturing of sterile preparations. Weigh accurately about 30 mg (potency) of Cefepime Dihydrochloride Hydrate, dissolve in water for bacterial endotoxins, and adjust the pH to 6.0 to 7.5 using 1 mol/L sodium hydroxide TS for bacterial endotoxins or 1 mol/L hydrochloric acid TS for bacterial endotoxins, and then add water for bacterial endotoxins again to make exactly 5 mL. Pipet a certain amount of this solution, add water for bacterial endotoxins to reach an appropriate concentration, and use this solution as the test solution.

Assay Weigh accurately about 60 mg (potency) each of Cefepime Dihydrochloride Hydrate and cefepime dihydrochloride hydrate RS, dissolve each in the mobile phase to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Proceed with 10 μL each of the test solution and the standard solution, and perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of cefepime in the test solution and the standard solution.

$$\text{Potency (μg) of cefepime } (C_{19}H_{24}N_6O_5S_2) = \text{Potency (μg) of cefepime dihydrochloride hydrate RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Adjust the pH of sodium 1-pentanesulfonate solution (261 in 100000) to 3.4 using acetic acid(100), and then adjust the pH to 4.0 using potassium hydroxide solution (13 in 20). Add 50 mL of acetonitrile to 950 mL of this solution.

Flow rate: Adjust the flow rate so that the retention time of cefepime is about 8 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; the number of theoretical plates of the peak of cefepime is NMT 1500.

System repeatability: Repeat the test 5 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of cefepime is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Cefepime Dihydrochloride for injection
주사용 세페핌염산염

Cefepime Dihydrochloride for injection, as an injection that is dissolved upon use, contains NLT 95.0% and NMT 110.0% of the labeled amount of cefepime ($C_{19}H_{24}N_6O_5S_2$: 480.56).

Method of preparation Prepare as directed under Injections, with Cefepime Dihydrochloride Hydrate.

Description Cefepime Dihydrochloride for injection occurs as a white to pale yellow powder.

Identification Perform the test with Cefepime Dihydrochloride for injection as directed under the Identification (1) and (3) under Cefepime Dihydrochloride Hydrate.

pH Dissolve an amount of Cefepime Dihydrochloride for injection equivalent to 0.1 g (potency) of cefepime dihydrochloride in 1 mL of water; the pH of this solution is between 4.0 and 6.0.

Purity (1) ***Clarity and color of solution***—Dissolve an amount of Cefepime Dihydrochloride for injection, equivalent to 0.5 g (potency) of cefotiam hydrochloride hydrate according to the labeled amount, in 5 mL of water; the resulting solution is colorless or pale yellow.

(2) ***N-Methylpyrrolidone***—Perform the test as directed under the Purity (2) under Cefepime Dihydrochloride Hydrate. However, weigh accurately about 0.2 g (potency) according to the labeled potency of Cefepime Dihydrochloride for injection, dissolve in diluted nitric acid (2 in 625) to make exactly 20 mL, and use this solution as the test solution (NMT 1.0%).

Water NMT 4.0%. However, perform the test as directed under the Water test under Cefepime Dihydrochlo-

ride Hydrate (volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Meets the requirements. Cefepime Dihydrochloride for injection is NLT 0.06 EU per mg (potency) of cefepime. However, dissolve about 0.1 g (potency) according to the labeled potency of Cefepime Dihydrochloride for injection in water for endotoxin assay, adjust the pH, if necessary, to between 6.0 and 7.5 using 0.1 mol/L sodium hydroxide TS for endotoxin assay or 0.1 mol/L hydrochloric acid TS for endotoxin assay, and add water for endotoxin assay to make a solution having a known concentration of about 0.1 g (potency) per mL. Pipet a certain amount of this solution, add water for endotoxin assay to reach an appropriate concentration, and use this solution as the test solution.

Particulate contamination: Visible particles Meets the requirements.

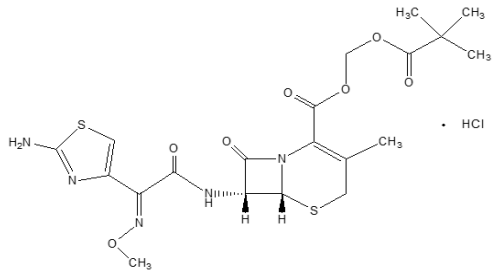
Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay under Cefepime Dihydrochloride Hydrate. However, weigh accurately about 60 mg (potency) according to the labeled potency of Cefepime Dihydrochloride for injection, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the test solution.

Packaging and storage Preserve in hermetic containers.

Cefetamet Pivoxil Hydrochloride
세페타메트피복실염산염



$C_{20}H_{25}N_5O_7S_2 \cdot HCl$: 548.04

(6*R*,7*R*)-(2,2-Dimethyl-1-oxopropoxy)methyl 7-[[(2*Z*)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid hydrochloride (1:1), [*65243-33-6*]

Cefetamet Pivoxil Hydrochloride contains NLT 653 μg (potency) of cefetamet $C_{14}H_{15}N_5O_5S_2$: 397.43) per mg, calculated on the anhydrous basis.

Description Cefetamet Pivoxil Hydrochloride occurs as a white to pale yellow crystalline powder.
It is odorless or has a slight, characteristic odor and a bitter taste.
It is very soluble in methanol or dimethylformamide, freely soluble in ethanol and practically insoluble in water or ether.

Identification (1) Weigh 10 mg (potency) of Cefetamet Pivoxil Hydrochloride, dissolve in 2 mL of diluted methanol (1 → 2), add 3 mL of a hydroxylamine hydrochloride-ethanol solution, and allow it to stand for 5 minutes. Add 1 mL of acidic ammonium iron(III) sulfate TS, and shake well to mix; the solution exhibits a reddish brown color.

(2) Weigh 50 mg (potency) of Cefetamet Pivoxil Hydrochloride, dissolve in 2 mL of methanol, add 3 ml of dilute nitric acid and 1 mL of silver nitrate TS, and shake well to mix; a white precipitate is formed.

(3) Determine the infrared spectra of Cefetamet Pivoxil Hydrochloride and cefetamet pivoxil hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) Determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy with a solution of Cefetamet Pivoxil Hydrochloride in 0.01mol/L hydrochloric acid TS (1 in 50000); it exhibits a maximum between 261 nm and 265 nm.

(5) Determine 1H as directed under the Nuclear Magnetic Resonance Spectroscopy with a solution (1 in 20) of deuterated dimethylsulfoxide for nuclear magnetic resonance spectrum of Cefetamet Pivoxil Hydrochloride and tetramethylsilane for nuclear magnetic resonance spectrum as internal standard; it exhibits a single line signal at around 1.2 ppm, 2.0 ppm, 3.9 ppm, and 6.9 ppm, and the area ratio strength of each signal is 9 : 3 : 3 : 1.

Optical rotation $[\alpha]_D^{20}$: Between +76° and +84° (0.25 g, calculated on the anhydrous basis, ethanol, 25 mL, 100 mm).

Absorbance $E_{1cm}^{1\%}$ (263 nm): Between 327 and 347 (20 mg, calculated on the anhydrous basis, 0.1 mol/L hydrochloric acid TS, 1000 mL).

Purity ***Heavy metals***—Proceed with 1.0 g of Cefetamet Pivoxil Hydrochloride according to Method 4 under the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Water NMT 1.0% (1.0 g, volumetric titration, direct titration).

Assay Weigh accurately about 20 mg (potency) of each Cefetamet Pivoxil Hydrochloride and cefetamet pivoxil hydrochloride RS, dissolve in diluent I to make exactly

50 mL. Pipet each 5 mL of this solution, add exactly 6 mL of the internal standard solution, add diluent II to make exactly 50 mL, and use this solution as the test solution and the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S of the peak area of Cefetamet Pivoxil Hydrochloride to that of the internal standard.

$$\text{Potency (μg) of cefetamet } (C_{14}H_{15}N_5O_5S_2) = \text{Potency (μg) of cefetamet pivoxil hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A diluent solution II of diethyl phthalate (1 in 500).

Diluent I—A mixture of water and acetonitrile (11 : 9).

Diluent II—Weigh 3.20 g of tetra *n*-heptylammonium bromide, dissolve in 360 mL of acetonitrile, and add 92 mL of methanol and 548 mL of water.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 263 nm).

Column: A stainless steel column about 6 mm in internal diameter and 150 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 20 °C.

Mobile phase: Weigh 5.796 g of anhydrous sodium dihydrogen phosphate and 3.522 g of potassium dihydrogen phosphate, dissolve in water to make exactly 1000 mL, and use this solution as the solution A. Weigh 20.256 g of citric acid and 7.840 g of sodium hydroxide, dissolve in water to make 1000 mL, and use this solution as the solution B. Weigh 3.20 g of tetra *n*-heptylammonium bromide, dissolve in 360 mL of acetonitrile, and add 92 mL of methanol, 500 mL of water, 44 mL of the solution A and 4 mL of the solution B.

Flow rate: Adjust the flow rate so that the retention time of cefetamet pivoxil is about 10 minutes.

Selection of column: Proceed with 10 μL of the standard solution according to the above conditions; cefetamet pivoxil and the internal standard are eluted in this order with the resolution being NLT 6.0.

Packaging and storage Preserve in tight containers.

Cefetamet Pivoxil Hydrochloride Tablets
세페타메트피복실염산염 정

Cefetamet Pivoxil Hydrochloride Tablets contain cefetamet ($C_{14}H_{15}N_5O_5S$: 397.43) equivalent to NLT 90.0% and NMT 120.0% of the labeled amount.

Method of preparation Prepare as directed under Tablets, with Cefetamet Pivoxil Hydrochloride.

Identification (1) Weigh about 20 mg (potency) according to the labeled amount of Cefetamet Pivoxil Hydrochloride Tablets, add 2 mL of methanol, shake to mix, and centrifuge at 2500 revolutions per minute for 10 minutes. To 1 mL of the clear supernatant, add 1 mL of water and 3 mL of hydroxylamine hydrochloride-ethanol TS, allow to stand for 5 minutes, add 1 mL of acidic ammonium iron(III) sulfate TS, and shake to mix; the resulting solution exhibits a reddish brown color.

(2) Weigh about 10 mg (potency) according to the labeled amount of Cefetamet Pivoxil Hydrochloride Tablets, add about 30 mL of 0.1 mol/L hydrochloric acid TS, and sonicate for 2 minutes. Add 0.1 mol/L hydrochloric acid TS to make 50 mL, and filter. To 5 mL of the filtrate, add 0.1 mol/L hydrochloric acid TS to make exactly 50 mL, and use this solution as the test solution. Perform the test with the test solution as directed under the Identification (4) of Cefetamet Pivoxil Hydrochloride.

(3) Weigh accurately about 0.1 g (potency) according to the labeled amount of Cefetamet Pivoxil Hydrochloride Tablets, add 8.8 mL of methanol, and shake to mix for 10 minutes. Then, add 1.0 mL of a solution of calcium chloride in methanol (1 in 8) and 0.2 mL of a mixture of methanol and strong ammonia water (3 : 2), shake to mix, and centrifuge at 3000 revolutions per minute for 10 minutes. Use the clear supernatant as the test solution. Separately, weigh about 20 mg (potency) of cefetamet pivoxil hydrochloride RS, dissolve in 2.0 mL of methanol, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the 0.2 mm-thick thin-layer chromatographic plate made using silica gel with fluorescent indicator for thin-layer chromatography prepared by combining 10 μm to 12 μm silica gel with octadecyl group. Develop the plate with a mixture of methanol and hydrochloric acid potassium chloride buffer solution TS (pH 2.0) (8 : 5) as the developing solvent to a distance of about 12 cm, and air-dry the plate, and examine the plate under ultraviolet light (main wavelength: 254 nm); the spots obtained from the test solution and the standard solution exhibit a dark violet color, and the Rf values obtained from the test solution and the standard solution are the same.

Water NMT 2.0% (0.5 g, volumetric titration, direct titration).

Dissolution Perform the test with 1 tablet of Cefetamet Pivoxil Hydrochloride Tablets at 100 revolutions per minute using a sinker according to Method 2 under the Dissolution, using 900 mL of Solution 1 in the Disintegration

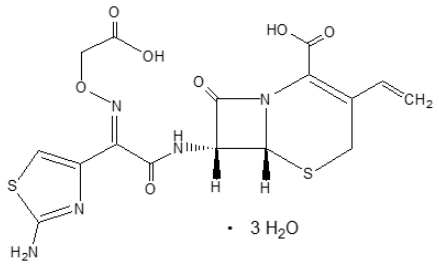
as the dissolution medium. Take 20 mL of the dissolved solution 60 minutes after starting the test, and filter through a membrane filter with a pore size of NMT 0.5 μm. Discard the first 10 mL of this filtrate, pipet a suitable amount of the subsequent filtrate, and add dissolution medium to dilute so that the dissolved solution contains 20 to 30 μg (potency). Use this solution as the test solution. Separately, weigh accurately about 15 mg of cefetamet pivoxil hydrochloride RS, and dissolve in the dissolution medium to make exactly 50 mL. Pipet 5 mL of this solution, add the dissolution medium to make exactly 50 mL, and use this solution as the standard solution. With the test solution and the standard solution, perform the test as directed under the Ultraviolet-visible Spectroscopy using the dissolution medium as a control solution, and determine the absorbances, A_T and A_S, at the wavelength of 263 nm. It meets the requirements when the amount dissolved of Cefetamet Pivoxil Hydrochloride Tablets in 60 minutes is NLT 75.0% of the labeled potency.

Uniformity of dosage units Meets the requirements.

Assay Proceed as directed under the Assay under Cefetamet Pivoxil Hydrochloride. Weigh accurately about 20 mg (potency) according to the labeled amount of Cefetamet Pivoxil Hydrochloride Tablets, dissolve in 40 mL of diluent I, sonicate for 2 minutes, and add diluent I again to make exactly 50 mL. Centrifuge this solution at 3000 revolutions per minute for 10 minutes, pipet 5 mL of the clear supernatant, add exactly 6 mL of the internal standard solution, and add diluent II to make exactly 50 mL. Use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Cefixime
세픽심수화물



Cefixime $C_{16}H_{15}N_5O_7S_2 \cdot 3H_2O$: 507.50
(6*R*,7*R*)-7-[(2*E*)-2-(2-Amino-1,3-thiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-ethenyl-3,4-didehydrocepham-4-carboxylic acid trihydrate [*125110-14-7*]

Cefixime Hydrate contains NLT 930 μg (potency) and NMT 1020 μg (potency) of cefixime ($C_{16}H_{15}N_5O_7S_2$: 453.45) per mg, calculated on the anhydrous basis.

Description Cefixime Hydrate occurs as a white to pale yellow crystalline powder.
It is freely soluble in methanol or dimethylsulfoxide, sparingly soluble in ethanol(99.5), and practically insoluble in water.

Identification (1) Determine the absorption spectra of solutions of Cefixime Hydrate and cefixime RS in 0.1 mol/L phosphate buffer solution, pH 7.0 (1 in 62500) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cefixime Hydrate and cefixime RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 50 mg of Cefixime Hydrate in 0.5 mL of a mixture of deuterated dimethylsulfoxide for nuclear magnetic resonance spectroscopy and deuterium oxide for nuclear magnetic resonance spectroscopy (4:1). With this solution, determine ^1H as directed under the Nuclear Magnetic Resonance Spectroscopy using tetramethylsilane
for nuclear magnetic resonance spectroscopy as the internal standard; the resulting spectrum exhibits the singlet signal A near δ 4.7 ppm, the multiplet signal B near δ 6.5 ppm to δ 7.4 ppm, and the area intensity ratio A : B of each signal is 1 : 1.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between -75° and -88° (0.45 g, calculated on the anhydrous basis, sodium bicarbonate (1 in 50), 50 mL, 100 mm).

pH The pH of a saturated solution of Cefixime Hydrate is between 2.4 and 4.1.

Absorbance $E_{1cm}^{1\%}$ (288 nm): Between 500 and 550 (70 mg, calculated on the anhydrous basis, 0.1 mol/L phosphate buffer (pH 7.0), 5 L).

Purity ***Related Substances***—Dissolve 0.1 g of Cefixime Hydrate in 100 mL of 0.1 mol/L phosphate buffer solution, pH 7.0, and use this solution as the test solution. With 10 μL of the test solution, perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method and determine their amounts by the percentage peak area method; the amount of each peak other than cefixime is NMT 1.0% and the total amount of peaks other than cefixime is NMT 2.5%.

Operating conditions

Proceed as directed under the operating conditions under the Assay.

System suitability

Test for required detectability: Pipet 1 mL of the test solution and add 0.1 mol/L phosphate buffer solution, pH 7.0, to make exactly 100 mL. Confirm that the height of the cefixime peak obtained from 10 μL of this solution is between 20 and 60 mm.

System performance: Dissolve about 2 mg of the cefixime RS in 200 mL of 0.1 mol/L phosphate buffer solution, pH 7.0, and use this solution as the system suitability solution. With 10 μL of this solution, proceed according to the above conditions; the number of theoretical plate and the symmetry factor of the peak of cefixime are NLT 4000 and NMT 2.0, respectively.

System repeatability: Repeat the test 6 times with 10 μL each of the system suitability solution according to the above conditions; the relative standard deviation of the peak areas of cefixime is NMT 2.0%.

Time span of measurement: About 3 times the retention time of cefixime from the solvent peak.

Water Between 9.0% and 12.0% (0.1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.1 g (potency) each of Cefixime Hydrate and cefixime RS, dissolve in 0.1 mol/L phosphate buffer solution, pH 7.0, to make exactly 100 mL. Pipet 10 mL each of these solutions, add 0.1 mol/L phosphate buffer solution, pH 7.0, to make exactly 50 mL, and use these solutions as the test solution and the standard solution. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas A_T and A_S of cefixime.

$$\text{Potency (μg) of cefixime } (C_{16}H_{15}N_5O_7S_2) = \text{Potency (μg) of cefixime RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 125 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (4 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Take 25 mL of a solution of tetrabutylammonium hydroxide TS (10 in 13), add water to make 1000 mL, and adjust the pH to 6.5 with diluted phosphoric acid (1 in 10). To 300 mL of this solution, add 100 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of cefixime is about 10 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the number of theoretical plates and the symmetry factor of cefixime are NLT 4000 and NMT 2.0, respectively.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the ratios of cefixime peak area is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Cefixime Fine Granules
세픽심 세립

Cefixime Fine Granules contain NLT 90.0% and NMT 120.0% of labeled amount of cefixime ($C_{16}H_{15}N_5O_7S_2$: 453.45).

Method of preparation Prepare microparticles as directed under Powders, with Cefixime Hydrate.

Identification (1) Weigh about 10 mg of Cefixime Fine Granules, dissolve in 0.5 mL of sodium bicarbonate solution (21 in 2500) and 1.5 mL of water, add 3 mL of hydroxylamine hydrochloride TS, and allow to stand for 5 minutes. Add 1 mL of dilute ammonium iron(III) sulfate TS and shake to mix; the resulting solution exhibits a reddish brown color.

(2) Weigh 1 mg of Cefixime Fine Granules, add 1 drop of sodium bicarbonate solution (21 in 2500) and 4 mL of water to dissolve, and add 1 mL of dilute hydrochloric acid while cooling with ice. Add 1 mL of freshly prepared sodium nitrite solution (1 in 100), shake to mix allow to stand in an iced water for 2 minutes, add 1 mL of ammonium sulfamate TS while cooling with ice, shake to mix, and allow to stand for 1 minute. Add 1 mL of *N*-(1-naphthyl)ethylenediamine dihydrochloride (1 in 1000); the resulting solution exhibits a reddish purple color.

(3) Weight about 2 mg (potency) of Cefixime Fine Granules according to the labeled potency, dissolve in 150 mL of 0.1 mol/L phosphate buffer solution (pH 7.0), and determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy; it exhibits absorption maximum between 286 nm and 290 nm.

Water NMT 3.0% (1.0 g, volumetric titration, direct titration). For the solvent, use a mixture of formamide for water determination and methanol, instead of methanol for water determination.

Particle size distribution estimation by analytical sieving Meets the requirements.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Weigh accurately 0.1 g (potency) of powdered

Cefixime Fine Granules according to the labeled potency, add 70 mL of 0.1 mol/L phosphate buffer solution (pH 7.0), shake to mix, and add 0.1 mol/L phosphate buffer solution, (pH 7.0) to make exactly 100 mL. Centrifuge this solution at 3000 rpm for 10 minutes, pipet 10 mL of the clear supernatant, add 10.0 mL of the internal standard solution and 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of cefixime RS, and add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 100 mL. Pipet 10 mL of this solution, add 10.0 mL of the internal standard solution and 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of cefixime to the internal standard, respectively.

$$\text{Potency (μg) of cefixime } (C_{16}H_{15}N_5O_7S_2) = \text{Potency (μg) of cefixime RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh about 0.37 g of 2-naphthalenesulfonic acid, and dissolve in 100 mL of 0.1 mol/L phosphate buffer solution (pH 7.0).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 25 to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (7 μm in particle diameter).

Mobile phase: Take 25 mL of 0.4 mol/L tetrabutylammonium hydroxide solution, add water to make 1000 mL, adjust the pH to 7.0 with diluted phosphoric acid (1 in 10). To 290 mL of this solution, add 110 mL of acetonitrile, and use after degassing.

Flow rate: Adjust the flow rate so that the retention time of cefixime is about 9 minutes.

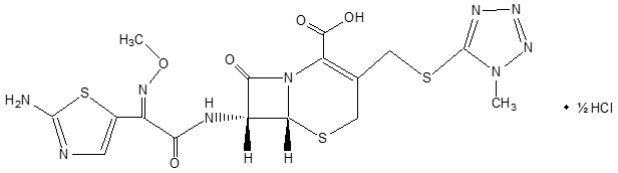
System suitability

System performance: Perform the test with 5 μL of the standard solution under the above operating conditions; cefixime and 2-naphthalenesulfonic acid are eluted in this order with the resolution between these peaks being NLT 4.0.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution according to the above conditions; the relative standard deviation of the ratios of the peak area of cefixime to that of the internal standard is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Cefmenoxime Hydrochloride
세프메녹심염산염



$C_{16}H_{17}N_9O_5S_3 \cdot ½HCl$: 529.79

(6*R*,7*R*)-7-[(2*E*)-2-(2-Amino-1,3-thiazol-5-yl)-2-methoxyiminoacetamido]-3-[2-(1-methyltetrazol-5-yl)sulfanylmethyl]-3,4-didehydrocepham-4-carboxylic acid hemihydrochloride [*75738-58-8*]

Cefmenoxime Hydrochloride contains NLT 890 μg (potency) and NMT 975 μg (potency) of cefmenoxime ($C_{16}H_{17}N_9O_5S_3$: 511.56) per mg, calculated on the anhydrous basis.

Description Cefmenoxime Hydrochloride occurs as white to pale orange-yellow crystals or a crystalline powder.

It is freely soluble in formamide or dimethylsulfoxide, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol(95).

Identification (1) Determine the absorption spectrum of a solution of Cefmenoxime Hydrochloride in 0.1 mol/L phosphate buffer (pH 6.8) (3 in 200000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima at the wavelengths between 230 nm and 234 nm and between 255 nm and 259 nm.

(2) Determine the infrared spectra of Cefmenoxime Hydrochloride and cefmenoxime hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Determine the nuclear magnetic resonance spectrum of a solution prepared by dissolving 50 mg (potency) of Cefmenoxime Hydrochloride in 0.5 mL of deuterated dimethylsulfoxide, as directed under the Nuclear Magnetic Resonance Spectroscopy (^1H); it exhibits 2 singlet signals at about 3.9 ppm and a singlet signal at about 6.8 ppm, with the ratio of area strength of the signals being 3 : 3 : 1.

(4) Dissolve 10 mg (potency) of Cefmenoxime Hydrochloride in 1 mL of diluted sodium carbonate TS (1 in 20), and add 5 mL of acetic acid(100) and 2 drops of silver nitrate TS; a white precipitate is formed.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between -27° and -35° [1 g, 0.1 mol/L phosphate buffer (pH 6.8), 100 mL, 100 mm].

pH Dissolve 10 g (potency) of Cefmenoxime Hydrochloride in 150 mL of water. The pH of this solution is

between 2.8 and 3.3.

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Cefmenoxime Hydrochloride in 10 mL of diluted sodium carbonate TS (1 in 4); the solution is clear and colorless to pale yellow.

(2) ***Heavy metals*—**Proceed with 1.0 g of Sodium Sulfamethoxazole as directed under Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic*—**Prepare the test solution with 1.0 g of Cefmenoxime Hydrochloride according to Method 4 and perform the test. After cooling, add 10 mL of dilute hydrochloric acid to the residue (NMT 2 ppm).

(4) ***Related substances*—**Weigh accurately about 0.1 g of Cefmenoxime Hydrochloride, dissolve in 20 mL of 0.1 mol/L phosphate buffer (pH 6.8), and add the mobile phase to make exactly 100 mL. Pipet 4 mL of this solution, add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of 1-methyl-1*H*-tetrazole-5-thiol and dissolve in the mobile phase to make exactly 100 mL. Pipet 4 mL of this solution. add the mobile phase to make exactly 250 mL and use this solution as the standard solution (1). Separately, weigh accurately about 0.1 g of cefmenoxime hydrochloride RS, dissolve in 20 mL of 0.1 mol/L phosphate buffer (pH 6.8), and add the mobile phase to make exactly 100 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 250 mL, and use this solution as the standard solution (2). Immediately after preparation, pipet 10 μL each of the test solutions, the standard solution (1) and the standard solution (2), perform the test with these solutions as directed under the Liquid Chromatography according to the following operating conditions, and determine individual peak areas in each of the respective solutions. Determine the amounts of 1-methyl-1*H*-tetrazole-5-thiol and total related substances according to the following equation; the amounts are NMT 1.0% and 3.0%, respectively.

$$\text{1-methyl-1}H\text{-tetrazole-5-thiol (\%)} = \frac{W_{Sa}}{W_T} \times \frac{A_{Ta}}{A_{Sa}} \times 20$$

$$\text{Content (\%) of total related substances} = \left\{\frac{W_{Sa}}{W_T} \times \frac{A_{Ta}}{A_{Sa}} \times 20\right\} + \left\{\frac{W_{Sb}}{W_T} \times \frac{A_T}{A_{Sb}} \times 5\right\}$$

W_{Sa}: Amount (g) of 1-methyl-1*H*-tetrazole-5-thiol

W_{Sb}: Amount (g) of cefmenoxime hydrochloride RS

W_T: Amount (g) of Cefotetan

A_{Sa}: Peak area of 1-methyl-1*H*-tetrazole-5-thiol in the standard solution (1)

A_{Sb}: Peak area of cefmenoxime in the standard solution (2)

A_{Ta}: Peak area of 1-methyl-1H-tetrazole-5-thiol in the test solution

S_T: The sum of peak areas, other than 1-methyl-1H-tetrazole-5-thiol and cefmenoxime, in the test solution

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

System performance: Proceed as directed under the system suitability under the Assay.

Test for required detectability: Pipet 5 mL of the standard solution (1) and add the mobile phase to make exactly 100 mL. The peak area of 1-methyl-1*H*-tetrazole-5-thiol obtained from 10 μL of this solution is within the range between 4.5% and 5.5% of the peak area of 1-methyl-1*H*-tetrazole-5-thiol from the standard solution (1). Next, pipet 2 mL of the standard solution (2) and add the mobile phase to make exactly 100 mL. Confirm that the peak area of cefmenoxime obtained from 10 μL of this solution is within the range between 1.5% and 2.5% of the peak area of cefmenoxime from the standard solution (2).

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution (1) according to the above conditions; the relative standard deviation of the peak area of 1-methyl-1H-tetrazole-5-thiol is NMT 1.0%.

Time span of measurement: About 2.5 times the retention time of cefmenoxime.

Water NMT 1.5% (1 g, volumetric titration, direct titration). For the solvent, use a mixture of formamide for water determination and methanol (2 : 1) instead of methanol for water determination.

Sterility It meets the requirements when Cefmenoxime Hydrochloride is used in a sterile preparation. However, it is excluded when there is a terminal sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins It is less than 0.083 EU per mg (potency) of cefmenoxime when used in a sterile preparation.

Assay Weigh accurately about 50 mg each of Cefmenoxime Hydrochloride and cefmenoxime hydrochloride RS, dissolve in 10 mL of 0.1 mol/L phosphate buffer (pH 6.8), and add the mobile phase to make exactly 50 mL. Pipet 4 mL each of these solutions, add exactly 20 mL of the internal standard solution to each, add the mobile phase to each to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following operating conditions, and calculate the peak area ratios, Q_T and Q_S, of cefmenoxime to the internal standard in the test solution and the standard solution, respectively.

$$\text{Potency (μg) of cefmenoxime } (C_{16}H_{17}N_9O_5S_3) = \text{Potency (μg) of cefmenoxime hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of phthalamide in methanol (3 in 2000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μ*m* in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: To 1000 mL of water, add 200 mL of acetonitrile and 20 mL of acetic acid(100).

Flow rate: Adjust the flow rate so that the retention time of cefmenoxime is about 8 minutes.

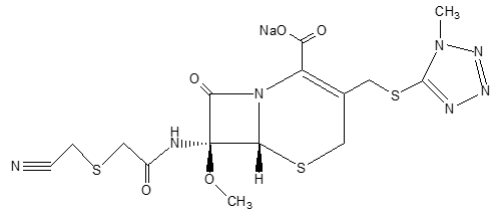
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; cefmenoxime and the internal standard are eluted in this order with the resolution being NLT 2.3.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area ratio of cefmenoxime to the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Cefmetazole Sodium
세프메타졸나트륨



$C_{15}H_{16}N_7NaO_5S_3$: 493.52

Sodium (6*R*,7*S*)-7-[2-(cyanomethylsulfanyl)acetamido]-7-methoxy-3-[2-(1-methyltetrazol-5-yl)sulfanylmethyl]-3,4-didehydrocepham-4-carboxylate [*56796-39-5*]

Cefmetazole Sodium contains NLT 860 μg (potency) and NMT 965 μg (potency) of cefmetazole ($C_{15}H_{17}N_7O_5S_3$: 471.53) per mg, calculated on the anhydrous basis.

Description Cefmetazole Sodium occurs as a white to pale yellowish white powder or a mass.

It is very soluble in water, freely soluble in methanol, slightly soluble in ethanol(95), and practically insoluble in tetrahydrofuran.

It is hygroscopic.

Identification (1) Dissolve 25 mg (potency) of Cefmetazole Sodium in water to make 1000 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at wavelengths between 270 nm and 274 nm.

(2) Determine the infrared spectra of Cefmetazole Sodium and cefmetazole sodium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Determine ^1H of a solution of Cefmetazole Sodium in deuterium oxide for nuclear magnetic resonance spectroscopy (1 in 10) as directed under the Nuclear Magnetic Resonance Spectroscopy; it exhibits singlet signals at about δ 3.6 ppm, δ 4.1 ppm and δ 5.2 ppm, with the ratio of area strength of the signals being 3 : 3 : 1.

(4) Cefmetazole Sodium responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between +73° and +85° (0.25 g, water, 25 mL, 100 mm).

pH Dissolve 1 g (potency) of Cefpiramide Sodium in 10 mL of water; the pH of this solution is between 4.2 and 6.2.

Absorbance $E_{1cm}^{1\%}$ (272 nm): Between 200 and 230 (25 mg, calculated on the anhydrous basis, water, 1000 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Cefmetazole Sodium in 10 mL of water; the solution is clear and colorless to pale yellow.

(2) ***Heavy metals***—Proceed with 1.0 g of Cefmetazole Sodium as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Prepare the test solution with 1.0 g of Cefmetazole Sodium according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.1 g of Cefmetazole Sodium in 2 mL of water, and use this solution as the test solution. Pipet 1 mL of the test solution, add water to make exactly 25 mL, and use this solution as the standard solution (1). Separately, weigh accurately about 0.10 g of 1-methyl-1*H*-tetrazole-5-thiol, dissolve in water to make exactly 100 mL, and use this solution as the standard solution (2). With these solutions, quickly perform the test as directed under the Thin Layer Chromatography. Spot 1 μL each of the test solutions, the standard solution (1) and the standard solution (2) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, water and acetic acid(100) (4 : 1 : 1) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Allow it to stand in iodine vapor; the spot obtained from the test solution that corresponds to the spot obtained from the standard solution (2) in terms of location is not more intense than the spot from

the standard solution (2), and the spots, other than the principal spot and the above spot, obtained from the test solution are not more intense than the spots from the standard solution (1).

Water NMT 1.0% (1.0 g, volumetric titration, direct titration).

Sterility It meets the requirements when Cefmetazole Sodium is used in a sterile preparation. But it is exempt from the requirements when there is a final sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins It is less than 0.06 EU per mg (potency) of cefmetazole when used in a sterile preparation.

Assay Weigh accurately about 50 mg (potency) each of Cefmetazole Sodium and cefmetazole RS, and add the mobile phase to each to make exactly 25 mL. Pipet 1 mL each of these solutions, add exactly 10 mL of the internal standard solution to each, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following operating conditions, and calculate the peak area ratios, Q_T and Q_S, of cefmetazole to the internal standard in the test solution and the standard solution, respectively.

$$\text{Potency (μg) of cefmetazole } (C_{15}H_{17}N_7O_5S_3) = \text{Potency (μg) of cefmetazole RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of methyl p-hydroxybenzoate in the mobile phase (1 in 10000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 5.75 g of ammonium dihydrogen phosphate in 700 mL of water. To this solution, add 280 mL of methanol, 20 mL of tetrahydrofuran and 3.2 mL of 40% tetrabutylammonium hydroxide TS, and adjust the pH to 4.5 with phosphoric acid.

Flow rate: Adjust the flow rate so that the retention time of cefmetazole is about 8 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; cefmetazole and the internal standard are eluted in this order with the resolution being NLT 10.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area ratio of cefmetazole to the internal standard is NMT 2.0%.

Packaging and storage Preserve in hermetic containers.

Cefmetazole Sodium for Injection
주사용 세프메타졸나트륨

Cefmetazole Sodium for Injection, as an injection that is dissolved upon use, contains NLT 90.0% and NMT 110.0% of the labeled amount of cefmetazole ($C_{15}H_{17}N_7O_5S_3$: 471.53).

Method of preparation Prepare as directed under Injections, with Cefmetazole Sodium.

Description Cefmetazole Sodium for Injection occurs as a white to light yellow powder or a mass.
It is hygroscopic.

Identification (1) Determine the absorption spectra of Cefmetazole Sodium for Injection and an aqueous solution of cefmetazole sodium for injection (1 in 40000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cefmetazole Sodium for Injection and cefmetazole sodium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

pH Dissolve an amount of Cefmetazole Sodium for Injection equivalent to 1.0 g (potency) of cefmetazole sodium in 10 mL of water; the pH of this solution is between 4.2 and 6.2.

Purity (1) ***Clarity and color of solution***—Dissolve an amount equivalent to 1.0 g (potency) of cefmetazole sodium according to the labeled amount of Cefmetazole Sodium for Injection in 10 mL of water; the resulting solution is clear and the color is not more intense than the following control solution.

Control solution—Pipet 5 mL of the colorimetric stock solution of cobalt(II) chloride hexahydrate and 5 mL of the colorimetric stock solution of iron(III) chloride, and add water to make exactly 50 mL. Pipet 15 mL of this solution and add water to make exactly 20 mL.

(2) ***Related substances***—Perform the test as directed under the Purity (4) under Cefmetazole Sodium.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.06 EU per mg (potency) of cefmetazole.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

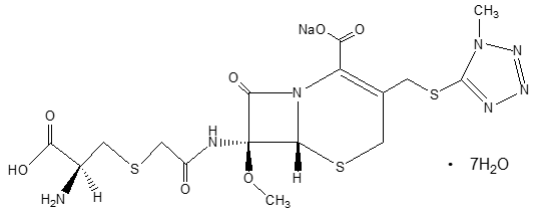
Assay Take 10 containers of Cefmetazole Sodium for Injection, dissolve the contents of each in the mobile phase, combine each solution, and add the mobile phase to make exactly 500 mL. Pipet a volume of this solution equivalent to about 0.2 g (potency) of cefmetazole sodium, and add the mobile phase to make exactly 100 mL. Pipet 1 mL of this solution, add exactly 10 mL of the internal standard solution, and use this solution as the test solution. Separately, weigh accurately an amount equivalent to about 50 mg (potency) of cefmetazole RS and dissolve in the mobile phase to make exactly 25 mL. Pipet 1 mL of this solution, add exactly 10 mL of the internal standard solution, mix, and use this solution as the standard solution. Perform the test as directed under the Assay under Cefmetazole Sodium.

$$\text{Potency (mg) of cefmetazole } (C_{15}H_{17}N_7O_5S_3) = \text{Potency (mg) of cefmetazole RS} \times \frac{Q_T}{Q_S} \times 4$$

Internal standard solution—A solution of methyl *p*-hydroxybenzoate in the mobile phase (1 in 10000).

Packaging and storage Preserve in hermetic containers. Plastic containers for aqueous injections may be used.

Cefminox Sodium Hydrate
세프미녹스나트륨수화물



Cefminox Sodium

$C_{16}H_{20}N_7NaO_7S_3 \cdot 7H_2O$: 667.66

Sodium (6*R*,7*S*)-7-[2-[(2*S*)-2-amino-2-carboxyethyl]sulfanyl]acetamido-7-methoxy-3-[2-(1-methyltetrazol-5-yl)sulfanylmethyl]-3,4-didehydrocepham-4-carboxylate heptahydrate [*88641-36-5*]

Cefminox Sodium Hydrate contains NLT 900 μg (potency) and NMT 970 μg (potency) of cefminox ($C_{16}H_{21}N_7O_7S_3$: 519.58) per mg, calculated on the anhydrous basis.

Description Cefminox Sodium Hydrate occurs as a white to pale yellowish white crystalline powder.
It is freely soluble in water, sparingly soluble in methanol, and practically insoluble in ethanol(95).

Identification (1) Determine the absorption spectra of respective aqueous solutions of Cefminox Sodium Hydrate and cefminox sodium RS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Determine the infrared spectra of Cefminox Sodium Hydrate and cefminox sodium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Determine ^1H of a solution of Cefminox Sodium Hydrate in deuterium oxide for nuclear magnetic resonance spectroscopy (1 in 30) as directed under the Nuclear Magnetic Resonance Spectroscopy, using sodium 3-thylsilylpropanesulfonate for nuclear magnetic resonance spectroscopy; it exhibits the multiplet signal A at about δ 3.2 ppm, singlet signal B at about δ 3.5 ppm, singlet signal C at about δ 4.0 ppm and singlet signal D at about δ 5.1 ppm, with the ratio of area strength of the signals A : B : C : D being about 2 : 3 : 3 : 1.

(4) A solution of Pravastatin Sodium (1 in 100) corresponds to the Qualitative Tests (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between +62° and +72° (50 mg, water, 10 mL, 100 mm).

pH Dissolve 0.70 g of Cefpirome Sulfate in 10 mL of water; the pH of this solution is between 4.5 and 6.0.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Cefminox Sodium Hydrate as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Prepare the test solution with 2.0 g of Cefminox Sodium Hydrate according to Method 3 and perform the test (NMT 1 ppm).

Water Between 18.0% and 20.0% (0.1 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in sterile preparations. However, it is excluded in cases where there is a final sterilization process in the manufacturing of a sterile preparation.

Bacterial endotoxins It is less than 0.05 EU per mg (potency) of cefminox when used in a sterile preparation.

Assay Weigh accurately about 70 mg (potency) each of

Cefminox Sodium Hydrate and cefminox sodium RS, add water to each to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of cefminox, respectively.

$$\text{Potency (μg) of cefminox } (C_{16}H_{21}N_7O_7S_3) = \text{Potency (μg) of cefminox sodium RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 273 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of buffer and methanol (9 : 1).

Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of cefminox is NMT 1.0%.

Buffer—Dissolve 2.04 g of sodium acetate trihydrate in 750 mL of water, adjust the pH to 4.0 with acetic acid, and add water to make exactly 1000 mL.

Packaging and storage Preserve in hermetic containers.

Cefminox Sodium for Injection
주사용 세프미녹스나트륨

Cefminox Sodium for Injection, as an injection that is dissolved before use, contains NLT 90.0% and NMT 120.0% of the labeled amount of cefminox ($C_{16}H_{21}N_7O_7S_3$: 519.58).

Method of preparation Prepare as directed under Injections, with Cefminox Sodium.

Description Cefminox Sodium for Injection occurs as a white to pale yellowish white crystalline powder.

Identification (1) Weigh 20 mg (potency) of Cefminox Sodium for Injection, dissolve in 2 mL of water, add 3 mL of hydroxylamine hydrochloride TS, and allow it to stand for 5 minutes. Add 1 mL of acidic ammonium iron(III) sulfate TS, and shake to mix; the resulting solution exhibits a reddish brown color.

(2) Weigh 10 mg (potency) of Cefminox Sodium for Injection, and dissolve in 1 mL of water. Spot 1 μL of this solution on a filter paper, spray evenly ninhydrin TS, and heat at 100 ℃ for 5 minutes; the solution exhibits a pale, bluish purple color.

(3) Determine the absorption spectrum of a solution of Cefminox Sodium for Injection (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum absorbance at 271 nm to 275 nm.

pH Dissolve 50 mg (potency) of Cefminox Sodium for Injection per mL in water; the pH of the solution is 4.5 to 6.0.

Water Between 18.0% and 20.0% (0.1 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.05 EU per mg (potency) of cefminox.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately an amount of Cefminox Sodium for Injection, equivalent to 70 mg (potency) of cefminox sodium, according to the labeled potency, dissolve in water to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 70 mg (potency) of cefminox sodium RS, dissolve in water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of cefminox in each solution.

$$\text{Potency (μg) of cefminox } (C_{16}H_{21}N_7O_7S_3) = \text{Potency (μg) of cefminox sodium RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 273 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: A mixture of buffer solution and methanol (9 : 1).

Flow rate: 1.0 mL/min

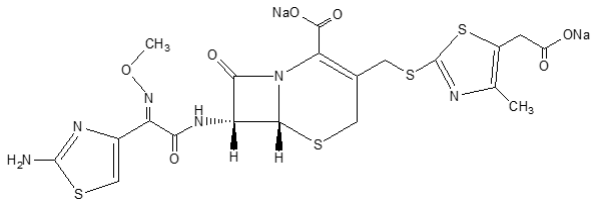
System suitability

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of cefminox is NMT 1.0%.

Buffer solution—Weigh 2.04 g of sodium acetate trihydrate, dissolve in 750 mL of water, adjust the pH to 4.0 with acetic acid, and add water to make exactly 1000 mL.

Packaging and storage Preserve in hermetic containers.

Cefodizime Sodium
세포디짐나트륨



$C_{20}H_{18}N_6Na_2O_7S_4$: 628.63

Disodium (6*R*,7*R*)-7-{2-[(2*E*)-2-(2-amino-1,3-thiazol-4-yl)-2-methoxyimino]acetamido}-3-{[(5-carboxylatomethyl)-4-methyl-1,3-thiazol-2-yl]sufanyl}methyl-3,4-didehydrocepham-4-carboxylate [*86329-79-5*]

Cefodizime Sodium contains NLT 890 μg (potency) of ethanol-free ($C_{20}H_{20}N_60_7S_4$: 584.67) per mg, calculated on the anhydrous basis.

Description Cefodizime Sodium occurs as a white to pale yellowish white crystalline powder.
It is very soluble in water and practically insoluble in acetonitrile or ethanol(99.5).

Identification (1) Determine the absorption spectra of solutions of Cefodizime Sodium and cefodizime sodium RS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelength.

(2) Determine the infrared spectra of Cefodizime Sodium and cefodizime sodium RS according to the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Determine ^1H as directed under the nuclear magnetic resonance spectrum using the heavy aqueous solution (1 in10) of Cefodizime Sodium for the nuclear magnetic resonance spectrum and sodium 3-trimethylsilylpropanesulfonate for the nuclear magnetic resonance spectrum as an internal standard; It exhibits single-line signals A, B, and C at around δ 2.3 ppm, δ 4.0 ppm, and δ 7.0 ppm, respectively, and the area intensity ratio A : B : C of each signal is about 3 : 3 : 1.

(4) Cefodizime Sodium responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between -56° and -62° (on the anhydrous and ethanol-free basis, 0.2 g, 20 mL of water, 100 mm).

pH Dissolve 1.0 g (potency) of Cefodizime Sodium in 10 mL of water; the pH is between 5.5 and 7.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Cefodizime Sodium in 10 mL of water; the solution is clear and exhibits a pale yellow color.

(2) ***Heavy metal***—Weigh about 1.0 g of Cefodizime Sodium in a crucible, loosely cover it with a lid, and heat gently to carbonize. After cooling, add 2mL of sulfuric acid, heat cautiously until white fumes are no longer evolved, and incinerate by ignition at 500 to 600 °C. Perform the test according to Method 2. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Cefodizime Sodium according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 30 mg of Cefodizime Sodium in 10 mL of the mobile phase and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Pipet 5 μL of the test solution and the standard solution, perform the test according to the Liquid Chromatography under the following conditions, and determine the peak area of each solution by the automatic integration method; the peak area from each peak other than cefodizime of the test solution is not larger than the peak area of cefodizime from the standard solution. In addition, the sum of peak areas other than cefodizime from the test solution is not greater than 3 times the peak area of cefodizime from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, perform the test as directed under the operating conditions under the Assay.

System suitability

For system performance and system repeatability, perform the test as directed under the system suitability under the Assay.

Test for required detectability: Pipet 2 mL of the standard solution and add the mobile phase to make exactly 20 mL. Confirm that the peak area of cefodizime obtained from 5 μL of this solution is within the range of 7 to 13% of the peak area of cefodizime in the standard solution.

Time span of measurement: About 4 times the retention time of cefodizime after the solvent peak.

(5) ***Ethanol***—Weigh accurately about 0.2 g of Cefodizime Sodium, add exactly 5 mL of the internal standard solution, put water to make exactly 25 mL, and use this solution as the test solution. Separately, pipet 2 mL of ethanol(99.5), add water to make exactly 100 mL., and use this solution as the standard stock solution. Pipet 0.25 mL of the standard stock solution, add exactly 5 mL of the internal standard solution, add water to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S of ethanol to that of the internal standard. Determine the amount of ethanol according to the following formula; it is NMT 2.0%.

$$\text{Content (\%) of ethanol} = 1 / W_T \times Q_T / Q_S \times 0.5 \times 0.79$$

W_T: Amount (g) of Cefodizime Sodium taken
0.79: Density (g/mL) of ethanol at 20 ℃

Internal standard solution—1-propanol solution (1 in 1000).

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A fused silica capillary column, 0.53 mm in internal diameter and 30 m in length, of which the inner surface is coated with 6% cyanopropylphenyl-94% polydimethylsiloxane for gas chromatography to a thickness of 3.0 μm.

Column temperature: Maintain at 50 °C for 5 minutes, then raise to 200 °C by 50 °C per minute, and keep at 200 °C for 5 minutes.

Sample injection port temperature: 210 ℃

Detector temperature: 280 °C.

Carrier gas: Nitrogen

Flow rate: 5 mL/min

Split ratio: 1 : 5

System suitability

System performance: Proceed with 1 μL of the standard solution under the above operating conditions; ethanol and the internal standard are eluted in this order.

System reproducibility: Repeat the test 6 times with 1 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area of ethanol with respect to that of the internal standard is NMT 2.0%.

Water NMT 4.0% (0.5 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in sterility preparations. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins It is less than 0.10 EU per mg (potency) of ceftazidime when used in the manufacturing of sterile preparations.

Assay Weigh assay about 50 mg (potency) each of Cefodizime Sodium and cefodizime sodium RS, dissolve in exactly 10 mL of the internal standard solution, and add water to make 100 mL. Use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions and calculate the peak area ratios, Q_T and Q_S, of cefodizime to that of the internal standard, respectively.

$$\text{Potency (μg) of ceftazidime } (C_{20}H_{20}N_6 0_7S_4) = \text{Potency (μg) of cefodizime sodium RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of anhydrous caffeine (3 in 400).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 0.80 g of potassium dihydrogen phosphate and 0.20 g of anhydrous sodium dihydrogen phosphate in water, add 80 mL of acetonitrile, and add water again to make 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of cefodizime is about 5 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution under the above conditions; cefodizime sodium and the internal standard are eluted in this order with the resolution being NLT 6.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area of cefodizime to that of the internal standard is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Cefodizime Sodium for Injection
주사용 세포디짐나트륨

Cefodizime Sodium for Injection, as an injection that is dissolved upon use, contains NLT 90.0% and NMT 120.0% of the labeled amount of cefodizime ($C_{20}H_{20}N_6O_7S_4$: 584.67).

Method of preparation Prepare as directed under Injections, with Cefodizime Sodium.

Description Cefodizime Sodium for Injection occurs as a white to pale yellowish white crystalline powder and is odorless.

Identification (1) Weigh 10 mg (potency) of Cefodizime Sodium for Injection, dissolve in 2 mL of water, add 3 mL of hydroxylamine hydrochloride-ethanol TS, allow it to stand for 5 minutes, add 1 mL of acidic ammonium iron(III) sulfate TS, and shake to mix; the resulting solution exhibits a reddish brown color.

(2) Weigh 1 mg (potency) of Cefodizime Sodium for Injection, dissolve in 4 mL of water, add 1 mL of dilute hydrochloric acid while cooling with iced water, add 1 mL of freshly prepared sodium nitrite solution (1 in 100), and allow it to stand for 2 minutes. While cooling again with ice, add 1 mL of ammonium sulfamate TS, allow it to stand for 1 minute, and add 1 mL of hydrochloric acid-*N*-1-naphthylethylenediamine hydrochloride solution (1 in 1000); the resulting solution exhibits a violet color.

(3) Weigh about 2 mg (potency) of Cefodizime Sodium for Injection, and dissolve in water to make 100 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelength of between 258 nm and 264 nm.

pH Dissolve Cefodizime Sodium for Injection in water to make 0.1 g/mL; the pH of the solution is between 5.5 and 7.5.

Water NMT 4.0% (0.2 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxin Below than 0.10 EU per mg (potency) of cefodizime.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately an amount of Cefodizime Sodium for Injection, equivalent to about 50 mg (potency) of cefodizime according to the labeled potency, add exactly 10 mL of the internal standard solution, dissolve in water to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately each about 50 mg (potency) of cefodizime sodium RS, proceed in the same manner as in the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of cefodizime to that of internal standard in each solution.

$$\text{Potency (μg) of cefodizime } (C_{20}H_{20}N_6O_7S_4) = \textit{Potency} \text{ (μg) of cefodizime sodium RS} \times \frac{Q_T}{Q_S} \times \frac{100}{(100-m)}$$

m: Water (%) of Cefodizime Sodium for Injection

Internal standard solution—A solution of anhydrous caffeine (3 in 400).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (8 μm to 10 μm in particle diameter).

Column temperature: Between 20 and 40 °C.

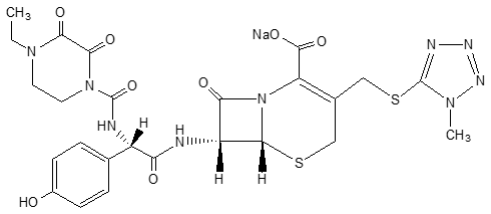
Mobile phase: Dissolve 0.80 g of potassium dihydrogen phosphate and 0.20 g of anhydrous sodium dihydrogen phosphate in water, add 80 mL of acetonitrile, and add water again to make 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of cefodizime is about 5 minutes.

Selection of column: Perform the test with 10 μL of the standard solution according to the above operating conditions; cefodizime and caffeine are eluted in this order with resolution being NLT 6.

Packaging and storage Preserve in hermetic containers.

Cefoperazone Sodium
세포페라존나트륨



$C_{25}H_{26}N_9NaO_8S_2$: 667.65

Sodium (6*R*,7*R*)-7-[[(2*R*)-2-[(4-ethyl-2,3-dioxopiperazine-1-carbonyl)amino]-2-(4-hydroxyphenyl)acet]amido]-3-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanylmethyl]-3,4-didehydrocepham-4-carboxylate [*62893-20-3*]

Cefoperazone Sodium contains NLT 871 μg (potency) of cefoperazone ($C_{25}H_{27}N_9O_8S$: 645.67) per mg, calculated on the anhydrous basis.

Description Cefoperazone Sodium occurs as a white to yellowish white crystalline powder.
It is freely soluble in water, soluble in methanol and slightly soluble in ethanol(99.5).

Identification (1) Determine the absorption spectra of solutions of Cefoperazone Sodium and cefoperazone sodium RS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the ^1H spectrum of a solution of Cefoperazone Sodium in deuterium oxide for nuclear magnetic resonance spectroscopy (1 in 10), using 3-(trimethylsilyl)propanesulfonic acid sodium salt for nuclear magnetic resonance spectroscopy as the internal standard, as directed under the Nuclear Magnetic Resonance Spectroscopy; it exhibits a triple signal A at around δ 1.2 ppm, and double signals B and C at around δ 6.8 ppm and at around δ 7.3 ppm, respectively, and the area intensity ratio of signals A : B : C is 3 : 2 : 2.

(3) Cefoperazone Sodium responds to the Qualitative Analysis (1) for sodium salt.

Crystallinity Meets the requirements, except for freeze-dried powder.

Optical rotation $[\alpha]_D^{20}$: Between -15° and -25° (1 g, water, 100 mL, 100 mm).

pH Dissolve 1.0 g of Cefoperazone Sodium in 4 mL of water; the pH of this solution is between 4.5 and 6.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Cefoperazone Sodium in 10 mL of water; the resulting solution is pale yellow and clear.

(2) ***Heavy metals***—Proceed with 2.0 g of Cefoperazone Sodium as directed under Method 4 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 5 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Cefoperazone Sodium as directed under Method 4 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Weigh accurately 0.1 g of Cefoperazone Sodium, dissolve in water to make exactly 100 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas of each solution by the automatic integration method, and calculate the ratio of each related substance from the test solution to 50 times the peak area of cefoperazone from the standard solution; the related substance having the retention time of about 8 minutes is NMT 5.0%, the related substance having the retention time of about 17 minutes is NMT 1.5%, and the sum of all related substances is NMT 7.0%. For the calculation of the peak areas of the related substances having the retention time of about 8 minutes and 17 minutes, multiply the areas obtained by the automatic integration method by the correction factors 0.90 and 0.75, respectively.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

Detection sensitivity: Pipet 1 mL of the standard solution and add the mobile phase to make exactly 20 mL. Proceed with 25 μL of this solution according to the operating conditions; the peak area of cefoperazone is equivalent to 3.5% to 6.5% of the area of each peak obtained from 25 μL of the standard solution.

System performance: Proceed with 25 μL of the standard solution according to the above conditions; the number of theoretical plates of the peak area of cefoperazone is NLT 5000 with the symmetry factor being NMT 1.5.

System repeatability: Repeat the test 6 times with 25 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of cefoperazone is NMT 2.0%.

Time span of measurement: About 3 times the retention time of cefoperazone beginning after the solvent peak.

Water NMT 5.0% for crystalline powder (0.2 g, volumetric titration, direct titration). NMT 2.0% for freeze-dried powder (0.5 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in a sterile preparation. However, it is excluded where there is a final sterilization process in the manufacturing of a sterile preparation.

Bacterial endotoxins Less than 0.20 EU per mg (potency) of cefoperazone, when used for manufacturing sterile preparations.

Assay Weigh accurately about 0.1 g (potency) of Cefoperazone Sodium and dissolve in water to make exactly 100 mL. Pipet 5 mL of this solution, add 5 mL of the internal standard solution, and use this solution as the test solution. Separately, weigh accurately about 0.1 g (potency) of cefoperazone RS, dissolve in 5 mL of 0.1 mol/L phosphate buffer solution (pH 7.0), and add water to make exactly 100 mL. Pipet 5 mL of this solution, add 5 mL of the internal standard solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratio, Q_T and Q_S, of cefoperazone to the internal standard, respectively.

Potency (μg) of cefoperazone ($C_{25}H_{27}N_9O_8S_2$)

$$= \text{Potency } (\mu g) \text{ of cefoperazone RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of acetanilide in a mixture of water and acetonitrile (43 : 7) (3 in 8000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 ℃.

Mobile phase: To 57 mL of acetic acid(100) and 139 mL of triethylamine, add water to make 1000 mL. To 20 mL of this solution, add 835 mL of water, 140 mL of acetonitrile and 5 mL of dilute acetic acid.

Flow rate: Adjust the flow rate so that the retention time of cefoperazone is about 10 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the internal standard and cefoperazone are eluted in this order with the resolution between these peaks being NLT 5.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio of cefoperazone to the internal standard is NMT 1.0%.

Packaging and storage Preserve in hermetic containers (in a cold place).

Cefoperazone Sodium for Injection
주사용 세포페라존나트륨

Cefoperazone Sodium for Injection, as an injection that is dissolved upon use, contains NLT 90.0% and NMT 120.0% of the labeled amount of cefoperazone ($C_{25}H_{27}N_9O_8S_2$: 645.67).

Method of preparation Prepare as directed under Injections, with Cefoperazone Sodium.

Description Cefoperazone Sodium for Injection occurs as white to yellowish white powder.

Identification (1) Determine the infrared spectra of Cefoperazone Sodium for Injection and cefoperazone as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Weigh appropriate amounts of each of Cefoperazone Sodium for Injection and cefoperazone RS, add a mixture of acetone and water (9 : 1) to prepare solutions each having a known concentration of 1.0 mg per mL, and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Develop the plate with a mixture of 2-butanone, acetic acid(100) and water (18 : 3 : 1 :) as the developing solvent, and examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values of the spots obtained from the test solution and the standard solution are the same.

(3) The retention times of the major peaks obtained from the test solution and the standard solution under the Assay are the same.

pH Dissolve an amount of Cefoperazone Sodium for Injection equivalent to 0.25 g (potency) of cefoperazone in 1 mL of water; the pH of this solution is between 4.5 and 6.5.

Water NMT 5.0% for crystalline powder (0.2 g, volumetric titration, direct titration), and NMT 2.0% for freeze-dried powder (0.5 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.20 EU per mg (potency) of cefoperazone.

Particulate contamination: Visible particles Meets the requirements.

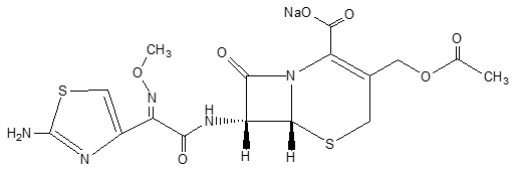
Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay under Cefoperazone Sodium. However, weigh accurately an amount equivalent to about 0.1 g (potency) according to the labeled potency of Cefoperazone Sodium for Injection, dissolve in water to make exactly 100 L. Pipet 10 mL of this solution, add exactly L of the internal standard solution, add the mobile phase to make exactly 50 mL, and use this solution as the test solution.

Packaging and storage Preserve in hermetic containers.

Cefotaxime Sodium
세포탁심나트륨



$C_{16}H_{16}N_5NaO_7S_2$: 477.45

Sodium (6*R*,7*R*)-7-{2-[(2*E*)-2-(2-amino-1,3-thiazol-4-yl)-2-methoxyimino]acetamido}-3-acetyloxymethyl-3,4-didehydrocepham-4-carboxylate [*64485-93-4*]

Cefotaxime Sodium contains NLT 916 μg (potency) of cefotaxime ($C_{16}H_{17}N_5O_7S_2$: 455.47) per mg, calculated on the anhydrous basis.

Description Cefotaxime Sodium occurs as a white to yellowish white, crystalline powder.
It is very soluble in water and sparingly soluble in ethanol(96) and very slightly soluble in methanol.

Identification (1) Dissolve 2 mg of Cefotaxime Sodium and cefotaxime sodium RS in 0.01 mol/L hydrochloric acid TS to make 100 mL. Determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cefotaxime Sodium and cefotaxime sodium RS according to the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Determine 1H as directed under the nuclear magnetic resonance spectrum using the heavy aqueous solution (1 in125) of Cefotaxime Sodium for nuclear magnetic resonance spectrum and sodium 3-trimethylsilylpropanesulfonate for the nuclear magnetic resonance spectrum as an internal standard; It exhibits single-line signals A, B, and C at around δ 2.1 ppm, δ 4.0 ppm, and δ 7.0 ppm, respectively, and the area intensity ratio A : B : C of each signal is about 3 : 3 : 1.

(4) Cefodizime Sodium responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between +58° and +64° (0.25 g calculated on the dried basis, water, 25 mL, 100 mm).

pH Dissolve 1 g of Cefotaxime Sodium in 10 mL of water; the pH of this solution is between 4.5 and 6.5.

Absorbance $E_{1cm}^{1\%}$ (235 nm): Between 360 and 390 (20 mg calculated on the dried basis, water, 1000 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Cefotaxime Sodium in 10 mL of water; the resulting solution is clear and bright yellow.

(2) ***Sulfate***—Dissolve 2.0 g of Cefotaxime Sodium in 40 mL of water and add 2 mL of dilute hydrochloric acid and water to make 50 mL, and shake well to mix, and filter. Discard the initial 10 mL of the filtrate, add water to 25 mL of the subsequent filtrate to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by taking 1.0 mL of 0.005 mol/L sulfuric acid, and adding 1 mL of dilute hydrochloric acid and water to make 50 mL (NMT 0.048%).

(3) ***Heavy metals***—Proceed with 1.0 g of Cefotaxime Sodium according to Method 2 and perform the test. Prepare the control solution with 2 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic***—Weigh accurately about 1.0 g of Cefotaxime Sodium, and perform the test according to Method 3 (NMT 2 ppm).

(5) ***related substances***—Perform the test as described under the Assay. However, weigh accurately about 25 mg of Cefotaxime Sodium, dissolve in the mobile phase to make exactly 25 mL, and use this solution as the test solution. However, the time span of measurement of the test solution is about 3.5 times the retention time of cefotaxime (each related substance is NMT 1.0%, total related substances are NMT 3.0%).

System suitability

For the system performance and repeatability, proceed as directed under the system suitability under the Assay.

Test for required detectability: Pipet 2 mL of the standard solution, and add the mobile phase A to make exactly 100 mL. Pipet 2 mL of this solution and add the mobile phase A to make exactly 20 mL. Confirm that the peak area of cefotaxime obtained from 10 μL of this solution is equivalent to 0.15 to 0.25% of the peak area of cefotaxime obtained from the standard solution.

(6) ***Dimethylaniline***—Weigh accurately about 1.0 g of Cefotaxime Sodium, add 5 mL of 1 mol/L sodium hydroxide TS and 1 mL of the internal standard solution, and then centrifuge it, if necessary. Use the clear supernatant as the test solution. Separately, weigh accurately 50 mg of dimethylaniline, and add 2.0 mL of hydrochloric acid and water to make 50 mL. Pipet 5.0 mL of this solution and add water to make exactly 250 mL. Pipet 1.0 mL of this solution, add 5.0 mL of 1 mol/L sodium hydroxide TS and 1 mL of the internal standard solution, and then centrifuge it if necessary. Use the clear supernatant as the standard solution. Perform the test with each 1 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak area, Q_T and Q_S of dimethylaniline to that of the internal standard (NMT 20 ppm).

$$\text{Content (ppm) of dimethylaniline} = \text{Amount (mg) of dimethylaniline taken} \times \frac{Q_T}{Q_S} \times \frac{Purity\ (\%) of\ dimethylaniline}{Amount\ (mg)\ of\ Cefotaxime\ Sodium\ taken} \times 4$$

Dissolve 50.0 mg of internal standard solution Naphthalene in cyclohexane to make 50 mL. Pipet 5.0

mL of this solution and add cyclohexane to make 100 mL, and use this solution as the internal standard solution.

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A tube about 2 mm in internal diameter and about 2 mm in length, packed with diatomaceous earth for gas chromatography coated with 3% by mass of 50% phenyl-50% methylpolysiloxane for gas chromatography.

Column temperature: 120 ℃

Sample injection port, detector temperature: 150 ℃

Carrier gas: Nitrogen

Flow rate: 30 mL/min

Loss on drying NMT 3.0% (1 g, 105 ℃, 3 hours).

Sterility It meets the requirements when used in sterile preparations. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins It is less than 0.05 EU per mg (potency) of cefotaxime when used in the manufacturing of sterile preparations.

Assay Weigh about 40 mg (potency) each of Cefotaxime Sodium and cefotaxime sodium RS, dissolve in the mobile phase A to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of cefotaxime.

$$\text{Potency (μg) of cefodizime } (C_{16}H_{17}N_5O_7S_2) = \text{Potency (μg) of cefodizime sodium RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 235 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Control the gradient elution by modifying the mixing ratio of mobile phases A and B as follows.

Mobile phase A: Add phosphoric acid to 0.05 mol/L dibasic sodium phosphate TS to adjust the pH to 6.25. Add 140 mL of methanol to 860 mL of this solution.

Mobile phase B: Add phosphoric acid to 0.05 mol/L dibasic sodium phosphate TS to adjust the pH to 6.25. Add 400 mL of methanol to 600 mL of this solution.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 7	100	0
7 - 9	100 → 80	0 → 20
9 - 16	80	20
16 - 45	80 → 0	20 → 100
45 - 50	0	100

Flow rate: Adjust the flow rate so that the retention time of cefotaxime is about 14 minutes (about 1.3 mL/min).

System suitability

System performance: Add 7.0 mL of water and 2.0 mL of methanol to 1 mL of the standard solution, and shake to mix. Add 25 mg of sodium carbonate decahydrate to this solution, shake to mix, and allow to stand at room temperature for 10 minutes. Add 3 drops of acetic acid(100) and 1 mL of standard solution, and shake to mix. Proceed with 10 μL of this solution according to the above operating conditions; desacetylcefotaxime with a relative retention time of about 0.3 and cefotaxime are eluted in this order with the resolution being NLT 20. The symmetry coefficient of the cefotaxime peak is NMT 2.

System repeatability: Repeat the test 6 times according to the above conditions with 10 μL of the standard solution each time; the relative standard deviation of the peak area of cefotaxime is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Cefotaxime Sodium for Injection
주사용 세포탁심나트륨

Cefotaxime Sodium for Injection, as an injection that is dissolved upon use, contains NLT 90.0% and NMT 120.0% of the labeled amount of cefotaxime ($C_{16}H_{17}N_5O_7S_2$: 455.47).

Method of preparation Prepare as directed under Injections, with Cefotaxime Sodium.

Description Cefotaxime Sodium for Injection occurs as a white to light yellowish white powder.

Identification (1) Perform the test as directed under the Identification (2) under Cefotaxime Sodium.

(2) Perform the test as directed under the Identification (4) under Cefotaxime Sodium.

(3) The retention times of the major peaks obtained from the test solution and the standard solution under the Assay are the same.

pH Dissolve an amount of Cefotaxime Sodium for Injec-

tion equivalent to 1.0 g (potency) of cefotaxime in 10 mL of water; the pH of this solution is between 4.5 and 6.5.

Purity ***Related substances***—Perform the test as directed under the Purity (5) under Cefotaxime Sodium. However, the time span of measurement is 8 times the peak retention of the principal constituent (NMT 1.0% for individual related substance and NMT 4.0% for total related substances).

Loss on drying NMT 3.0% (1 g, 105 °C, 3 hours).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.05 EU per mg (potency) of cefotaxime.

Particulate contamination: Visible particles Meets the requirements.

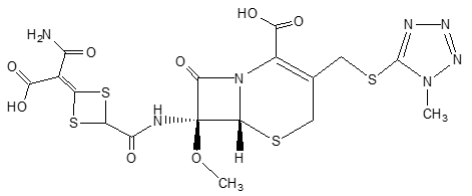
Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay under Cefotaxime Sodium. Weigh accurately an amount equivalent to about 40 mg (potency) according to the labeled potency of Cefotaxime Sodium for Injection, dissolve in the mobile phase A to make exactly 50 mL, and use this solution as the test solution.

Packaging and storage Preserve in hermetic containers.

Cefotetan
세포테탄



$C_{17}H_{17}N_7O_8S_4$: 575.62

(6*R*,7*S*)-7-[[4-(2-Amino-1-carboxy-2-oxoethylidene)-1,3-dithietane-2-carbonyl]amino]-7-methoxy-3-[(1-methyltetrazol-5-yl)sulfanylmethyl]-3,4-didehydrocepham-4-carboxylic acid [*69712-56-7*]

Cefotetan contains NLT 960 μg (potency) and NMT 1010 μg (potency) of cefotetan ($C_{17}H_{17}N_7O_8S_4$: 575.62) per mg, calculated on the anhydrous basis.

Description Cefotetan occurs as a white to pale yellowish white powder.
It is sparingly soluble in methanol and slightly soluble in water or in ethanol(95).

Identification (1) Determine the absorption spectra of Cefotetan and cefotetan RS in 1% phosphate buffer solution (pH 6.5) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cefotetan and cefotetan RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 50 mg of Cefotetan in 0.5 mL of a solution of sodium bicarbonate in heavy water for nuclear magnetic resonance spectroscopy (1 in 25), and determine the ^1H spectrum of this solution as directed under the Nuclear Magnetic Resonance Spectroscopy; it exhibits signals of single lines at around δ 3.6 ppm, at around δ 4.0 ppm, at around δ 5.1 ppm and at around δ 5.2 ppm, and the integrated intensity ratio of these signals is 3 : 3 : 1 : 1.

Optical rotation $[\alpha]_D^{20}$: Between +112° and +124° (0.5 g, calculated on the anhydrous basis, sodium bicarbonate solution (1 in 200), 50 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Cefotetan in a solution of sodium bicarbonate (1 in 30); the resulting solution is colorless to pale yellow and clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Cefotetan according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances—***Weigh accurately about 0.1 g of Cefotetan, dissolve in methanol, add exactly 2 mL of the internal standard solution, add methanol to make 20 mL, and use this solution as the test solution. Separately, weigh accurately about 3 mg of 1-methyl-1*H*-tetrazole-5-thiol RS for liquid chromatography, previously dried in a desiccator (in vacuum, silica gel) for 2 hours, and about 2 mg of cefotetan RS, calculated on the anhydrous basis, and dissolve in methanol to make exactly 20 mL. Pipet 2 mL of this solution, add exactly 2 mL of the internal standard solution, add methanol to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_{Ta}, Q_{Tb}, Q_{Tc}, Q_{Td}, Q_{Te} and Q_{Tf}, of 1-methyl-1*H*-tetrazole-5-thiol, cefotetan lactone, eluted at the relative retention time of about 0.5 with respect to cefotetan, Δ2-cefotetan, eluted at the relative retention time of about 1.2 with respect to cefotetan, isothiazole substance, eluted at the relative retention time of about 1.3 with respect to cefotetan, each of other related substances and the total amount other related substances, respectively, to the internal standard, obtained from the test solution, and the peak area ratios, Q_{Sa} and Q_{Sb}, of 1-methyl-1*H*-tetrazole-5-thiol and cefotetan, respectively,

to the peak area of the internal standard, obtained from the standard solution. Calculate the amount of each related substance using the following equations; the amount of 1-methyl-1*H*-tetrazole-5-thiol is NMT 0.3%, the amount of cefotetan lactone is NMT 0.3%, the amount of Δ2-cefotetan is NMT 0.5%, the amount of isothiazole substance is NMT 0.5%, the amount of each of other related substances is NMT 0.2%, and the total amount of related substances is NMT 0.4%.

$$\text{1-methyl-1}H\text{-tetrazole-5-thiol (\%)} = \frac{W_{Sa}}{W_T} \times \frac{Q_{Ta}}{Q_{Sa}} \times \frac{1}{100}$$

$$\text{Content (\%) of cefotetan lactone} = \frac{W_{Sa}}{W_T} \times \frac{Q_{Tb}}{Q_{Sb}} \times \frac{1}{100}$$

$$\text{Content (\%) of } \Delta\text{2-cefotetan} = \frac{W_{Sb}}{W_T} \times \frac{Q_{Tc}}{Q_{Sb}} \times \frac{1}{100}$$

$$\text{Content (\%) of isothiazole substance} = \frac{W_{Sb}}{W_T} \times \frac{Q_{Td}}{Q_{Sb}} \times \frac{1}{100}$$

$$\text{Content (\%) of each of other related substances} = \frac{W_{Sb}}{W_T} \times \frac{Q_{Te}}{Q_{Sb}} \times \frac{1}{100}$$

$$\text{Total content (\%) of other related substances} = \frac{W_{Sb}}{W_T} \times \frac{Q_{Tf}}{Q_{Sb}} \times \frac{1}{100}$$

W_{Sa}: Amount (mg) of 1-methyl-1*H*-tetrazole-5-thiol
W_{Sb}: Amount (mg) of cefotetan RS, calculated on the anhydrous basis
W_T: Amount (g) of Cefotetan

Internal standard solution—A solution of anhydrous caffeine in methanol (3 in 10000).

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

System performance: Proceed as directed under the system suitability under the Assay.

Test for required detectability: Pipet 15 mL of the standard solution and add methanol to make exactly 100 mL. Confirm that the peak area of cefotetan obtained from 5 μL of this solution is equivalent to 12% to 18% of the peak area of cefotetan from the standard solution.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio of cefotetan to the peak area of the internal standard is NMT 2.0%.

Time span of measurement: About 3.5 times the retention time of cefotetan.

Isomer ratio Dissolve 10 mg of Cefotetan in 20 mL of methanol and use this solution as the test solution. Perform the test with 5 μL of the test solution as directed under the Liquid Chromatography according to the following conditions, and calculate the area of the adjacent two peaks that appear at the retention time of around 40 minutes, one having a shorter retention time (*l*-form) and another having a longer retention time (*d*-form). Calculate the amount of *l*-form by the percentage peak area method; it is between 35% and 45%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of 0.1 mol/L phosphate buffer solution (pH 7.0), water and a solution of tetrabutylammonium hydrogen sulfate in acetonitrile (1 in 150) (9 : 9 : 2).

Flow rate: Adjust the flow rate so that the retention time of the *l*-form is about 40 minutes.

System suitability

System performance: Proceed with 5 μL of the test solution according to the above conditions; the *l*-form and the *d*-form are eluted in this order with the resolution between these peaks being NLT 1.5.

System repeatability: Pipet 1 mL of the test solution, and add methanol to make exactly 10 mL. Repeat the test 6 times with 5 μL each of these solutions; the relative standard deviation of the peak area of the *l*-form is NMT 5.0%.

Water NMT 2.5% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Sterility It meets the requirements when Cefotetan is used for manufacturing sterile preparations. However, it is excluded when there is a terminal sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins Less than 0.17 EU/mg (potency) of cefotetan, when used for manufacturing sterile preparations.

Assay Weigh accurately about 50 mg (potency) each of Cefotetan and cefotetan RS, dissolve each in 0.1 mol/L phosphate buffer solution (pH 6.5), and add water to make exactly 50 mL. Pipet 15 mL each of these solutions, add exactly 10 mL each of the internal standard solutions, add 0.1 mol/L phosphate buffer solution (pH 6.5) to make exactly 50 mL, and use these solutions as the test solution

and the standard solution, respectively. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of cefotetan to that of the internal standard, respectively.

$$\text{Potency (μg) of cefotetan } (C_{17}H_{17}N_7O_8S_4) = \text{Potency (μg) of cefotetan RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of anhydrous caffeine solution (1 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 11.53 g of phosphoric acid in 1000 mL of water. To 850 mL of this solution, add 50 mL of acetonitrile, 50 mL of acetic acid(100) and 50 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of cefotetan is about 17 minutes.

System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; caffeine and cefotetan are eluted in this order with the resolution between these peaks being NLT 8.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area ratio of cefotetan to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers (below 5 °C).

Cefotetan Sodium for Injection
주사용 세포테탄나트륨

Cefotetan Sodium for Injection, as an injection that is dissolved upon use, contains NLT 90.0% and NMT 120.0% of the labeled amount of cefotetan ($C_{17}H_{17}N_7O_8S_4$: 575.62).

Method of preparation Prepare as directed under Injections with Cefotetan by adding sodium bicarbonate to make cefotetan disodium.

Description Cefotetan Sodium for Injection occurs as a white to pale yellowish white powder.

Identification (1) Dissolve an amount of Cefotetan Sodium for Injection equivalent to about 10 mg (potency) of cefotetan in 2 mL of hydroxylamine hydrochloride TS, allow to stand for 3 minutes, add 1 mL of acidic ammonium iron(III) sulfate TS, and agitate; the resulting solution exhibits a reddish brown color.

(2) Dissolve an amount of Cefotetan Sodium for Injection equivalent to about 10 mg (potency) of cefotetan in 1% phosphate buffer solution (pH 6.5) to make 1000 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelength of between 283 nm and 287 nm.

(3) Perform the test with Cefotetan Sodium for Injection as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; it exhibits absorption at the wavenumbers of about 1760 cm^{-1}, 1630 cm^{-1}, 1520 cm^{-1}, 1580 cm^{-1} and 1080 cm^{-1}.

pH Dissolve an amount of Cefotetan Sodium for Injection equivalent to 0.1 g (potency) of cefotetan in 1 mL of water; the pH of this solution is between 4.5 and 6.5.

Water NMT 1.5% (1.0 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.17 EU per mg (potency) of cefotetan.

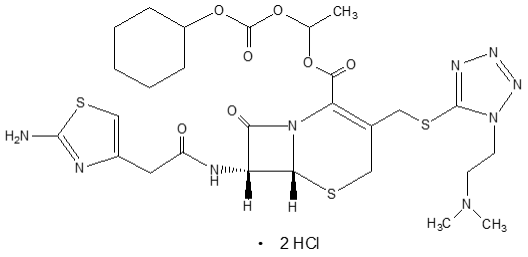
Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay under Cefotetan. However, weigh an appropriate amount of Cefotetan Sodium for Injection, and dilute with 1% phosphate buffer solution (pH 6.5) to prepare a solution having a known concentration of 1 mg (potency) per mL. Pipet 15 mL of this solution, add exactly 10 mL of the internal standard solution, add 0.1 mol/L phosphate buffer solution (pH 6.5) to make exactly 50 mL, and use this solutions as the test solution.

Packaging and storage Preserve in hermetic containers.

Cefotiam Hexetil Hydrochlorid
세포티암헥세틸염산염



$C_{27}H_{37}N_9O_7S_3 \cdot 2HCl$: 768.76

1-Cyclohexyloxycarbonyloxyethyl (6*R*,7*R*)-7-[[2-(2-amino-1,3-thiazol-4-yl)acet]amido]-3-[[1-[2-(dimethylamino)ethyl]tetrazol-5-yl]sulfanyl-methyl]-3,4-didehydrocepham-4-carboxylate dihydrochloride [*95789-30-3*]

Cefotiam Hexetil Hydrochloride contains NLT 615 μg (potency) and NMT 690 μg (potency) of cefotiam ($C_{18}H_{23}N_9O_4S_3$: 525.63) per mg, calculated on the anhydrous basis.

Description Cefotiam Hexetil Hydrochloride occurs as a white to pale yellowish white powder.
It is very soluble in water, in methanol or in ethanol(95), freely soluble in dimethylsulfoxide and slightly soluble in acetonitrile.
It dissolves in 0.1 mol/L hydrochloric acid TS.
It is hygroscopic.

Identification (1) Determine the absorption spectra of solutions of Cefotiam Hexetil Hydrochloride and cefotiam hexetil hydrochloride RS in 1 mol/L hydrochloric acid TS (3 in 125000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the ^1H spectrum of a solution of Cefotiam Hexetil Hydrochloride in deuterated dimethylsulfoxide for nuclear magnetic resonance spectroscopy (1 in 20) as directed under the Nuclear Magnetic Resonance Spectroscopy, using tetramethylsilane for nuclear magnetic resonance spectroscopy as the internal standard; it exhibits single signals A and B at around δ 2.8 ppm and at around δ 6.6 ppm, respectively, and a multiple signal C at around δ 6.9 ppm, and the area intensity ratio of signals A, B and C is about 6 : 1 : 1.

(3) To an aqueous solution of Cefotiam Hexetil Hydrochloride (1 in 200), add 2 mL of dilute nitric acid and 1 mL of silver nitrate TS and mix; a white precipitate is formed.

O**ptical rotation** $[\alpha]_D^{20}$: Between +52° and +60° (0.1 g, calculated on the anhydrous basis, 0.1 mol/L hydrochloric acid TS, 10 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Cefotiam Hexetil Hydrochloride as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Proceed with 2.0 g of Cefotiam Hexetil Hydrochloride as directed under Method 3 and perform the test. Use a solution of magnesium nitrate hexahydrate in ethanol(95) (1 in 5) (NMT 1 ppm).

(3) ***Related substance I***—Weigh accurately about 50 mg of Cefotiam Hexetil Hydrochloride and dissolve in a mixture of diluted phosphoric acid (1 in 100) and acetonitrile (4 : 1) to make exactly 50 mL. Pipet 10 mL of this solution, add a mixture of diluted phosphoric acid (1 in 100) and acetonitrile (4 : 1) to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of cefotiam hexetil hydrochloride RS and dissolve in a mixture of diluted phosphoric acid (1 in 100) and acetonitrile (4 : 1) to make exactly 50 mL. Pipet 1 mL of this solution, add a mixture of diluted phosphoric acid (1 in 100) and acetonitrile (4 : 1) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and determine the area of each peak obtained from each solution by the automatic integration method. Calculate the amount of related substances by the following equation; the amount of the related substance having a relative retention time of about 1.2 with respect to one of the two peaks of cefotiam hexetil, which has the longer retention time, is NMT 2.0%, and the amount of each of other related substances is NMT 0.5%. For the calculation of the area of the peak having a relative retention time of about 1.2 with respect to one of the two peaks of cefotiam hexetil, which has the longer retention time, multiply the area obtained by the automatic integration method by the correction factor 0.78.

$$\text{Content (\%) of each related substance} = \frac{Potency\ (g)\ of\ cefotiam\ hexetil\ hydrochloride\ RS}{W_T} \times \frac{A_T}{A_S} \times 5$$

W_T: Amount (g) of Cefotiam Hexetil Hydrochloride taken

A_S: Sum of the two peak areas of cefotiam hexetil obtained from the standard solution

A_T: Peak area of each related substance obtained from the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: Adjust so that the mixing rate of the mobile phase A and the mobile phase B is changed linearly from 1 : 0 to 0 : 1 for 30 minutes.

Mobile phase A: A mixture of diluted 0.2 mol/L

potassium dihydrogen phosphate TS (1 in 2), acetonitrile and acetic acid(100) (72 : 28 : 1).

Mobile phase B: A mixture of diluted 0.2 mol/L potassium dihydrogen phosphate TS (1 in 2), acetonitrile and acetic acid(100) (60 : 40 : 1).

Flow rate: 0.7 mL/min

System suitability

Test for required detectability: Pipet 1 mL of the standard solution and add a mixture of diluted phosphoric acid (1 in 100) and acetonitrile (4 : 1) to make exactly 50 mL. Confirm that each area of the two peaks of cefotiam hexetil obtained from 10 μL of this solution is equivalent to 1.6% to 2.4% of that from the standard solution.

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the resolution between the two peaks of cefotiam hexetil is NLT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the sum of the two peak areas of cefotiam hexetil is NMT 2.0%.

Time span of measurement: About 3 times the retention time of one of the two peaks of cefotiam hexetil, which is eluted first, beginning after the solvent peak.

(4) ***Related substance II*—**Weigh accurately about 20 mg of Cefotiam Hexetil Hydrochloride, dissolve in 2 mL of methanol, add a mixture of a solution of dibasic ammonium phosphate (79 in 20000) and acetic acid(100) (200 : 3) to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg of cefotiam hydrochloride RS and dissolve in the mobile phase to make exactly 50 mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and determine the area of each peak obtained from each solution by the automatic integration method. Calculate the amount of the related substances by the following equation; the amount of the related substance having the relative retention time of about 0.1 and 0.9 with respect to cefotiam is NMT 1.0%, and the amount of each of the other related substances is NMT 0.5%. For the calculation of the area of the peak having the relative retention time of about 0.9 with respect to cefotiam, multiply the area obtained by the automatic integration method by the correction factor 0.76.

$$\text{Content (\%) of each related substance} = \frac{Potency\ (g)\ of\ cefotiam\ hexetil\ hydrochloride\ RS}{W_T} \times \frac{A_T}{A_S} \times 4$$

W_T: Amount (g) of Cefotiam Hexetil Hydrochloride taken

A_S: Peak area of cefotiam obtained from the standard solution

A_T: Peak area of each related substance obtained from the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of a solution of dibasic ammonium phosphate (79 in 20000), methanol and acetic acid(100) (200 : 10 : 3).

Flow rate: Adjust the flow rate so that the retention time of cefotiam is about 15 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution and add the mobile phase to make exactly 50 mL. Confirm that the peak area of cefotiam obtained from 10 μL of this solution is equivalent to 1.6% to 2.4% of that from the standard solution.

System performance: To 1 mL of a solution of acetaminophen in the mobile phase (1 in 50000), add 3 mL of the standard solution, and mix well. Proceed with 10 μL of this solution according to the above conditions; acetaminophen and cefotiam are eluted in this order with the resolution between these peaks being NLT 4.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of cefotiam is NMT 2.0%.

Time span of measurement: About twice the retention time of cefotiam after the solvent peak.

(5) ***Total related substances*—**The total amount of related substances obtained under Related substance I and Related substance II is NMT 6.5%.

Water NMT 3.5% (0.1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Isomer ratio Perform the test with 20 μL of the test solution used in the Assay as directed under the Assay, and determine the areas of the two peaks, A_a for the peak with the shorter retention time, and A_b for the peak with the longer retention time, both of which appear at the retention time of around 10 minutes; $A_a/(A_a+A_b)$ is NLT 0.45 and NMT 0.55.

Assay Weigh accurately about 30 mg (potency) each of Cefotiam Hexetil Hydrochloride and cefotiam hexetil hydrochloride RS, dissolve each in a mixture of diluted phosphoric acid (1 in 100) and acetonitrile (4 : 1) to make 50 mL. Pipet 5 mL each of these solutions, add exactly 5

ml each of the internal standard solutions, add a mixture of diluted phosphoric acid (1 in 100) and acetonitrile (4 : 1) to make 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of cefotiam hexetil to that of the internal standard, respectively. For this calculation, use the sum of the two peak areas that appear at the retention time of around 10 minutes as the peak area of cefotiam hexetil.

$$\text{Potency (μg) of cefotiam } (C_{18}H_{23}N_9O_4S_3) = \text{Potency (μg) of cefotiam hexetil hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of benzoic acid in a mixture of diluted phosphoric acid (1 in 100) and acetonitrile (4 : 1) (7 in 10000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase A: A mixture of diluted 0.2 mol/L potassium dihydrogen phosphate TS (1 in 2), acetonitrile and acetic acid(100) (72 : 28 : 1).

Flow rate: Adjust the flow rate so that the retention time of the peak of cefotiam hexetil that is eluted first is about 9 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the internal standard and cefotiam hexetil are eluted in this order with the resolution between these peaks being NLT 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area ratio of cefotiam hexetil to the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Cefotiam Hexetil Hydrochloride Tablets
세포티암헥세틸염산염 정

Cefotiam Hexetil Hydrochloride Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of cefotiam ($C_{18}H_{23}N_9O_4$: 525.63).

Method of preparation Prepare as directed under Tablets, with Cefotiam Hexetil Hydrochloride.

Identification (1) Weigh about 50 mg (potency) according to the labeled potency of Cefotiam Hexetil Hydrochloride Tablets, add 25 mL of water, shake vigorously for 5 minutes to mix, and centrifuge. To 10 mL of the clear supernatant, add 1 mL of hydroxylamine hydrochloride solution (1 in 10) and 2 mL of 1 mol/L sodium hydroxide TS, allow it to stand for 5 minutes, add 3 mL of 1 mol/L hydrochloric acid and 3 drops of iron(III) chloride TS, and shake vigorously to mix; the resulting solution exhibits a deep reddish purple color.

(2) Take 1 mL of the filtrate in (1), and add water to make 100 mL. Determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum absorbance between 257 nm and 262 nm.

Water NMT 3.0% (0.5 g, volumetric titration, direct titration).

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately an amount, equivalent to about 1 g (potency) of cefotiam, according to the labeled potency of Cefotiam Hexetil Hydrochloride Tablets, and add a mixture of diluted phosphoric acid (1 in 100) and acetonitrile (4 : 1) to obtain a solution containing 1 mg (potency) per mL. Pipet 20 mL of this solution, add exactly 5.0 mL of the internal standard solution, make exactly 300 mL with a mixture of diluted phosphoric acid (1 in 100) and acetonitrile (4 : 1), and filter through a membrane filter. Use the filtrate as the test solution. Separately, weigh accurately about 50 mg (potency) of cefotiam hexetil hydrochloride RS, and dissolve in a mixture of diluted phosphoric acid (1 in 100) and acetonitrile (4 : 1) to make exactly 50 mL. Pipet 20 mL of this solution, add exactly 5.0 mL of the internal standard solution, and then make exactly 300 mL with a mixture of diluted phosphoric acid (1 in 100) and acetonitrile (4 : 1). Use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, of cefotiam hexetil to that of internal standard in each solution. Since cefotiam hexetil is detected with two peaks, use the sum of the two peak areas as the peak area of cefotiam hexetil.

$$\text{Potency (μg) of cefotiam } (C_{18}H_{23}N_9O_4S_3) = \text{Potency (μg) of cefotiam hexetil hydrochloride} \times \frac{Q_T}{Q_S} \times 20$$

Internal standard solution—Pipet 25 mL of a solution of sodium benzoate (21 in 500), add 6 mL of 2 mol/L

hydrochloric acid TS, and add 120 mL of methanol and a mixture of diluted phosphoric acid (1 in 100) and acetonitrile (4 : 1) to make exactly 250 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

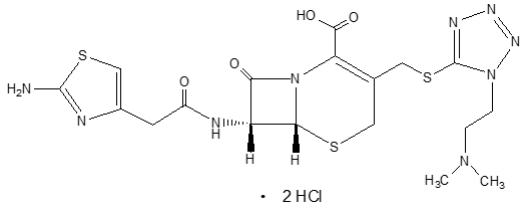
Mobile phase: To 720 mL of the diluted 0.2 mol/L potassium dihydrogen phosphate (1 in 2), add 280 mL of acetonitrile and 10 mL of acetic acid(100).

Flow rate: Adjust the flow rate so that the retention time of the peak eluted first is about 9 minutes.

Selection of column: Perform the test with 20 μL of the standard solution according to the above operating conditions; the resolution of the two peaks of cefotiam hexetil is NLT 2.0.

Packaging and storage Preserve in tight containers.

Cefotiam Hydrochloride
세포티암염산염



· 2 HCl

$C_{18}H_{23}N_9O_4S_3 \cdot 2HCl$: 598.55

(6*R*,7*R*)-7-[[2-(2-Amino-1,3-thiazol-4-yl)acet]amido]-3-[[1-[2-(dimethylamino)ethyl]tetrazol-5-yl]sulfanylmethyl]-3,4-didehydrocepham-4-carboxylic acid dihydrochloride [*66309-69-1*]

Cefotiam Hydrochloride contains NLT 810 μg (potency) and NMT 890 μg (potency) of cefotiam ($C_{18}H_{23}N_9O_4S_3$: 525.63) per mg, calculated on the anhydrous basis.

Description Cefotiam Hydrochloride occurs as white to pale yellowish white crystals or a crystalline powder.
It is freely soluble in water, in methanol or in formamide, slightly soluble in ethanol and practically insoluble in acetonitrile.

Identification (1) Determine the absorption spectra of aqueous solutions of Cefotiam Hydrochloride and cefotiam hydrochloride RS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cefotiam Hydrochloride and cefotiam hydrochloride RS as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Determine the ^1H spectrum of a solution of Cefotiam Hydrochloride in deuterium oxide for nuclear magnetic resonance spectroscopy (1 in 10), using 3-(trimethylsilyl)propanesulfonic acid sodium salt for nuclear magnetic resonance spectroscopy as the internal standard, as directed under the Nuclear Magnetic Resonance Spectroscopy; it exhibits single signals A and B at around δ 3.1 ppm and at around δ 6.7 ppm, respectively, and the area intensity ratio of signals A and B is about 6 : 1.

(4) Dissolve 0.1 g of Cefotiam Hydrochloride in 5 mL of dilute nitric acid and immediately add 1 mL of silver nitrate TS; a white precipitate is formed.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between +60° and +72° (1 g, calculated on the anhydrous basis, water, 100 mL, 100 mm).

pH Dissolve about 1.0 g (potency) of Cefotiam Hydrochloride in 10 mL of water; the pH of this solution is between 1.2 and 1.7.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Cefotiam Hydrochloride in 10 mL of water; the resulting solution is colorless to yellow and clear.

(2) ***Heavy metals***—To about 1.0 g of Cefotiam Hydrochloride, add 1 mL of sulfuric acid and heat gently to carbonize. After cooling, add 10 mL of a solution of magnesium nitrate hexahydrate in ethanol(95) (1 in 10), fire the ethanol to burn, and then heat gradually to incinerate. If a carbonized substance still remains, moisten with a small amount of sulfuric acid, and ignite again to incinerate. After cooling, add 2 mL of hydrochloric acid to the residue, warm on a steam bath to dissolve, and then heat it to evaporate to dryness. To the residue, add 10 mL of water and warm on a steam bath to dissolve. After cooling, adjust the pH to between 3 and 4 with ammonia TS, filter if necessary, and wash the residue with 10 mL of water. Then, transfer the filtrate and the washings into a Nessler tube and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 2.0 mL of lead standard solution in the same manner as in the preparation of the test solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Cefotiam Hydrochloride as directed under Method 4 and perform the test. After cooling, add 10 mL of dilute hydrochloric acid to the residue (NMT 2 ppm).

Water NMT 7.0% (0.25 g, volumetric titration, direct titration. Use a mixture of formamide for water determination and methanol for water determination (2 :

1) instead of methanol for water determination.)

Sterility It meets the requirements when Cefotiam Hydrochloride is used in a sterile preparation. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of a sterile preparation.

Bacterial endotoxins Less than 0.125 EU/mg (potency) of cefotiam, when Cefotiam Hydrochloride is used in a sterile preparation.

Assay Weigh accurately 0.1 g (potency) each of Cefotiam Hydrochloride and cefotiam hydrochloride RS, dissolve each in the mobile phase to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and calculate the peak areas, A_T and A_S, of cefotiam, respectively.

$$\text{Potency (μg) of cefotiam } (C_{18}H_{23}N_9O_4S_3) = \text{Potency (μg) of cefotiam hydrochloride RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 125 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: To 800 mL of 0.05 mol/L dibasic sodium phosphate TS, add 0.05 mol/L potassium dihydrogen phosphate TS to adjust the pH to 7.7. To 440 mL of this solution, add 60 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of cefotiam is about 14 minutes.

System suitability

System performance: Dissolve 0.04 g of orcin in 10 mL of the standard solution. Proceed with 10 μL of this solution according to the above conditions; orcin and cefotiam are eluted in this order with the resolution between these peaks being NLT 5.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of cefotiam is NMT 1.0%.

Packaging and storage Preserve in hermetic containers.

Cefotiam Hydrochloride for Injection
주사용 세포티암염산염

Cefotiam Hydrochloride for Injection, as an injection that is dissolved upon use, contains NLT 90.0% and NMT 110.0% of the labeled amount of cefotiam ($C_{18}H_{23}N_9O_4S_3$: 525.63).

Method of preparation Prepare as directed under Injections, with Cefotiam Hydrochloride.

Description Cefotiam Hydrochloride for Injection occurs as a white to pale yellow powder.

Identification (1) Determine the absorption spectrum with Cefotiam Hydrochloride for Injection and an aqueous solution of cefotiam hydrochloride for injection (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelength of between 257 nm and 261 nm.

(2) Determine the ^1H spectrum of a solution of Cefotiam Hydrochloride for Injection in deuterium oxide for nuclear magnetic resonance spectroscopy (1 in 10), as directed under the Nuclear Magnetic Resonance Spectroscopy; it exhibits single signals A and B between δ 2.7 ppm and 3.0 ppm and at around δ 6.5 ppm, respectively, and the area intensity ratio of signals A and B is about 6 : 1.

pH Dissolve an amount equivalent to 0.5 g (potency) of Cefotiam Hydrochloride for Injection in 5 mL of water; the pH of this solution is between 5.7 and 7.2.

Purity ***Clarity and color of solution***—Dissolve an amount equivalent to 1.0 g (potency) of cefotiam hydrochloride according to the labeled amount of Cefotiam Hydrochloride for Injection in 10 mL of water; the resulting solution is clear. Perform the test 10 minutes after dissolving as directed under the Ultraviolet-visible Spectroscopy; the absorbance of the solution at the wavelength of 450 nm is NMT 0.20.

Loss on drying NMT 6.0% (0.5 g, in vacuum, 60 °C, 3 hours).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.125 EU per mg (potency) of cefotiam.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

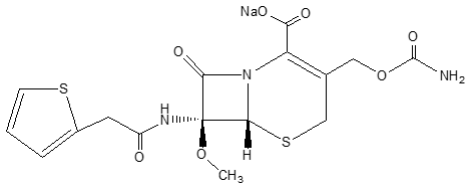
Assay Weigh accurately the mass of the contents of NLT 10 containers of Cefotiam Hydrochloride for Injection. Weigh accurately an amount equivalent to about 50 mg (potency) of cefotiam hydrochloride according to the labeled amount, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the test solution.

Separately, weigh accurately about 50 mg (potency) of cefotiam hydrochloride RS, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test as directed under the Assay under Cefotiam Hydrochloride.

$$\text{Potency (μg) of cefotiam } (C_{18}H_{23}N_9O_4S_3) = \text{Potency (μg) of cefotiam hydrochloride RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in hermetic containers. Plastic containers for aqueous injections may be used.

Cefoxitin Sodium
세폭시틴나트륨



$C_{16}H_{17}N_3NaO_7S_2$: 449.44

Sodium (6*R*,7*R*)-7-[2-(thiophen-2-yl)acetamido]-3-carbamoyloxymethyl-3,4-didehydrocepham-4-carboxylate [*33564-30-6*]

Cefoxitin Sodium contains NLT 927 μg and NMT 970 μg (potency) of cefoxitin ($C_{16}H_{17}N_3O_7S_2$: 427.46) per mg, calculated on the anhydrous, acetone-free, and methanol-free basis.

Description Cefoxitin Sodium occurs as a white to pale yellowish white particle or a powder.
It is very soluble in water, soluble in methanol, slightly soluble in ethanol(95), and practically insoluble in ether.

Identification (1) The retention time of the major peak obtained from the test solution corresponds to that from the standard solution, as obtained in the Assay.

(2) Dissolve 25 mg of Cefoxitin Sodium in 0.05 mol/L phosphate buffer (pH 7.0) to make 1000 mL, and determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima at the wavelengths of between 234 nm and 238 nm and between 260 nm and 264 nm.

(3) Dissolve 20 mg each of Cefoxitin Sodium and cefoxitin sodium RS in methanol to make 10 mL, and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, acetone and formic acid (10 : 9 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray 4-dimethylaminocinnamaldehyde TS on the plate and heat the plate at about 80 ℃ for 5 minutes; the R_f values of the purple spots from the test solution and the standard solution are the same.

(4) Cefoxitin Sodium responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between +206° and +214° (0.25 g, calculated on the anhydrous basis, acetone-free, and methanol-free basis, methanol, 25 mL, 100 mm).

pH Dissolve 1 g of Cefoxitin Sodium in 10 mL of water. The pH of this solution is between 4.2 and 7.0.

Absorbance $E_{1cm}^{1\%}$ (262 nm): Between 190 and 210 (2.0 mg, calculated on the anhydrous basis, 0.05 mol/L phosphate buffer (pH 7.0), 100 mL).

Purity (1) ***Heavy metals*—**Proceed with 1.0 g of Cefoxitin Sodium as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 20 ppm).

(2) ***Cefoxitin lactone*—**Weigh accurately about 0.1 g of Cefoxitin Sodium, dissolve in methanol to make exactly 10 mL, and use this solution as the test solution. Pipet 1 mL of the test solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, acetone and formic acid (10 : 9 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly 4-dimethylaminobenzaldehyde TS on the plate and heat the plate at about 80 ℃ for 5 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution (NMT 1.0%).

Water NMT 1.0% (0.5 g, volumetric titration, direct titration). Use a mixture of ethylene glycol and pyridine (3 : 1) instead of methanol.

Sterility It meets the requirements when used in a sterile preparation. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of a sterile preparation.

Bacterial endotoxins It is less than 0.10 EU per mg of cefoxitin when used in a sterile preparation.

Assay Weigh accurately about 50 mg (potency) of Cefoxitin Sodium, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh 10 mg of cefoxitin sodium RS, dissolve in the mobile phase to make exactly 20 mL, and use

this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of cefoxitin, respectively.

Potency (μg) of cefoxitin ($C_{16}H_{17}N_3O_7S_2$)
= Potency (μg) of cefoxitin RS × A_T / A_S

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of water, methanol and acetic acid(100) (50 : 50 : 1).

Flow rate: Adjust the flow rate so that the retention time of cefoxitin is about 6 minutes.

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of cefoxitin is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Cefoxitin Sodium for Injection
주사용 세폭시틴나트륨

Cefoxitin Sodium for Injection, as an injection that is dissolved upon use, contains NLT 90.0% and NMT 120.0% of the labeled amount of cefoxitin ($C_{16}H_{17}N_3O_7S_2$: 427.46).

Method of preparation Prepare as directed under Injections, with Cefoxitin Sodium.

Description Cefoxitin Sodium for Injection occurs as a white to pale yellowish white powder.

Identification Perform the test as directed under the Identification (1), (2) and (3) under Cefoxitin Sodium.

pH Dissolve an amount of Cefoxitin Sodium for Injection equivalent to 1.0 g (potency) of cefoxitin sodium in 10 mL of water; the pH of this solution is between 4.2 and 7.0.

Water NMT 2.0% (0.5 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.10 EU per mg (potency) of cefoxitin.

Particulate contamination: Visible particles Meets the requirements.

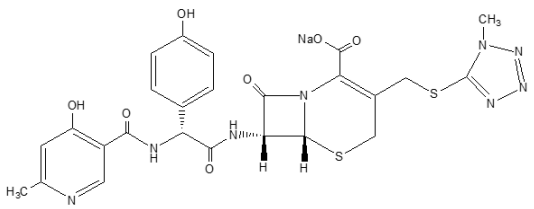
Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay under Cefoxitin Sodium. However, weigh accurately an amount equivalent to about 50 mg (potency) according to the labeled potency of Cefoxitin Sodium for Injection, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution.

Packaging and storage Preserve in hermetic containers.

Cefpiramide Sodium
세프피라미드나트륨



$C_{25}H_{23}N_8NaO_7S_2$: 634.62

Sodium (6*R*,7*R*)-7-[[(2*R*)-2-(4-hydroxyphenyl)-2-[(4-hydroxy-6-methylpyridin-3-yl)carbonylamino]acetamido]-3-[(1-methyltetrazol-5-yl)sulfanyl methyl]-3,4-didehydrocepham-4-carboxylate [*74849-93-7*]

Cefpiramide Sodium contains NLT 900 μg and NMT 990 μg (potency) of cefpiramide ($C_{25}H_{24}N_8O_7S_2$: 612.64) per mg, calculated on the anhydrous basis.

Description Cefpiramide Sodium occurs as a white to yellowish white powder.
It is very soluble in dimethylsulfoxide, freely soluble in water, sparingly soluble in methanol and slightly soluble in ethanol(95).

Identification (1) Determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy with 0.05 mol/L phosphate buffer solution (pH 7.0) (1 → 50000) of Cefpiramide Sodium; it exhibits an absorption maximum between 270 nm and 275 nm.

(2) Determine the nuclear magnetic resonance spectrum as directed under the Nuclear Magnetic Resonance Spectroscopy (^{1}H) with the deuterated dimethylsulfoxide solution (1 in 10) of Cefpiramide Sodium; it exhibits singlet signals at around 2.3 ppm, around 3.9 ppm and around 8.2 ppm, and the area intensity ratio of each signal is 3 : 3 : 1.

(3) Cefpiramide Sodium responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between -33° and -40° (0.2 g calculated on the anhydrous basis, 0.05 mol/L phosphate buffer solution (pH 7.0), 10 mL, 100 mm).

pH Dissolve 1 g (potency) of Cefpiramide Sodium in 10 mL of water; the pH of this solution is between 5.5 and 8.0.

Purity (1) ***Dissolution*—**Dissolve 1.0 g of Cefpiramide Sodium in 0.05 mol/L phosphate buffer solution (pH 7.0); the solution is clear and colorless to pale yellow.

(2) ***Heavy metals*—**Weigh 1.0 g of Cefpiramide Sodium and perform the test according to Method 2. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances*—**Weigh accurately about 25 mg of Cefpiramide Sodium and dissolve it in 0.03 mol/L phosphate buffer solution (pH 7.5) to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately an amount, equivalent to about 25 mg of 1-methyl-1*H*-tetrazole-5-thiol RS and about 75 mg (potency) of cefpyramide RS, previously dried for 2 hours in a desiccator (in vacuum, silica gel), and dissolve in 0.03 mol/L phosphate buffer solution (pH 7.5) to make exactly 100 mL. Pipet 2 mL of this solution, add 0.03 mol/L phosphate buffer solution (pH 7.5) to make exactly 100 mL, and use this solution as the standard solution. Pipet 5 μL each of the test and standard solutions and perform the test as directed under the Liquid Chromatography according to the following operating conditions, and measure each peak area of each solution. Determine each amount using the following formula; 1-methyl-1*H*-tetrazole-5-thiol is NMT 1.0%, other related substances are NMT 1.5%, and the sum of other related substances is NMT 4.0%.

Content (%) of 1-methyl-1*H*-tetrazole-5-thiol ($C_2H_4N_4S$)

$$= \frac{W_{Sa}}{W_T} \times \frac{A_{Ta}}{A_{Sa}}$$

Content (%) of other individual related substances

$$= \frac{W_{Sb}}{W_T} \times \frac{A_{Tc}}{A_{Sb}}$$

W_{Sa}: Amount (mg) of 1-methyl-1*H*-tetrazole-5-thiol

W_{Sb}: Amount [mg (potency)] of cefpiramide sodium RS

W_T: Amount (mg) of cefpiramide sodium

A_{Sa}: Peak area of 1-ethyl-1*H*-tetrazole-5-thiol in the standard solution

A_{Sb}: peak area of the cefpiramide of the standard solution

*A*Ta: Peak area of 1-methyl-1H-tetrazole-5-thiol in the test solution

A_{Tc}: Each peak area other than 1-methyl-1H-tetrazole-5-thiol and cefpiramide in the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with 10 μm octylsilyl silica gel for liquid chromatography.

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of 0.03 mol/L phosphate buffer solution (pH 7.5) and methanol (3 : 1).

Flow rate: Adjust so that the retention time of the cefpiramide is about 11 minutes.

System suitability

Test for required detectability: Pipet 5 mL of the standard solution and add 0.03 mol/L phosphate buffer solution (pH 7.5) to make exactly 50 mL. Confirm that the peak area of 1-methyl-1*H*-tetrazole-5-thiol obtained from 5 μL of this solution is 8% to 12% of the peak area of 1-methyl-1*H*-tetrazole-5-thiol from the standard solution.

System performance: Weigh 25 mg of cefpiramide RS and 7 mg of cinnamic acid and dissolve in the mobile phase to make 50 mL. Proceed with 5 μL of this solution according to the above conditions: cinnamic acid and cefpiramide are eluted in this order with the resolution being NLT 3.

System repeatability: Repeat the test 6 times according to the above conditions with 5 μL each of the standard solutions; the relative standard deviation of the peak area of 1-methyl-1H-tetrazole-5-thiol is NMT 2.0%.

Time span of measurement: About 2 times the retention time of cefpiramide.

Water NMT 7.0% (0.35 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, it is excluded in cases where there is a final sterilization process in the manufacturing of a sterile preparation.

Bacterial endotoxins It is less than 0.06 EU per mg (potency) of cefpiramide when used in the manufacturing of sterile preparations,

Assay Weigh accurately about 50 mg (potency) of Cefpiramide Sodium and cefpiramide RS, add exactly 5 mL of the internal standard solution to each, and dissolve in the mobile phase to make exactly 100 mL. Use these solutions as the test solution and the standard solution, respectively. Perform the test with 5 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and measure the peak area ratio, Q_T and Q_S, of cefpiramide to the peak area of the internal standard in the test solution and the standard solution.

Potency (μg) of cefpiramide ($C_{25}H_{24}N_8O_7S_2$)

$$= \text{Potency } (\mu g) \text{ of cefpiramide RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—4-dimethylaminoantipyrine solution (1 in 100).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of 0.01 mol/L phosphate buffer solution (pH 6.8), acetonitrile, tetrahydrofuran and methanol (22 : 1 : 1 : 1).

Flow rate: Adjust so that the retention time of cefpiramide is about 7 minutes.

System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; cefpiramide and the internal standard are eluted in this order with the resolution being NLT 7.0.

System repeatability: Repeat the test 6 times according to the above conditions with 5 μL each of the standard solutions; the relative standard deviation of the peak area ratio of cefpiramide to that of the internal standard is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers (NMT 5 °C).

Cefpiramide Sodium for Injection
주사용 세프피라미드나트륨

Cefpiramide Sodium for Injection is a preparation for injections, which is dissolved before use, and contains NLT 90.0% and NMT 120.0% of the labeled amount of cefpiramide ($C_{25}H_{24}N_8O_7S_2$: 612.64).

Method of preparation Prepare as directed under Injections, with Cefpiramide Sodium.

Description Cefpiramide Sodium for Injection occurs as a white to pale yellowish white powder.

Identification (1) Dissolve about 10 mg (potency) of Cefpiramide Sodium for Injection in 2 mL of water, add 2 mL of hydroxylammonium hydrochloride TS and allow to stand for 5 minutes. Add 1 mL of dilute ammonium iron(III) sulfate TS and shake to mix; the resulting solution exhibits a reddish brown color.

(2) Weigh 10 mg (potency) of Cefpiramide Sodium for Injection, dissolve in 2 mL of water, add 2 mL of sodium carbonate solution (1 in 100) and 3 mL of diazobenzenesulfonic acid TS, and shake to mix; the resulting solution exhibits an orange red color.

(3) Weigh 2 mg (potency) of Cefpiramide Sodium for Injection, and dissolve in 0.05 mol/L phosphate buffer solution (pH 7.0) to make 100 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 270 nm and 275 nm.

pH Dissolve 1.0 g of Cefpiramide Sodium for Injection in 10 mL of water; the pH of this solution is between 6.0 and 8.0.

Water NMT 3.0% (0.2 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.06 EU per mg (potency) of cefpiramide.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately about 1.0 g (potency) of Cefpiramide Sodium for Injection according to the labeled potency, and dissolve in water to obtain a solution containing 10 mg (potency) per mL. Pipet 5 mL of this solution, add 5.0 mL of the internal standard solution, then add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg (potency) of cefpiramide RS, add exactly 5 mL of the internal standard solution, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of cefpiramide to that of the internal standard, respectively.

$$\text{Potency } (\mu g) \text{ of cefpiramide } (C_{25}H_{24}N_8O_7S_2) = Potency \text{ } (\mu g) \text{ of cefpiramide RS} \times \frac{Q_T}{Q_S} \times 20$$

Internal standard solution—Weigh 1 g of aminopyrine, and dissolve in water to make 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography

(10 μm in particle diameter).

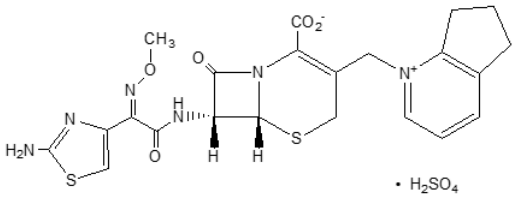
Mobile phase: A mixture of 0.01 mol/L phosphate buffer solution (pH 6.8), methanol, acetonitrile and tetrahydrofuran (880 : 40 : 40 : 40).

Flow rate: Adjust the flow rate so that the retention time of cefpiramide is about 7 minutes.

Selection of column: Perform the test with 5 μL of the standard solution according to the above operating conditions. Use a column giving elution of cefpiramide and aminopyrine in this order with the resolution between these peaks being NLT 7.0.

Packaging and storage Preserve in light-resistant, hermetic containers.

Cefpirome Sulfate
세프피롬황산염



$C_{22}H_{22}N_6O_5S_2 \cdot H_2SO_4$: 612.66

bis[(7*R*)-7-[(2*Z*)-2-(2-Amino-1,3-thiazol-4-yl)-2-methoxyiminoacetamido]-3-[(6,7-dihydro-5*H*-cyclopenta[b]pyridin-1-ium-1-yl)methyl]-3,4-didehydrocepham-4-carboxylate] sulfate [*98753-19-6*]

Cefpirome Sulfate contains NLT 760 μg (potency) of cefpirome ($C_{22}H_{22}N_6O_5S_2$: 514.58) per mg, calculated on the anhydrous basis.

Description Cefpirome Sulfate occurs as a white to pale yellowish white crystalline powder and has a slight characteristic odor.

It is soluble in water and practically insoluble in ethanol(95) or ether.

It is hygroscopic.

Identification (1) Dissolve 10 mg of Cefpirome Sulfate in 2 mL of water, add 3 mL of hydroxylamine hydrochloride-ethanol TS, allow to stand for 5 minutes, add 1 mL of acidic ammonium iron(III) sulfate TS, and shake to mix; the resulting solution exhibits a reddish brown color.

(2) Dissolve 1 mg of Cefpirome Sulfate in 4 mL of water and add 1 mL of dilute hydrochloric acid while cooling in an ice bath. To this solution, add 1 mL of freshly prepared sodium nitrite solution (1 in 100) and allow to stand for 2 minutes. While cooling again in an ice bath, add 1 mL of ammonium sulfate TS, allow to stand for 1 minute, and add 1 mL of *N*-1-naphthylethylenediamine dihydrochloride (1 in 1000); the resulting solution exhibits a violet color.

(3) Weigh 5 mg of Cefpirome Sulfate, dissolve in a mixture of 1 mL of ethanol(95) and 1 mL of water, add 0.1 g of 1-chloro-2,4-dinitrobenzene, and heat on a steam bath for 5 minutes. After cooling, add 2 to 3 drops of sodium hydroxide (1 in 10) and 3 mL of ethanol(95); the resulting solution exhibits a reddish brown color.

(4) Determine the absorption spectra of solutions of Cefpirome Sulfate and cefpirome sulfate RS 0.01 mol/L hydrochloric acid (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(5) With deuterium oxide for nuclear magnetic resonance spectroscopy(1 in 25) of Cefpirome Sulfate, determine ^1H as directed under the Nuclear Magnetic Resonance Spectroscopy using sodium 3-trimethylsilylpropanesulfonate as the internal standard; it exhibits a singlet signal A at around δ 4.1 ppm, a doublet signal B at around δ 5.9 ppm, a singlet signal C at around δ 7.1 ppm a multiplet signal D at around δ 7.8 ppm, and the area intensity ratio of each signal, A : B : C : D is about 3 : 1 : 1 : 1.

(6) An aqueous solution of Cefpirome Sulfate (1 in 250) responds to the Qualitative Analysis (1) for sulfate.

Optical rotation $[\alpha]_D^{20}$: Between -27° and -33° (0.5 g, calculated on the anhydrous basis, 20 mL of a solution prepared by adding water to 25 mL of acetonitrile to make 50 mL, 100 mm).

pH Dissolve 0.1 g of Cefpirome Sulfate in 10 mL of water; the pH of this solution is between 1.6 and 2.6.

Absorbance $E_{1cm}^{1\%}$ (270 nm): Between 405 and 435 (50 mg, calculated on the anhydrous basis, 0.01 mol/L hydrochloric acid TS, 2500 mL).

Purity ***Heavy metals***—Proceed with 1.0 g of Cefpirome Sulfate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 20 ppm).

Water—NMT 2.5% (0.5 g, volumetric titration, direct titration).

Sterility—It meets the requirements when used in sterile preparations. However, it is exempt from the requirements when there is a final sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins—Less than 0.10 EU per mg (potency) of cefpirome when used in sterile preparations.

Assay Weigh accurately about 50 mg (potency) of Cefpirome Sulfate and cefpirome sulfate RS, and dissolve each in water to make exactly 100 mL. To 5 mL each of these solutions, add water to make exactly 20 mL, and use these solutions as the test solution and the standard solution. Perform the test with 20 μL of each of these solutions as directed under the Liquid Chromatography method according to the following conditions, and determine the peak areas A_T and A_S of cefpirome.

Potency (μg) of cefpirome ($C_{22}H_{22}N_6O_5S_2$)

$$= \text{Potency (μg) of cefpirome sulfate RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 270 nm).

Column: A stainless steel column about 4.6 mm internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 3.45 g of ammonium dihydrogen phosphate in 1000 mL of water and adjust to pH 3.3 with phosphoric acid. Add 100 mL of acetonitrile to 800 mL of this solution.

Flow rate: Adjust the flow rate so that the retention time of cefpirome is about 7.5 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the number of theoretical plates of the cefpirome peak is NLT 3600.

System repeatability: Repeat the test 5 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of cefpirome is NMT 1.0%.

Packaging and storage Preserve in hermetic containers (at 2 ℃ to 8 ℃).

Cefpirome Sulfate for Injection
주사용 세프피롬황산염

Cefpirome Sulfate for Injection is a preparation for injections, which is dissolved before use, and contains NLT 90.0% and NMT 120.0% of the labeled amount of cefpirome ($C_{22}H_{22}N_6O_5S_2$: 514.58).

Method of preparation Prepare as directed under Injections, with Cefpirome Sulfate.

Description Cefpirome Sulfate for Injection occurs as a white to pale yellow crystalline powder.

Identification (1) Dissolve about 10 mg (potency) of Cefpirome Sulfate for Injection in 2 mL of water, add 3 mL of hydroxylammonium hydrochloride-ethanol TS, and allow to stand for 5 minutes. Add 1 mL of acidic ammonium iron(III) sulfate TS, and shake to mix; the resulting solution exhibits a reddish brown color.

(2) Weigh 1 mg (potency) of Cefpirome Sulfate for Injection, dissolve in 4 mL of water, cool in iced water, and add 1 mL of dilute hydrochloric acid. Add 1 mL of freshly prepared sodium nitrite solution (1 in 100), and allow to stand for 2 minutes. Cool the solution again in iced water, add 1 mL of ammonium sulfamate TS, allow to stand for 1 minute, and add 1 mL of N-(naphthyl) ethylenediamine hydrochloride solution (1 in 1000); the resulting solution exhibits a violet color.

(3) Weigh 5 mg (potency) of Cefpirome Sulfate for Injection, dissolve in 1 mL of ethanol and 1 mL of water, add 0.1 g of 2,4-dinitrochlorobenzene, and heat on a steam bath for 5 minutes. After cooling, add 2 to 3 drops of sodium hydroxide solution (1 in 10) and 3 mL of ethanol; the resulting solution exhibits a reddish brown color.

pH Dissolve 1 g (potency) of Cefpirome Sulfate for Injection per 10 mL in water, and remove air bubbles; the pH of the solution is 5.5 to 7.5.

Loss on drying NMT 2.5% (0.2 g, NMT 0.7 kPa, phosphorus pentoxide, 3 hours).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.15 EU per mg of cefpirome sulfate.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately an amount of Cefpirome Sulfate for Injection equivalent to about 50 mg (potency) of cefpirome according to the labeled potency, and dissolve in water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg (potency) of cefpirome sulfate RS, and dissolve in water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 20 mL and use this solution as the standard solution. Perform the test with 20 μL of these solutions as directed under the Liquid Chromatography according to the following conditions and determine the peak areas of cefpirome, A_T, and A_S, respectively, from each solution.

$$\text{Potency (μg) of cefpirome } (C_{22}H_{22}N_6O_5S_2) = \text{Potency (μg) of cefpirome RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 3.45 g of ammonium dihydrogen phosphate in water to make 1000 mL, and adjust the pH to 3.3 with phosphoric acid. Mix this solution with

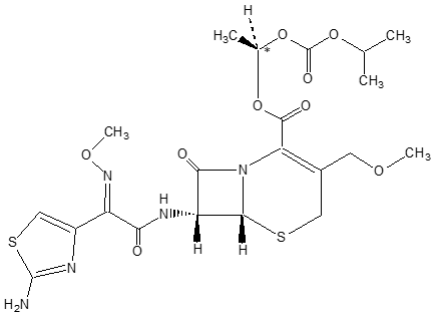
acetonitrile at a ratio of 8 : 1.

Flow rate: Adjust the flow rate so that the retention time of cefpirome is 6 to 9 minutes.

Selection of column: Perform the test with 20 μL of the standard solution according to the above conditions. Use a column giving the number of theoretical plate NLT 3600.

Packaging and storage Preserve in hermetic containers.

Cefpodoxime Proxetil
세프포독심프록세틸



and C* epimer

$C_{21}H_{27}N_5O_9S_2$: 557.60

1-(1-Methylethyloxycarbonyloxy)ethyl (6*R*,7*R*)-7-[(2*E*)-2-(2-aminothiazol-4-yl)-2-methoxyimino-acetamido]-3-methoxymethyl-3,4-didehydrocepham-4-carboxylate [*87239-81-4*]

Cefpodoxime Proxetil contains NLT 706 μg (potency) and NMT 774 μg (potency) of cefpodoxime ($C_{15}H_{17}N_5O_6S_2$: 427.46) per mg, calculated on the anhydrous basis.

Description Cefpodoxime Proxetil occurs as a white or pale brown powder.

It is very soluble in acetonitrile, methanol or chloroform, freely soluble in ethanol(99.5), and very slightly soluble in water.

Identification (1) Determine the absorption spectra of solutions of Cefpodoxime Proxetil and cefpodoxime proxetil RS in acetonitrile (3 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cefpodoxime Proxetil and cefpodoxime proxetil RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) With a solution of deuterated chloroform (1 in 10) of Cefpodoxime Proxetil, determine ^1H as directed under the Nuclear Magnetic Resonance Spectroscopy; the resulting spectrum exhibits doublet signals near δ 1.3 ppm and δ 1.6 ppm, and singlet signals near δ 3.3 ppm and δ 4.0, respectively. The area intensity ratio of each signal is 2 : 1 : 1 : 1.

Optical rotation $[\alpha]_D^{20}$: Between +24.0° and +31.4° (0.1 g, calculated on anhydrous basis, acetonitrile, 20 mL, 100 mm).

Absorbance $E_{1cm}^{1\%}$ (234 nm): Between 324 and 360 (0.1 g, calculated on the anhydrous basis, acetonitrile, 1000 mL).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Cefpodoxime Proxetil according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 50 mg of Cefpodoxime Proxetil in 50 mL of a mixture of water, acetonitrile and acetic acid(100) (1 : 1 : 2), and use this solution as the test solution. With 20 μL of the test solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine each peak area. If necessary, proceed with 20 μL a mixture of water, acetonitrile and acetic acid(100) (99 : 99 : 2) in the same manner to calibrate the solvent peak and baseline fluctuations. Calculate the amount of related substances by the percentage peak area method; the peak having the relative retention time for isomer B of cefpodoxime proxetil of about 0.8, is NMT 2.0%, the peaks other than cefpodoxime proxetil are NMT 1.0%, and the total area of the peaks other than cefpodoxime proxetil is NMT 6.0%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless-steel column about 4.6 nm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 22 ℃.

Mobile phase: Use the mobile phases A and B to control the step or the gradient elution as follows.

Mobile phase A: A mixture of water, methanol, and formic acid (11 : 8 : 1).

Mobile phase B: A mixture of methanol and formic acid (1 in 50) (19 : 1).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 65	95	5
65 - 145	95 → 15	5 → 85
145 - 155	15	85

Flow rate: Adjust the flow rate so that the retention time of isomer B of cefpodoxime proxetil is about 60 minutes.

System suitability

Test for required detectability: Pipet 5 mL of the

test solution, add a mixture of water, acetonitrile and acetic acid(100) (99 : 99 : 2) to make exactly 200 mL, and use this solution for the detection confirmation solution. Pipet 2 mL of the detection confirmation solution and add a mixture of water, acetonitrile and acetic acid(100) (99 : 99 : 2) to make exactly 100 mL. Confirm that the peak areas of isomer A and isomer B of cefpodoxime proxetil obtained from 20 μL of this solution are between 1.4% to 2.6% of the peak areas of isomer A and isomer B of cefpodoxime proxetil from the detection confirmation solution.

System performance: Dissolve 1 mg of Cefpodoxime Proxetil in 100 mL of a mixture of water, acetonitrile and acetic acid(100) (99 : 99 : 2). Proceed with 20 μL of this solution according to the above conditions; isomer A and isomer B of cefpodoxime proxetil are eluted in this order with the resolution being NLT 6.0.

System repeatability: Dissolve 1 mg of Cefpodoxime Proxetil in 100 mL of a mixture of water, acetonitrile and acetic acid(100) (99 : 99 : 2) Repeat the test 5 times with 20 μL each of this solution according to the above conditions; the relative standard deviation of ratios of the peak areas isomer A and isomer B of cefpodoxime proxetil is NMT 2.0%, respectively.

Time span of measurement: About 2.5 times the retention time of isomer B of cefpodoxime proxetil after the solvent peak.

Water NMT 2.5% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.2% (1 g).

Isomer ratio Perform the test with 5 μL of the test solution obtained under the Assay as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas the two isomers of cefpodoxime proxetil, A_a for the isomer with the shorter retention time and A_b for the isomer with the longer retention time; Ab/(Aa+Ab) is between 0.50 and 0.60.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

System performance and system repeatability: Proceed as directed under the system suitability under the Assay.

Assay Weigh accurately about 60 mg (potency) each of Cefpodoxime Proxetil and cefpodoxime proxetil RS, dissolve in 80 mL of acetonitrile, add exactly 4 mL of the internal standard solution to each, and add acetonitrile to make exactly 100 mL. Use these solutions as the test solution and the standard solution. Perform the test with 5 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_{T1}, Q_{T2}, Q_{S1}, and Q_{S2} of the peak area of cefpodoxime proxetil and its isomers to that of the internal standard from the test solution and the standard solution.

$$\text{Potency (μg) of cefpodoxime proxetil } (C_{15}H_{17}N_5O_6S_2) = \text{Potency (μg) of cefpodoxime proxetil RS} \times \frac{Q_{T1}+Q_{T2}}{Q_{S1}+Q_{S2}}$$

Internal standard solution—Dissolve 0.3 g of propyl p-hydroxybenzoate-ethylin a solution of citric acid monohydrate in acetonitrile (1 in 2000) to make 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of methanol and water (9:11).

Flow rate: Adjust the flow rate so that the retention time of the internal standard is about 11 minutes.

System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; propyl p-hydroxybenzoate-ethyl, isomer A of cefpodoxime proxetil, and isomer B of cefpodoxime proxetil are eluted in this order with the resolution between the isomers being NLT 4.0.

System repeatability: Repeat the test 5 times with 5 μL each of the standard solutions according to the above conditions; the relative standard deviation of ratios of the peak area of isomer B of cefpodoxime proxetil to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Cefpodoxime Proxetil for Syrup
시럽용 세프포독심프록세틸

Cefpodoxime Proxetil for Syrup is a preparation for syrup, which is dissolved before use, and contains NLT 90.0% and NMT 120.0% of the labeled amount of cefpodoxime ($C_{15}H_{17}N_5O_6S_2$: 427.46).

Method of preparation Prepare as directed under Syrups, with Cefpodoxime Proxetil.

Identification (1) Dissolve an amount of powdered Cefpodoxime Proxetil for Syrup, equivalent to 10 mg (potency) of cefpodoxime, in 2 mL of hydroxylamine hydrochloride TS, allow to stand for 5 minutes, add 1 mL of acidic ammonium iron(III) sulfate TS, and shake to mix; a reddish brown color develops.

(2) Dissolve an amount of powdered Cefpodoxime Proxetil for Syrup, equivalent to 1 mg (potency) of cefpodoxime, in 4 mL of water, and add 1 mL of dilute sulfuric acid while cooling on ice. Add 1 mL of a freshly prepared sodium nitrite solution (1 in 100), shake, and allow to stand for 2 minutes. Add 1 mL of ammonium amidosulfate solution (1 in 100) while cooling on ice, shake well to mix, allow to stand for 1 minute, and add 1 mL of N-(1-Naphthyl)ethylenediamine hydrochloride TS; a purple color develops.

(3) Dissolve an amount of powdered Cefpodoxime Proxetil for Syrup, equivalent to 15 mg (potency) of cefpodoxime, in acetonitrile to make 1000 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelength of between 232 nm and 236 nm.

pH Dissolve Cefpodoxime Proxetil for Syrup according to the label; the pH of the resulting solution is between 4.0 and 5.5.

Water NMT 2.0% (0.5 g, volumetric titration, direct titration).

Uniformity of dosage units (distribution) Meets the requirements.

Assay Proceed as directed under the Assay under Cefpodoxime Proxetil. However, weigh accurately an amount of Cefpodoxime Proxetil for Syrup, equivalent to about 0.1 g (potency) according to the labeled potency, transfer it to a blender, add exactly 30 mL of the internal standard solution, and blend at high speed. Filter, pipet 3 mL of the filtrate, add acetonitrile to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg (potency) of cefpodoxime proxetil RS, dissolve in acetonitrile, add 15 mL of the internal standard solution and acetonitrile to make exactly 100 mL, and use this solution as the standard solution.

Internal standard solution—Dissolve 0.2 g of ethylparaben in a solution of citric acid monohydrate in acetonitrile (1 in 2000) to make 300 mL.

Packaging and storage Preserve in tight containers.

Cefpodoxime Proxetil Tablets
세프포독심프록세틸 정

Cefditoren Pivoxil Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of cefpodoxime ($C_{15}H_{17}N_5O_6S_2$: 427.46).

Method of preparation Prepare as directed under Tablets, with Cefpodoxime Proxetil.

Identification (1) Weigh an amount of Cefpodoxime Proxetil Tablets, previously powdered, equivalent to 10 mg (potency) of cefpodoxime, dissolve in 2 mL of hydroxylamine hydrochloride TS, allow to stand for 5 minutes, add 1 mL of acidic ammonium iron(III) sulfate TS, and shake to mix; the resulting solution exhibits a reddish brown color.

(2) Weigh an amount of Cefpodoxime Proxetil Tablets, previously powdered, equivalent to 1 mg (potency) of cefpodoxime, dissolve in 4 mL of water, cool with ice, and add 1 mL of dilute sulfuric acid. Add 1 mL of freshly prepared sodium nitrite solution (1 in 100), shake to mix, and allow to stand for 2 minutes. Cool with ice again, add 1 mL of ammonium amidosulfate solution (1 in 100), shake well to mix, allow to stand for 1 minute, and add 1 mL of hydrochloric acid *N*-(1-naphthyl)ethylenediamine hydrochloride TS; the resulting solution exhibits a reddish purple color.

(3) Weigh an amount of Cefpodoxime Proxetil Tablets, previously powdered, equivalent to 15 mg (potency) of cefpodoxime, and dissolve in acetonitrile to make 1000 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 232 nm and 236 nm.

Water NMT 5.0% (0.2 g, volumetric titration, direct titration).

Dissolution Perform the test with 1 tablet of Cefpodoxime Proxetil Tablets at 75 revolutions per minute according to the Method 2 under the Dissolution. Put 54.5 g of glycine and 42.6 g of sodium chloride in a 1000-mL flask, previously filled with about 500 mL of water, add carefully 14.2 mL of hydrochloric acid while shaking the flask, cool, and add water to make 1000 mL. Take 50 mL of the resulting solution, add water to make 900 mL, and adjust the pH to 3.0±0.1 with 10 mol/L sodium hydroxide, if needed. Use this solution as the test solution. Take the dissolved solution after 30 minutes from the start of the test, and filter. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately an appropriate amount of cefpodoxime proxetil RS, dissolve in a small amount of methanol, add the test solution to make the same concentration as the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength near 259 nm as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as a control solution. It meets the requirements when the dissolution rate in 30 minutes is NLT 70% (Q).

Dissolution rate (%) with respect to the labeled amount of cefpodoxime proxetil ($C_{15}H_{17}N_5O_6S_2$)

$$= C_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 90000$$

Cs: Concentration [mg (potency)/mL] of the standard solution

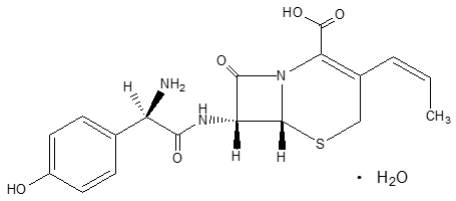
C: Labeled amount [mg (potency)] of cefpodoxime proxetil ($C_{15}H_{17}N_5O_6$) in 1 tablet

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay under Cefpodoxime Proxetil. However, weigh accurately the mass of NLT 20 tablets of Cefpodoxime Proxetil Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 60 mg (potency) according to the labeled potency of Cefpodoxime Proxetil Tablets, put in a blender, add 40 mL of acetonitrile, mix at high speed, and filtrate. Pipet 20 mL of the filtrate, add exactly 2 mL of the internal standard solution, and add acetonitrile to make exactly 50 mL. Use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Cefprozil Hydrate
세프프로질수화물



Cefprozil $C_{18}H_{19}N_3O_5S \cdot H_2O$: 407.44
(6*R*,7*R*)-7-[(2*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3-[(*Z*)-prop-1-enyl]-3,4-didehydro-cepham-4-carboxylic acid monohydrate [*121123-17-9*]

Cefprozil Hydrate contains NLT 900 μg (potency) and NMT 1050 μg (potency) of cefprozil ($C_{18}H_{19}N_3O_5S$: 389.43) per mg, calculated on the anhydrous basis.

Description Cefprozil Hydrate occurs as a white to pale yellow powder.
It is sparingly soluble in methanol, slightly soluble in water or dimethylsulfoxide, and practically insoluble in ethanol(95) and acetone.

Identification (1) Determine the infrared spectra of Cefprozil Hydrate and cefprozil(*Z*) isomer RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Crystalline Meets the requirements.

pH Dissolve 1 g of Cefprozil Hydrate in 200 mL of water; the pH of this solution is between 3.5 and 6.5.

Cefprozil(E) isomer Perform the test under the Assay and calculate according to the following formula (content ratio: between 0.06 and 0.11).

$$\text{Content ratio of cefprozil } (E) \text{ isomer} = \frac{Amount\ (\mu g/mg)\ of\ \text{cefprozil } (E) \text{ isomer}}{Amount\ (\mu g/mg) of\ \text{cefprozil } (Z) \text{isomer} + \text{Amount } (\mu g/mg) \text{ of cefprozil } (E) \text{ isomer}}$$

Water Between 3.5% and 6.5% (0.2 g, volumetric titration, direct titration).

Assay Weigh accurately about 25 mg (potency) of Cefprozil Hydrate, dissolve in water to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg (potency) of cefprozil(*Z*) isomer RS, dissolve in water to make exactly 100 mL, and use this solution as the cefprozil(*Z*) isomer standard solution. Separately, weigh accurately about 25 mg (potency) of cefprozil(E) isomer RS, dissolve in water to make exactly 100 mL, pipet 5 mL of this solution, and add water to make exactly 50 mL. Use this solution as the cefprozil(E) isomer standard solution. Perform the test with exactly 10 μL each of the test solution and standard solutions as directed under the Liquid Chromatography according to the following conditions.

Potency (μg) in 1 mg of Cefprozil Hydrate = Amount (μg) of cefprozil(*Z*) isomer in 1 mg of Cefprozil Hydrate + Amount (μg) of cefprozil(E) isomer in 1 mg of Cefprozil Hydrate

$$\text{Amount (μg) of cefprozil(Z) isomer in 1 mg of Cefprozil Hydrate} = \frac{W_1}{W} \times P_1 \times \frac{A_1}{T_1}$$

$$\text{Amount (μg) of cefprozil(E) isomer in 1 mg of Cefprozil Hydrate} = \frac{W_2}{W} \times P_2 \times \frac{A_2}{T_2}$$

W Amount (mg) of Cefprozil Hydrate taken
W_1 Amount (mg) of cefprozil(*Z*) isomer RS taken
A_1 Peak area of cefprozil(*Z*) isomer in the test solution
T_1 Peak area of cefprozil *Z*) isomer in the standard solution
P_1 Potency (μg/mg) of cefprozil(*Z*) isomer RS
W_2: Amount (mg) of cefprozil(*E*) isomer RS taken
A_2 Peak area of cefprozil(*E*) isomer in the test solution
T_2 Peak area of cefprozil(E) isomer in the standard solution
P_2 Potency (μg/mg) of cefprozil(*E*) isomer RS

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 20.7 g of ammonium dihydrogenphosphate in 1800 mL of water, adjust the pH to 4.4 with phosphoric acid, and add 200 mL of acetonitrile.

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Cefprozil for Syrup
시럽용 세프프로질

Cefprozil for Syrup is a preparation for syrup, which is suspended before use, and contains NLT 90.0% and NMT 120.0% of the labeled amount of cefprozil ($C_{18}H_{19}N_3O_5S$: 389.43).

Method of preparation Prepare as directed under Syrups, with Cefprozil Hydrate.

Identification (1) Dissolve about 50 mg (potency) each of Cefprozil for Syrup and cefprozil (Z) isomer RS in 10 mL of a mixture of acetone and 0.1 mol/L hydrochloric acid TS (4 : 1) and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on a plate of silica gel for thin-layer chromatography, and develop the plate with a mixture of 1-butanol, acetic acid and water (60 : 20 : 20). Expose the plate to iodine vapor; the R_f values of the spots obtained from the test solution and the standard solution are the same.

(2) Perform the test as directed in Identification (2) under Cefprozil Hydrate.

pH Dissolve Cefprozil for Syrup according to the label; the pH of the resulting solution is between 4.0 and 6.0.

Water NMT 3.0% (0.2 g, volumetric titration, direct titration).

Uniformity of dosage units (distribution) Meets the requirements.

Assay Proceed as directed under the Assay under Cefprozil Hydrate. Weigh accurately an amount of Cefprozil for Syrup, equivalent to about 25 mg (potency), dissolve in water to make exactly 100 mL, centrifuge, and use the clear supernatant as the test solution.

Packaging and storage Preserve in tight containers.

Cefprozil Tablets
세프프로질 정

Cefprozil Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of cefprozil ($C_{18}H_{19}N_3O_5S$: 389.43).

Method of preparation Prepare as directed under Tablets, with Cefprozil Hydrate.

Identification Powder Cefprozil Tablets, and perform the test as directed under the Identification of Cefprozil for Syrup.

Water NMT 7.0% (0.1 g, volumetric titration, direct titration).

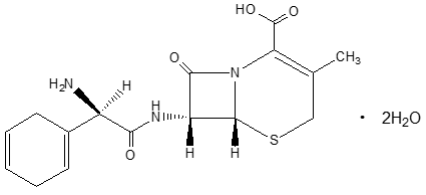
Dissolution Perform the test with 1 tablet of Cefprozil Tablets at 100 revolutions per minute according to Method 1 under the Dissolution, using 900 mL of water as the dissolution medium. Take a certain amount of the dissolved solution 45 minutes after starting the start, filter through a membrane filter with a pore size NMT 0.5 μm, and dilute with water so that it contains 0.3 mg (potency) per mL. Use this solution as the test solution. Perform the test according to the operating conditions under the Assay and calculate the dissolution rate; it meets the requirements if the dissolution rate of Cefprozil Tablets in 45 minutes is NLT 75%.

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay under Cefprozil Hydrate. Weigh accurately the mass of NLT 20 tablets of Cefprozil Tablets and powder. Weigh accurately an amount, equivalent to about 25 mg (potency), add water, shake well to mix to make exactly 100 mL, and centrifuge. Use the clear supernatant as the test solution.

Packaging and storage Preserve in tight containers.

Cefradine Hydrate
세프라딘수화물



Cefradine $C_{16}H_{19}N_3O_4S \cdot 2H_2O$: 385.44

(6*R*,7*R*)-7-[2-Amino-2-(cyclohexa-1,4-dien-1-yl)aceamido]-3-methyl-3,4-didehydrocepham-4-

carboxylic acid monohydrate [*31828-50-9*]

Cefradine Hydrate contains NLT 900 μg (potency) and NMT 1050 μg (potency) of cefradine ($C_{16}H_{19}N_3O_4S$: 349.41) per mg, calculated on the anhydrous basis.

Description Cefradine Hydrate occurs as a white to pale yellowish white crystalline powder.
It is odorless or has a slight characteristic odor and has a bitter taste.
It is sparingly soluble in water, slightly soluble in methanol, very slightly soluble in ethanol(95), and practically insoluble in ether.

Identification Determine the infrared spectra of Cefradine Hydrate and cefradine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the spectra, dissolve each in methanol, and repeat the test with the respective residues.

Crystallinity Meets the requirements.

pH Dissolve 0.1 g of Cefradine Hydrate in 10 mL of water. The pH of this solution is between 3.5 and 6.0.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Cefradine Hydrate as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm). (NMT 10 ppm).

(2) ***Arsenic***—Prepare the test solution with 2.0 g of Cefradine Hydrate according to Method 4 and perform the test (NMT 1 ppm).

(3) ***Cefalexin***—Perform the test as directed under the Assay and determine the amount of cefalexin according to the following equation (NMT 5.0%).

$$\text{Content (\%) of cefalexin } (C_{16}H_{17}N_3O_4S) = \frac{A_T}{A_S} \times 100$$

A_T: Peak area of cefalexin obtained from the test solution

A_S: Sum of peak areas of cefradine and cefalexin obtained from the test solution

Water Between 8.5% and 10.5% (0.2 g, volumetric titration, direct titration).

Sterility It meets the requirements when Cefradine Hydrate is used in a sterile preparation. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of a sterile preparation.

Bacterial endotoxins It is less than 0.20 EU per mg of cefradine when Cefradine Hydrate is used in a sterile preparation.

Assay Weigh accurately about 50 mg (potency) each of Cefradine Hydrate and cefradine RS, add the mobile phase to each to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 mL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and determine the amount of cefradine according to the following equation.

$$\text{Potency (μg) of cefradine } (C_{16}H_{19}N_3O_4S) = \text{Potency (μg) of cefradine RS} \times \frac{A_T}{A_S}$$

A_T: Sum of peak areas of cefradine and cefalexin obtained from the test solution

A_S: Sum of peak areas of cefradine and cefalexin obtained from the standard solution

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of water, methanol, 0.5 mol/L sodium acetate and 0.7 mol/L acetic acid (782 : 200 : 15 : 3).

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 20 μL of the system suitability solution according to the above conditions; the relative retention times of cefalexin and cefradine are 0.8 and 1.0, respectively, with the resolution between the two peaks being NLT 2.0.

System repeatability: Repeat the test 5 times with 20 μL each of the system suitability solutions according to the above conditions; the relative standard deviation of the peak of cefradine is NMT 2.0%.

System suitability solution—Dissolve suitable quantities of cefradine RS and cefalexin RS in the mobile phase, respectively, to make respective solutions having a concentration of 0.5 mg per mL.

Packaging and storage Preserve in light-resistant, tight containers.

Cefradine Capsules
세프라딘 캡슐

Cefradine Capsules contain NLT 90.0% and NMT 120.0% of the labeled amount of cefradine ($C_{16}H_{19}N_3O_4S$: 349.41).

Method of preparation Prepare as directed under Capsules, with Cefradine Hydrate.

Identification Weigh an amount equivalent to about 0.25 g (potency) of Cefradine Capsules, according to the labeled potency, transfer to a stoppered test tube, add 10 mL of water and 5 mL of hydrochloric acid, and boil on a steam bath for 10 minutes. After cooling, and centrifuge; the resulting solution exhibits an orange color.

Loss on drying NMT 7.0% (0.1 g, 0.7 kPa, 60 ℃, 3 hours).

Dissolution Perform the test with 1 capsule of Cefradine Capsule at 100 revolutions per minute according to Method 1 under the Dissolution, using 900 mL of 0.12 mol/L hydrochloric acid TS as the dissolution medium. Take the dissolved solution after 45 minutes from the start of the test and filter. Discard the first 10 mL of the filtrate, pipet V mL of the subsequent filtrate, add the dissolution medium to make exactly V′ mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of cefradine RS, dissolve in the dissolution medium to obtain the same concentration as the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength near 255 nm as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as a control solution. It meets the requirements when the dissolution rate of Cefradine Capsules in 45 minutes is NLT 75% (Q).

$$\text{Dissolution rate (\%) of the labeled amount of cefradine } (C_{16}H_{19}N_3O_4S) = C_s \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 90000$$

Cs: Concentration [mg (potency)/mL] of the standard solution

C: Labeled amount (mg) of cefradine ($C_{16}H_{19}N_3O_4S$) in 1 capsule

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay of Cefradine Hydrate. However, weigh accurately the mass of NLT 20 Cefradine Capsules, weigh accurately an amount equivalent to about 50 mg (potency), dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Cefradine for Injection
주사용 세프라딘

Cefradine for Injection, as an injection that is dissolved upon use, contains NLT 90.0% and NMT 120.0% of the labeled amount of cefradine ($C_{16}H_{19}N_3O_4S$: 349.41).

Method of preparation Prepare as directed under Injections, with Cefradine.

Description Cefradine for Injection occurs as a white to pale yellowish white powder.

Identification Perform the test as directed under the Identification under Cefradine Capsules.

pH Dissolve an amount of Cefradine for Injection equivalent to 1 g (potency) of cefradine in 100 mL of water; the pH of this solution is between 8.0 and 9.6.

Loss on drying NMT 5.0% (0.1 g, 0.7 kPa, 60 ℃, 3 hours).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.20 EU per mg (potency) of cefradine.

Particulate contamination: Visible particles Meets the requirements.

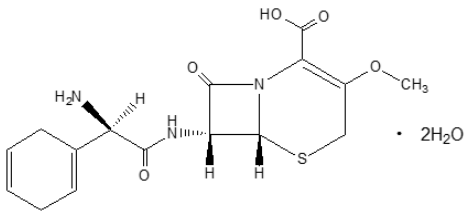
Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay under Cefradine Hydrate. However, weigh accurately an amount equivalent to about 50 mg (potency) according to the labeled potency of Cefradine for Injection, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution.

Packaging and storage Preserve in hermetic containers.

Cefroxadine Hydrate
세프록사딘수화물



Cefroxadine $C_{16}H_{19}N_3O_5S \cdot 2H_2O$: 401.43

(6*R*,7*R*)-7-[2-Amino-2-(cyclohexa-1,4-dien-1-yl)aceamido]-3-methyloxy-3,4-didehydrocepham-4-carboxylic acid monohydrate [*95615-72-8*]

Cefroxadine Hydrate contains NLT 930 μg (potency) and NMT 1020 μg (potency) of cefroxadine

($C_{16}H_{19}N_3O_5S$: 365.40) per mg, calculated on the anhydrous basis.

Description Cefroxadine Hydrate occurs as a pale yellowish white to pale yellow crystalline grain or a powder.
It is freely soluble in formic acid, slightly soluble in methanol, and very slightly soluble in acetonitrile or ethanol(95).
It dissolves in 0.001 mol/L hydrochloric acid TS or dilute acetic acid.

Identification (1) Determine the absorption spectra of respective solutions of Cefroxadine Hydrate and cefroxadine RS in 0.001 mol/L hydrochloric acid TS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine ^1H of a solution of Cefroxadine Hydrate in deuterated formic acid for nuclear magnetic resonance spectroscopy (1 in 10) as directed under the Nuclear Magnetic Resonance Spectroscopy, using tetramethylsilane for nuclear magnetic resonance spectroscopy as the internal standard; it exhibits the sharp singlet signals A, B and C at about δ 2.8 ppm, δ 4.1 ppm and δ 6.3 ppm, respectively, with the ratio of area strength of the signals A : B : C being about 4 : 3 : 1.

Optical rotation $[\alpha]_D^{20}$: Between +95° and +108° (0.1 g, calculated on the anhydrous basis, 100 mL of diluted acetic acid(100) (3 in 25), 100 mm).

Purity (1) ***Heavy metals***—Place 1.0 g of Cefroxadine Hydrate in a porcelain crucible, and add 10 mL of a solution of magnesium nitrate hexahydrate in ethanol(95) (1 in 10) to mix. Light the ethanol to burn and lightly heat to carbonize. After cooling, add 2 mL of nitrogen acid, heat carefully, and ignite to 500 to 600 ℃ to ash. If there is a residual carbide, wet it with a small amount of nitric acid and ignite again to ash. After cooling, add 6 mL of hydrochloric acid, and evaporate to dryness on a steam bath. Wet the residue with 3 drops of hydrochloric acid, add 10 mL of hot water, and warm on a steam bath to dissolve. After cooling, add ammonia TS dropwise to adjust the pH to between 3 and 4, add 2 mL of dilute acetic acid, and if necessary, filter. Place the resultant material in a Nessler tube, wash the porcelain crucible with 10 mL of water, and combine the washings with new water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by proceeding in the same manner as the preparation of the test solution with 2.0 mL of lead standard solution and 10 mL of a solution of magnesium nitrate hexahydrate in ethanol(95) (1 in 10) placed in a porcelain crucible (NMT 20 ppm).

(2) ***Arsenic***—Prepare the test solution with 1.0 g of Cefroxadine Hydrate according to Method 4 and perform the test (NMT 2 ppm).

(3) ***Related substances***—Dissolve 10 mg of Cefroxadine Hydrate in 100 mL of the mobile phase, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to it make exactly 100 mL, and use this solution as the standard solution. Perform the test with 40 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine individual peak areas in each of the respective solutions according to the automatic integration method; the peak areas with the relative retention times with respect to cefroxadine of about 0.07, 0.6 and 0.8, respectively, obtained from the test solution are not larger than 2 times the peak area of cefroxadine, 4 times the peak area of cefroxadine, and the peak area of cefroxadine, respectively, from the standard solution, each peak area, other than cefroxadine and the peaks above, obtained from the test solution is not larger than 1/2 of the peak area of cefroxadine from the standard solution, and the sum of peak areas other than cefroxadine obtained from the test solution is not larger than 6 times the peak area of cefroxadine from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 1.4 g of sodium perchlorate in 1000 mL of a mixture of water and acetonitrile (489 : 11).

Flow rate: Adjust the flow rate so that the retention time of cefroxadine is about 20 minutes.

System suitability

Test for required detectability: Pipet 2 mL of the standard solution and add the mobile phase to make exactly 20 mL. Confirm that the peak area of cefroxadine obtained from 40 μL of this solution is within the range between 7% and 13% of the peak area of cefroxadine obtained from the standard solution.

System performance: Dissolve 3 mg of Cefroxadine Hydrate and 15 mg of orcin in 100 mL of the mobile phase. Proceed with 40 μL of this solution according to the above conditions; orcin and cefroxadine are eluted in this order with the resolution being NLT 3.

System repeatability: Repeat the test 6 times with 40 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of cefroxadine is NMT 2.0%.

Time span of measurement: About 2 times the retention time of cefroxadine.

Water **Between** 8.5% and 12.0% (0.1 g, volumetric titration, direct titration).

Assay Weigh accurately about 50 mg (potency) of Cefroxadine Hydrate and cefroxadine RS, dissolve each in a respective mixture of dilute acetic acid and phosphor-

ic acid (500 : 1), add exactly 5 mL of the internal standard solution to each, and add a mixture of dilute acetic acid and phosphoric acid (500 : 1) to each to make 200 mL. Use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following operating conditions, and calculate the peak area ratios, Q_T and Q_S, of cefroxadine to the internal standard, respectively.

$$\text{Potency (μg) of cefroxadine } (C_{16}H_{19}N_3O_5S) = \text{Potency (μg) of cefroxadine RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Dissolve 1.6 g of vanillin in 5 mL of methanol, and add a mixture of dilute acetic acid and phosphoric acid (500 : 1) to make 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of ammonium sulfate solution (1 in 50) and acetonitrile (97 : 3).

Flow rate: Adjust the flow rate so that the retention time of cefroxadine is about 10 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; cefroxadine and the internal standard are eluted in this order with the resolution being NLT 1.5.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area ratio of cefroxadine to the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Cefroxadine Capsules
세프록사딘 캡슐

Cefroxadine Capsules contain NLT 90.0% and NMT 120.0% of the labeled amount of cefroxadine ($C_{16}H_{19}N_3O_5S$: 365.41).

Method of preparation Prepare as directed under Capsules, with Cefroxadine.

Identification (1) Weigh 5 mg (potency) of Cefroxadine Capsules, dissolve in 2 mL of hydroxylamine hydrochloride-acetate TS, allow it to stand for 3 minutes, and add 1 mL of acidic ammonium iron(III) sulfate TS; the resulting solution exhibits a reddish brown color.

(2) Weigh 5 mg (potency) of Cefroxadine Capsules, transfer into a test tube, add 2 drops of a solution of benzoyl peroxide in acetone (1 in 10), evaporate to dryness on a steam bath, and fix a glass rod coated with concentrated chromotropic acid TS at the bottom, in a test tube with a cork stopper. Heat at 120 to 130 ℃ on a steam bath for several minutes; concentrated chromotropic acid TS exhibits a reddish violet color.

(3) Weigh 2 mg (potency) of Cefroxadine Capsules, dissolve in 0.001 mol/L hydrochloric acid TS to make 100 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum absorbance between 267 nm and 271 nm.

Water NMT 12.0% (0.1 g, volumetric titration, direct titration).

Dissolution Perform the test with 1 capsule of Cefroxadine Capsule at 100 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of Solution 1 as the dissolution medium. Take the dissolved solution 45 minutes after starting the test, and filter. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add the dissolution medium to make *V'* mL of a solution containing about 200 μg of cefroxadine ($C_{16}H_{19}N_3O_5S$) per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 20 mg of cefroxadine RS, dissolve in the dissolution medium to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Assay, and determine the peak areas, A_T and A_S, of cefroxadine ($C_{16}H_{19}N_3O_5S$) in each solution. It meets the requirements when the amount dissolved of Cefroxadine Capsules in 45 minutes is NLT 80%.

$$\text{Amount dissolved (\%) of the labeled amount of cefroxadine } (C_{16}H_{19}N_3O_5S) = W_S \times (V'/V) \times (A_T/A_S) \times (1/C) \times 900$$

W_S: Amount (mg) of cefroxadine RS

C: Labeled amount (mg) of cefroxadine ($C_{16}H_{19}N_3O_5S$) in 1 capsule

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the contents of NLT 20 Cefroxadine Capsules. Weigh accurately about Cefroxadine Capsules, equivalent to about 25 mg (potency) of cefroxadine according to the labeled potency, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg (potency) of cefroxadine RS, add the mobile phase to make exactly 100 mL, and use this solution as

the standard solution. Pipet 10 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of cefroxadine in each solution.

Amount [potency (mg)] of cefroxadine ($C_{16}H_{19}N_3O_5S$)
= Amount [potency (mg)] of cefroxadine RS × (A_T / A_S)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 267 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of 0.1 mol/L phosphoric acid solution and acetonitrile (17 : 3).

Flow rate: 1.0 mL/min

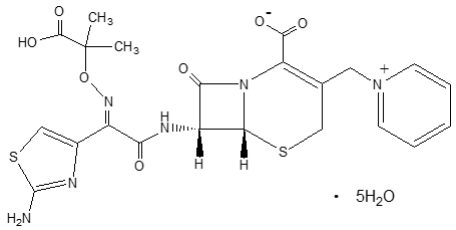
System suitability

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of cefroxadine is NMT 2.0%.

0.1 mol/L phosphoric acid—To 6.8 mL of 85% phosphoric acid, add water to make 1000 mL.

Packaging and storage Preserve in tight containers.

Ceftazidime Hydrate
세프타지딤수화물



Ceftazidime $C_{22}H_{22}N_6O_7S_2 \cdot 5H_2O$: 636.65
(6*R*,7*R*)-7-[(2*E*)-2-(2-Amino-1,3-thiazol-4-yl)-2-(2-carboxypropan-2-yloxyimino)acetamido]-3-(pyridin-1-ium-1-yl)methyl-3,4-didehydrocepham-4-carboxylate pentahydrate [*78439-06-2*]

Ceftazidime Hydrate contains NLT 950 μg and NMT 1020 μg (potency) of netilmicin ($C_{22}H_{22}N_6O_7S_2$: 546.58) per mg, calculated on the dried basis.

Description Ceftazidime Hydrate occurs as a white to pale yellowish white crystalline powder.
It is sparingly soluble in water and very slightly soluble in acetonitrile or ethanol(95).

Identification (1) Determine the absorption spectra of solutions of Ceftazidime Hydrate and ceftazidime RS in phosphate buffer solution, pH 6.0 (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Ceftazidime Hydrate and ceftazidime RS according to the potassium bromide disk method as directed under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Weigh 50 mg of Ceftazidime Hydrate, add 5 mg of dried sodium carbonate, and dissolve in 0.5 mL of deuterium oxide for nuclear magnetic resonance spectroscopy. With this solution, measure ^1H according to the Nuclear Magnetic Resonance Spectroscopy, using 3-(Trimethylsilyl)propanesulfonic acid sodium salt for nuclear magnetic resonance spectroscopy as the internal standard; it exhibits singlet signals A and B at around δ 1.5 ppm and δ 6.9 ppm, and a multiplet signal C at δ 7.9 to 9.2 ppm. The area intensity ratio of each signal, A : B : C is 6 : 1 : 5.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between -28° and -34° (0.5 g, calculated on the dried basis, phosphate buffer solution (pH 6.0), 100 mL, 100 mm).

pH Dissolve 0.5 g of Ceftazidime Hydrate in 100 mL of water; the pH of this solution is between 3.0 and 4.0.

Purity (1) ***Clarity and color of solution***—Add 5 g of anhydrous sodium dihydrogen phosphate and 1 g of potassium dihydrogen phosphate to 1.0 g of Ceftazidime Hydrate, dissolve in water to make 100 mL; the resulting solution is clear. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at the wavelength of 420 nm is NMT 0.20.

(2) ***Free pyridine***—Weigh accurately about 50 mg of Ceftazidime Hydrate, dissolve in the mobile phase to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of pyridine and dissolve in the mobile phase to make exactly 100 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography under the following conditions. Determine the peak height, H_T and H_S; the amount of free pyridine is NMT 0.3%.

$$\text{Amount (mg) of free pyridine} = \text{Amount (mg) of the pyridine taken} \times \frac{H_T}{H_S} \times \frac{1}{1000}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 20 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 2.88 g of ammonium dihydrogen phosphate in 500 mL of water, add 300 mL of acetonitrile, and add water to make 1 L. Put ammonia water(28) to adjust the pH to 7.0.

Flow rate: Adjust the flow rate so that the retention time of pyridine is about 4 minutes.

System suitability

Test for required detectability: Confirm that the peak height of pyridine obtained from 10 μL of the standard solution reaches about 50% of the full scale of the data collection device.

System performance: Dissolve 5 mg of Ceftazidime Hydrate in 100 mL of the mobile phase solution of pyridine (1 in 20000). Proceed with 10 μL of this solution under the above operating conditions; ceftazidime and pyridine are eluted in this order with the resolution being NLT 9.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above operating conditions; the relative standard deviation (RSD) of the peak height for pyridine is NMT 5.0%.

(3) ***Heavy metals***—Proceed with 1.0 g of Ceftazidime Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic***—Prepare the test solution with 1.0 g of Ceftazidime Hydrate according to Method 3 and perform the test (NMT 2 ppm).

(5) ***Related substances (Trityl-t-butyl and t-butyl)***—Dissolve 0.1 g of Ceftazidime Hydrate in 2 mL of diluted dibasic sodium phosphate TS (1 in 3), and use this solution as the test solution. Pipet 1 mL of this solution, add diluted dibasic sodium phosphate TS (1 in 3) to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the test solution and the standard solution onto a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of n-butyl acetate, acetic acid(100), acetic acid buffer solution (pH 4.5) and 1-butanol (16 : 16 : 13 : 3) to a distance of about 12cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots above the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

(6) ***Other related substances***—Dissolve 20 mg of Ceftazidime Hydrate in 10 mL of the mobile phase, and use this solution as the test solution. Pipet 1 mL of this solution, dissolve in the mobile phase to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by automatic integration method; each peak area other than the peak of ceftazidime is not greater than the peak area of ceftazidime from the standard solution. In addition, the sum of peak areas other than ceftazidime in the test solution is not greater than 5 times the peak area of ceftazidime in the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 20 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 5.0 g of ammonium dihydrogen phosphate in 750 mL of water, adjust the pH to 3.5 with phosphoric acid, and add water to make 870 mL. To this solution, add 130 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of ceftazidime is about 4 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution and add the mobile phase to make exactly 5 mL. Confirm that the peak area of ceftazidime obtained from 5 μL of this solution is 15% to 25% of the peak area of ceftazidime obtained from 5 μL of the standard solution.

System performance: Dissolve 10 mg each of Ceftazidime Hydrate and acetanilide in 20 mL of the mobile phase. Proceed with 5 μL of this solution under the above operating conditions; ceftazidime and acetanilide are eluted in this order with the resolution being NLT 10.

System repeatability: Repeat the test 6 times with 5 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area for ceftazidime is NMT 2.0%.

Time span of measurement: About 3 times the retention time of ceftazidime after the solvent peak.

Loss on drying Between 13.0 and 15.0% (0.1 g, NMT 0.67 kPa, 60 °C, 3 hours).

Sterility It meets the requirements when used in a sterile preparation. However, it is excluded in cases where there is a final sterilization process in the manufacturing of a sterile preparation.

Bacterial endotoxins It is less than 0.10 EU per mg of ceftazidime (potency) when used in the manufacturing of sterile preparations.

Assay Weigh accurately about 0.1 g (potency) each of Ceftazidime Hydrate and ceftazidime RS and dissolve in a 0.05 mol/L phosphate buffer solution (pH 7.0) to make exactly 100 mL. Pipet 10 mL each of this solution, put exactly 5 mL of the internal standard solution, add 0.05 mol/L phosphate buffer solution (pH 7.0) to make 50 mL, and use this solution as the test solution and the standard solution, respectively. Perform the test with 5 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions and calculate the peak area ratios, Q_T and Q_S, of ceftazidime to that of the internal standard.

$$\text{Potency (μg) of ceftazidime } (C_{22}H_{22}N_6O_7S_2) = \text{Potency (μg) of minocycline hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard—0.05 mol/L phosphate buffer solution (pH 7.0) of dimedon (11 in 10000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 10 cm in length, packed with hexyl silyl silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 4.26 g of anhydrous sodium dihydrogen phosphate and 2.72 g of potassium dihydrogen phosphate in 980 mL of water and add 20 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of ceftazidime is about 4 minutes.

System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; the internal standard and ceftazidime are eluted in this order with the resolution being NLT 3.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution as directed under the above conditions, the relative standard deviation of peak area ratios of ceftazidime to the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Ceftazidime for Injection
주사용 세프타지딤

Ceftazidime for Injection contains NLT 93.0% and NMT 107.0% of the labeled amount of ceftazidime ($C_{22}H_{22}N_6O_7S_2$: 546.58), calculated as dissolve injections.

Method of preparation Prepare as directed under Injections, with Ceftazidime Hydrate.

Description Ceftazidime for Injection occurs as a white to pale yellowish white powder.

Identification Determine the absorption spectrum of a solution of Ceftazidime for Injection in phosphate buffer solution (pH 6.0) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at 255 nm to 259 nm.

pH Dissolve an amount of Ceftazidime for Injection, equivalent to 1.0 g (potency) of ceftazidime, in 10 mL of water; the pH of this solution is 5.8 to 7.8.

Purity ***Clarity and color of solution***—Weigh an amount of Ceftazidime for Injection, equivalent to 1.0 g (potency) of ceftazidime hydrate, according to the labeled amount, dissolve in 10 mL of a solution prepared by dissolving 5 g of anhydrous sodium dihydrogen phosphate and 1 g of potassium dihydrogen phosphate in water to make 100 mL; the resulting solution is clear. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance of the solution at 420 nm is NMT 0.3.

Loss on drying NMT 14.0% (0.1 g, in vacuum at a pressure NMT 0.67 kPa, 60 °C, 3 hours).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.067 EU per mg (potency) of ceftazidime.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

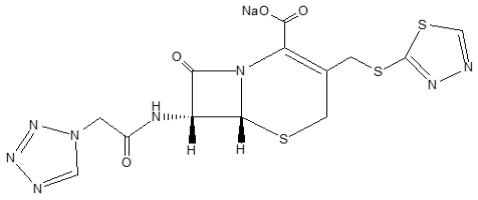
Assay Weigh accurately the mass of NLT 10 samples of Ceftazidime for Injection. Weigh accurately an amount equivalent to about 0.25 g (potency) of ceftazidime hydrate, and dissolve in 0.05 mol/L phosphate buffer solution (pH 7.0) to make exactly 250 mL. Pipet 10 mL of this solution, add exactly 5 mL of the internal standard solution, add again 0.05 mol/L phosphate buffer solution (pH 7.0) to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg (potency) of ceftazidime RS, and dissolve in 0.05 mol/L phosphate buffer solution (pH 7.0) to make exactly 25 mL. Pipet 10 mL of this solution, add exactly 5 mL of the internal standard solution, add 0.05 mol/L phosphate buffer solution (pH 7.0) to make 50 mL and use this solution as the standard solution. Perform the test as directed under the Assay of Ceftazidime Hydrate.

Potency (Mg) of ceftazidime ($C_{22}H_{22}N_6O_7S_2$)
= Potency (μg) of ceftazidime RS× $\frac{Q_T}{Q_S}$ ×10

Internal standard solution—A solution of dimedon in 0.05 mol/L phosphate buffer solution (pH 7.0) (11 in 10000)

Packaging and storage Preserve in light-resistant, hermetic containers.

Ceftezole Sodium
세프테졸나트륨



$C_{13}H_{11}N_8NaO_4S_3$: 462.47
(6*R*,7*R*)-8-Oxo-7-[[2-(1*H*-tetrazol-1-yl)acetyl]amino]-3-[(1,3,4-thiadiazol-2-ylthio)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt (1:1), [*41136-22-5*]

Ceftezole Sodium contains NLT 860 μg (potency) of ceftezole ($C_{13}H_{12}N_8O_4S_3$: 440.48) per mg, calculated on the anhydrous basis.

Description Ceftezole Sodium occurs as white to pale yellowish white crystals or a crystalline powder.
It is freely soluble in water, sparingly soluble in methanol, and practically insoluble in ethanol, acetone, chloroform or ether.

Identification (1) Dissolve about 10 mg (potency) of Ceftezole Sodium in 2 mL of water, add 3 mL of hydroxylamine hydrochloride TS, allow it to stand for 5 minutes, and add 1 mL of acidic ammonium iron(III) sulfate TS and shake to mix; the resulting solution exhibits a reddish brown color.

(2) Dissolve about 50 mg (potency) of Ceftezole Sodium in 50 mL of 0.1 mol/L hydrochloric acid TS, heat on a steam bath for 10 minutes, cool it down, and transfer 20 mL of this solution to a separatory funnel. Add 20 mL of chloroform, shake well to mix, take the chloroform layer, and filter through cotton wool in a funnel where a small amount of anhydrous sodium sulfate is placed on. To 10 mL of the filtrate, add 1 mL of cobalt acetate tetrahydrate TS; the solution exhibits an orange color.

(3) Dissolve 10 mg (potency) of Ceftezole Sodium in water to make 500 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 270 nm and 274 nm.

(4) With deuterium oxide solution for nuclear magnetic resonance spectroscopy (1 in 10) of Ceftezole Sodium, determine 1H as directed under the Nuclear Magnetic Resonance Spectroscopy using sodium 3-trimethylsilylpropanesulfonate for nuclear magnetic resonance spectroscopy as the internal reference compound; the resulting spectrum exhibits singlet signals near 9.3 ppm and 9.4 ppm, respectively, and the area ratio of each signal is 1 : 1.

(5) Ceftezole Sodium responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between -5° and -9° (2.5 g, water, 25 mL, 100 mm).

pH Dissolve Ceftezole Sodium in water to make 0.1 g/mL; the pH of the solution is between 4.5 and 6.5.

Absorbance $E_{1cm}^{1\%}$ (272 nm): Between 270 and 300 (1.6 mg, water, 100 mL).

Water NMT 5.0% (0.2 g, volumetric titration, direct titration).

Sterility It meets the requirements when Ceftezole Sodium is used in sterile preparations. But it is exempt from the requirements when there is a final sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins Less than 0.062 EU per mg of Ceftezole Sodium.

Assay Weigh accurately about 0.1 g (potency) each of Ceftezole Sodium and ceftezole sodium RS, add 10 mL of the internal standard solution, dissolve in 0.1 mol/L of phosphate buffer solution, pH 7.0, to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of ceftezole to that of internal standard, respectively.

Potency (μg) of ceftezole ($C_{13}H_{12}N_8O_4S_3$)
= Potency (μg) of ceftezole RS× $\frac{Q_T}{Q_S}$

Internal standard solution—Weigh 0.5 g of anhydrous caffeine and dissolve in 0.1 mol/L of phosphate buffer solution, pH 7.0, to make exactly 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column, about 4 mm in internal diameter and about 15 cm - 20 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: Dissolve 3 g of citric acid in 930 mL of water and add 70 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of ceftezole is about 9 minutes.

Selection of column: Proceed with 5 μL of the standard solution under the above operating conditions; use a column giving elution of anhydrous caffeine and ceftezole in this order with the resolution between these peaks being NLT 2.5.

Packaging and storage Preserve in tight containers.

Ceftezole Sodium for Injection
주사용 세프테졸나트륨

Ceftezole Sodium for Injection is a preparation for injection, which is dissolved before use, and contains NLT 90.0% and NMT 120.0% of the labeled amount of ceftezole ($C_{13}H_{12}N_8O_4S_3$: 440.48).

Method of preparation Prepare as directed under Injections, with Ceftezole Sodium.

Description Ceftezole Sodium for Injection occurs as a white to pale yellowish white crystalline powder or a powder.

Identification Perform the test as directed under the Identification (1), (2) and (3) of Ceftezole Sodium.

pH Dissolve 0.1 g of Ceftezole Sodium for Injection in 10 mL of water; the pH of this solution is 4.5 to 6.5.

Water NMT 5.0% (0.2 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.075 EU per mg of ceftezole sodium.

Particulate contamination: Visible particles Meets the requirements.

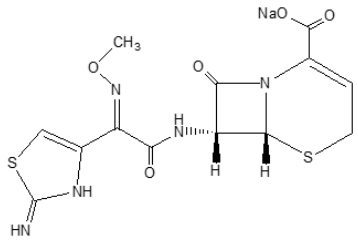
Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay of Ceftezole Sodium. However, weigh accurately about 0.1 g (potency) of Ceftezole Sodium for Injection according to the labeled potency, add 10.0 mL of the internal standard solution, dissolve in 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 100 mL and use this solution as the test solution.

Packaging and storage Preserve in hermetic containers.

Ceftizoxime Sodium
세프티족심나트륨



$C_{13}H_{12}N_5NaO_5S_2$: 405.38

Sodium (6*R*,7*R*)-7-[(2*E*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3,4-didehydrocepham-4-carboxylate [*68401-82-1*]

Ceftizoxime Sodium contains NLT 925 μg (potency) and NMT 965 μg (potency) of ceftizoxime ($C_{13}H_{13}N_5O_5S_2$: 383.40) per mg, calculated on the anhydrous basis.

Description Diclofenac Sodium occurs as white to pale yellow crystals or a crystalline powder.
It is very soluble in water, slightly soluble in methanol, and practically insoluble in ethanol(95).

Identification (1) Determine the absorption spectrum with an aqueous solution of Ceftizoxime Sodium (1 in 63000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 233 nm and 237 nm.

(2) Determine the infrared spectra of Ceftizoxime Sodium and ceftizoxime sodium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) With deuterium oxide for nuclear magnetic resonance spectroscopy (1 in 10) of Ceftriaxone Sodium Hydrate, determine ^1H as directed under the Nuclear Magnetic Resonance Spectroscopy; the resulting spectrum exhibits a singlet signal near δ 4.0 ppm, a multiplet signal near δ 6.3 and a singlet signal near δ 7.0 ppm, and the area intensity ratio of each signal is 3 : 1 : 1.

(4) Ceftizoxime Sodium responds to the Qualitative Analysis (1) for sodium salt.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between +125° and +145° (0.25 g as anhydrous basis, water, 25 mL, 100 mm).

pH Dissolve 1.0 g (potency) of Ceftizoxime Sodium in 10 mL of water; the pH of this solution is between 6.0 and 8.0.

Absorbance $E_{1cm}^{1\%}$ (235 nm): Between 410 and 450 (1.6 mg calculated on the anhydrous basis, water, 100 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Ceftizoxime Sodium in 10 mL of water; the solution is clear and colorless to pale yellow.

(2) ***Heavy metals***—Proceed with 2.0 g of Ceftizoxime Sodium according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Prepare test solution with 2.0 g of Ceftizoxime Sodium according to Method 3 and perform the test (NMT 1 ppm).

(4) ***Related substances***—Dissolve 0.11 g of Ceftizoxime Sodium in 100 mL of 0.1 mol/L phosphate buffer solution, pH 7.0, and use this solution as the test solution. With 5 μL of the test solution, perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the total area of the peaks other than ceftizoxime is NMT 0.5% of the peak area of the ceftizoxime. The total area of the peaks other than ceftizoxime is NMT 1.0% of the peak area of the ceftizoxime.

Operating conditions

For the detector, column and column temperature, comply with the operating conditions under the Assay.

Mobile phase: Dissolve 2.31 g of dibasic sodium phosphate and 1.42 g of citric acid monohydrate in 1000 mL of water and adjust the pH to 3.6 with dilute phosphoric acid (1 in 10) or dilute sodium hydroxide TS. To 200 mL of this solution, add 10 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of ceftizoxime is about 12 minutes.

System suitability

Test for required detectability: Pipet 1mL of the test solution, add 0.1 mol/L phosphate buffer solution, pH 7.0, to make exactly 100 mL, and use this solution as the detection confirmation solution. Pipet 1 mL of the detection confirmation solution, add 0.1 mol/L phosphate buffer solution, pH 7.0, to make exactly 10 mL, and confirm that the peak area of ceftizoxime obtained from a 5 μL of this solution is 7% to 13% of the peak area of ceftriaxone in the detection confirmation solution.

System performance: Dissolve about 10 mg of the ceftizoxime RS in 100mL of 0.1 mol/L phosphate buffer solution, pH 7.0, and use this solution as the detection confirmation solution. Proceed with 5 μL of this solution according to the above conditions; the number of theoretical plates and symmetry factor of the peak of ceftizoxime is NLT 4000 and NMT 2.0, respectively.

System repeatability: Repeat the test 6 times with 5 μL each of the system suitability solutions according to the above conditions; the relative standard deviation of the peak areas for ceftizoxime is NMT 2.0%.

Time span of measurement: A range of about 5 times the retention time of ceftizoxime after the solvent peak.

Water NMT 8.5% (0.4 g, volumetric titration, direct titration).

Sterility It meets the requirements when Ceftizoxime Sodium is used in sterile preparations. But it is exempt from the requirements when there is a final sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins Less than 0.10 EU per mg (potency) of ceftizoxime when used for the manufacturing of sterile preparations.

Assay Weigh accurately about 0.1 g (potency) each of Ceftizoxime Sodium and ceftizoxime RS, dissolve in the phosphate buffer solution, pH 7.0, to make exactly 20 mL, and use these solutions as the test stock solution and the standard stock solution, respectively. Pipet 2 mL each of the test stock solution and the standard stock solution, add 10.0 mL of the internal standard solution to each solution, add 0.1 mol/L phosphate buffer solution, pH 7.0, to make exactly 20 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 5 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of ceftizoxime to that of the internal standard in the test solution and the standard solution, respectively.

$$\text{Potency (μg) of ceftizoxime } (C_{13}H_{13}N_5O_5S_2) = \text{Potency (μg) of ceftizoxime RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of 0.1 mol/L phosphate buffer solution, pH 7.0, in m-hydroxybenzoic acid (3 in 500).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: Dissolve 2.31 g of dibasic sodium phosphate and 1.42 g of citric acid monohydrate in 1000 mL of water and adjust the pH to 3.6 with dilute phosphoric acid (1 in 10) or dilute sodium hydroxide TS. To 450 mL of this solution, add 50 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of ceftizoxime is about 4 minutes.

System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; ceftizoxime and the internal standard are eluted in this order with the resolution being NLT 7.0. The symmetry

factor of each peak is NMT 2.0.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution according to the above conditions; the relative standard deviation of ratios of the peak area of ceftizoxime to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Ceftizoxime Sodium for Injection
주사용 세프티족심나트륨

Ceftizoxime Sodium for Injection contains NLT 90.0% and NMT 120.0% of the labeled amount of ceftizoxime ($C_{13}H_{13}N_5O_5S_2$: 383.41), calculated as dissolve injections.

Method of preparation Prepare as directed under Injections, with Ceftizoxime Sodium.

Description Ceftizoxime Sodium for Injection occurs as a white to pale yellow powder.

Identification (1) Weigh an amount of Ceftizoxime Sodium for Injection, equivalent to 10 mg (potency) of ceftizoxime, dissolve in 2 mL of water, add 3 mL of hydroxylamine hydrochloride TS, and allow to stand for 5 minutes. Then add 1 mL of acidic ammonium iron(III) sulfate TS; the resulting solution exhibits a reddish brown color.

(2) Weigh an amount of Ceftizoxime Sodium for Injection, equivalent to 1 mg (potency) of ceftizoxime, dissolve in 4 mL of water, and cool on an ice bath while adding 1 mL of dilute hydrochloric acid. Add 1 mL of freshly prepared sodium nitrite solution (1 in 100), and allow to stand for 2 minutes. While cooling again on an ice bath, add 1 mL of ammonium sulfate TS, allow to stand for 1 minute, and add 1 mL of N-(1-Naphthyl)ethylenediamine hydrochloride solution (1 in 1000); the resulting solution exhibits a violet color.

(3) Perform the test as directed under the Identification (1) of Ceftizoxime Sodium.

pH Dissolve 1.0 g (potency) of ceftizoxime in Ceftizoxime Sodium for Injection in 10 mL of water; the pH of this solution is 6.0 to 8.0.

Water NMT 8.5% (0.1 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.10 EU per mg (potency) of ceftizoxime.

Particulate contamination: Visible particles Meets the requirements.

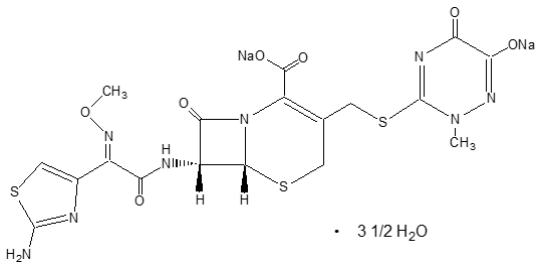
Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay of Ceftizoxime Sodium. However, weigh accurately an amount of Ceftizoxime Sodium for Injection, equivalent to about 0.5 g (potency), according to the labeled potency, and dissolve in 0.1 mol/L phosphate buffer solution (pH 7.0) to prepare a solution containing about 5 mg (potency) per mg. Pipet 2 mL of this solution, add exactly 10 mL of the internal standard solution, add 0.1 mol/L phosphate buffer solution (pH 7.0) to make exactly 20 mL, and use this solution as the test solution.

Packaging and storage Preserve in hermetic containers.

Ceftriaxone Sodium Hydrate
세프트리악손나트륨수화물



Ceftriaxone Sodium

$C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3½H_2O$: 661.60

Disodium (6*R*,7*R*)-7-[(2*E*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-(2,5-dihydro-2-methyl-6-oxido-5-oxo-1,2,4-triazin-3-ylsulfanylmethyl)-3,4-didehydrocepham-4-carboxylate hemi-heptahydrate [*104376-79-6*]

Ceftriaxone Sodium Hydrate contains NLT 905 μg (potency) and NMT 935 μg (potency) of ceftriaxone ($C_{18}H_{18}N_8O_7S_3$: 554.58) per mg, calculated on the anhydrous basis.

Description Ceftriaxone Sodium Hydrate occurs as a white to yellowish white crystalline powder.
It is freely soluble in water, slightly soluble in methanol, very slightly soluble in ethanol(99.5), and practically insoluble in acetonitrile.

Identification (1) Determine the absorption spectra of solutions of Ceftriaxone Sodium Hydrate and ceftriaxone sodium RS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) With deuterated dimethylsulfoxide for nucle-

ar magnetic resonance spectroscopy (1 in 10) of Ceftriaxone Sodium Hydrate, determine ^1H as directed under the Nuclear Magnetic Resonance Spectroscopy, using tetramethylsilane for nuclear magnetic resonance spectroscopy as the internal standard; the resulting spectrum exhibits singlet signals A, B, C and D near δ 3.5 ppm, δ 3.8 ppm, δ 6.7 ppm and δ 7.2 ppm, respectively, and the area intensity ratio of each signal A : B : C : D is 3 : 3 : 1 : 2. Furthermore, since the signal near δ 3.5 ppm overlaps with the signal of water, the measurement is conducted while maintaining the probe temperature at about 50 ℃.

(3) Ceftriaxone Sodium Hydrate responds to the Qualitative Analysis (1) for sodium salt.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between -153° and -170° (50 mg, calculated on the anhydrous basis, water, 2.5 mL, 20 mm).

pH Dissolve 0.6 g of Ceftriaxone Sodium Hydrate in 5 mL of water; the pH of this solution is between 6.0 and 8.0.

Purity (1) ***Clarity and color of solution***—Dissolve 0.6 g of Ceftriaxone Sodium Hydrate in 5 mL of water; the resulting solution is clear and bright yellow.

(2) ***Heavy metals***—Proceed with 1.0 g of Ceftriaxone Sodium Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Ceftriaxone Sodium Hydrate according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—(i) Dissolve 20 mg of Ceftriaxone Sodium Hydrate in 10 mL of mobile phase and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of water and acetonitrile (11 : 9) to make 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the peak area of related substances I with a relative retention time of about 0.5, and the peak area of related substances II with a relative retention time of about 1.3 from the test solution is NMT the peak area of the ceftriaxone from the standard solution. However, the peak areas of related substances I and related substances II are determined by multiplying the areas measured using the automatic integration method by their respective correction factors of 0.9 and 1.2.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase A: Dissolve 5.796 g of anhydrous sodium dihydrogen phosphate and 3.522 g of potassium dihydrogen phosphate in water to make exactly 1000 mL and use this solution as solution A. Dissolve 20.256 g of citric acid monohydrate and 7.840 g of sodium hydroxide in water to make exactly 1000 mL and use this solution as solution B. Dissolve 4.0 g of tetra n-heptylammonium bromide in 450 mL of acetonitrile. To this solution, add 490 mL of water, 55 mL of the solution A and 5 mL of the solution B.

Flow Rate: Adjust the flow rate so that the retention time of ceftriaxone is about 7 minutes.

System suitability

Test for required detectability: Pipet 5 mL of the test solution, add a mixture of water and acetonitrile (11 : 9) to make exactly 200 mL, and use this solution as the system suitability solution. Pipet 1 mL of this solution and add a mixture of water and acetonitrile (11 : 9) to make exactly 100 mL. Confirm that the peak area of ceftriaxone obtained from 10 μL of this solution is 0.9% - 1.1% of the peak area of ceftriaxone obtained from 10 μL of the system suitability solution.

System performance: Dissolve 10 mg of Ceftriaxone Sodium Hydrate in a mixture of water and acetonitrile (11 : 9) to make 5 mL. To this solution, add 5 mL of a mixture of water and acetonitrile in diethyl terephthalate (11 : 9) (9 in 5000) and add a mixture of water and acetonitrile (11 : 9) to make 200 mL. Proceed with 10 μL of this solution according to the above conditions; ceftriaxone and diethyl terephthalate are eluted in this order with the resolution being NLT 6.

System repeatability: Repeat the test 6 times with 10 μL each of the system suitability solution according to the above conditions; the relative standard deviation of the peak areas of ceftriaxone is NMT 1.0%.

Time span of measurement: About 2 times the retention time of ceftriaxone.

(ii) Dissolve 0.01 g of Ceftriaxone Sodium Hydrate in 10 mL of the mobile phase and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of acetonitrile and water (23 : 11) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the peak areas of each related substance that are eluted after the peak of ceftriaxone from the test solution are not greater than the peak area of ceftriaxone from the standard solution. Also, the total area of peaks of related substances is not greater than 2.5 times the peak area of the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer

(wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase A: Dissolve 5.796 g of anhydrous sodium dihydrogen phosphate and 3.522 g of potassium dihydrogen phosphate in water to make exactly 1000 mL and use this solution as solution A. Dissolve 20.256 g of citric acid monohydrate and 7.840 g of sodium hydroxide in water to make exactly 1000 mL and use this solution as solution B. Dissolve 4.0 g of tetra n-heptylammonium bromide in 450 mL of acetonitrile. To this solution, add 490 mL of water, 55 mL of the solution A and 5 mL of the solution B and add 700 mL of acetonitrile again.

Flow Rate: Adjust the flow rate so that the retention time of ceftriaxone is about 3 minutes.

System suitability

Test for required detectability: Pipet 5 mL of the test solution, add a mixture of acetonitrile and water (23 : 11) to make exactly 100 mL, and use this solution as the system suitability solution. Pipet 1 mL of this solution and add a mixture of acetonitrile and water (23 : 11) to make exactly 100 mL. Confirm that the peak area of ceftriaxone obtained from 10 μL of this solution is 0.9% - 1.1% of the peak area of ceftriaxone obtained from 10 μL of the system suitability solution.

System performance: Dissolve 10 mg of Ceftriaxone Sodium Hydrate in a mixture of acetonitrile and water (23 : 11) to make 5 mL. To this solution, add 5 mL of a mixture of water and acetonitrile in diethyl terephthalate (11 : 9) (9 in 5000) and add a mixture of water and acetonitrile (23 : 11) to make exactly 200 mL. Proceed with 10 μL of this solution according to the above conditions; ceftriaxone and diethyl terephthalate are eluted in this order with the resolution being NLT 3.

System repeatability: Repeat the test 6 times with 10 μL each of the system suitability solutions according to the above conditions; the relative standard deviation of the peak areas of ceftriaxone is NMT 1.0%.

Time span of measurement: About 10 times the retention time of ceftriaxone.

Water Between 8.0% and 11.0% (0.15 g, volumetric titration, direct titration).

Sterility It meets the requirements when Ceftriaxone Sodium Hydrate is used in sterile preparations. But it is exempt from the requirements when there is a final sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins Less than 0.20 EU per mg of ceftriaxone (potency) when used for the manufacturing of sterile preparations.

Assay Weigh accurately about 0.1 g (potency) each of Ceftriaxone Sodium Hydrate and ceftriaxone sodium RS and dissolve in a mixture of water and acetonitrile (11: 9) to make exactly 50 mL, respectively. Pipet 5 mL each of these solutions, add exactly 5 mL of the internal standard solution to each, add a mixture of water and acetonitrile (11 : 9) to make 200 mL, and use these solutions as the test solution and the standard solution. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of peak areas of ceftriaxone to that of the internal standard, respectively.

$$\text{Potency (μg) of ceftriaxone } (C_{18}H_{18}N_8O_7S_3) = \text{Potency (μg) of minocycline ceftriaxone sodium RS} \times \frac{Q_T}{Q_S}$$

Internal standard—A mixture of water and acetonitrile in diethyl terephthalate (11 : 9) (9 in 5000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase A: Dissolve 5.796 g of anhydrous sodium dihydrogen phosphate and 3.522 g of potassium dihydrogen phosphate in water to make exactly 1000 mL and use this solution as solution A. Dissolve 20.256 g of citric acid monohydrate and 7.840 g of sodium hydroxide in water to make exactly 1000 mL and use this solution as solution B. Dissolve 4.0 g of tetra n-heptylammonium bromide in 450 mL of acetonitrile. To this solution, add 490 mL of water, 55 mL of the solution A and 5 mL of the solution B.

Flow rate: Adjust the flow rate so that the retention time of ceftriaxone is about 7 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; ceftriaxone and internal standard are eluted in this order with the resolution being NLT 6.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the ratios of the peak area of ceftriaxone to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Ceftriaxone Sodium for Injection
주사용 세프트리악손나트륨

Ceftriaxone Sodium for Injection contains NLT 90.0% and NMT 120.0% of the labeled amount of ceftriaxone ($C_{18}H_{18}N_8O_7S_3$: 554.58), calculated as dissolve injections.

Method of preparation Prepare as directed under Injections, with Ceftriaxone Sodium Hydrate.

Description Ceftriaxone Sodium for Injection occurs as a white to yellowish white powder.

Identification Determine the infrared spectra of Ceftriaxone Sodium for Injection and ceftriaxone sodium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit the same intensities of absorption at the same wavenumbers.

pH Dissolve an amount of Ceftriaxone Sodium for Injection, equivalent to 1.2 g (potency) of ceftriaxone, in 10 mL of water; the pH of this solution is 6.0 to 8.0.

Water Between 8.0% and 11.0% (0.1 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.20 EU per mg (potency) of ceftriaxone.

Particulate contamination: Visible particles Meets the requirements.

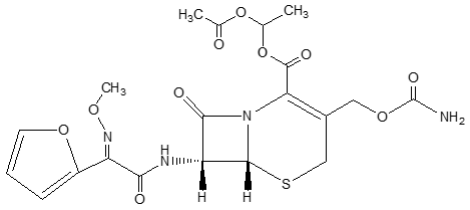
Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Proceed as directed under the Assay under Ceftriaxone Sodium Hydrate. However, weigh accurately an amount of Ceftriaxone Sodium for Injection, equivalent to about 0.1 g (potency), according to the labeled potency, and dissolve in a mixture of water and acetonitrile (11 : 9) to make exactly 50 mL. Pipet 5 mL of this solution, add exactly 5 mL of the internal standard solution, add a mixture of water and acetonitrile (11 : 9) to make exactly 200 mL, and use this solution as the test solution.

Packaging and storage Preserve in hermetic containers.

Cefuroxime Axetil
세푸록심악세틸



$C_{20}H_{22}N_4O_{10}S$: 510.47

(1RS)-1-Acetoxyethyl (6R,7R)-3-carba moyloxymethyl-7-[(Z)-2-furan-2-yl-2-(methoxyimino)acetylamino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate [*64544-07-6*]

Cefuroxime Axetil contains NLT 800 μg (potency) and NMT 850 μg (potency) of cefuroxime ($C_{16}H_{16}N_4O_8S$: 424.39) per mg, calculated on the anhydrous basis.

Description Cefuroxime Axetil occurs as a white to yellowish white, amorphous powder.
It is freely soluble in dimethylsulfoxide, soluble in methanol, sparingly soluble in ethanol(95), and very slightly soluble in water.

Identification (1) Determine the absorption spectra of respective solutions of Cefuroxime Axetil and cefuroxime axetil RS in methanol (3 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cefuroxime Axetil and cefuroxime axetil RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Determine ^1H of a solution of Cefuroxime Axetil in deuterated dimethylsulfoxide for nuclear magnetic resonance spectroscopy (1 in 20) as directed under the Nuclear Magnetic Resonance Spectroscopy, using tetramethylsilane for nuclear magnetic resonance spectroscopy as the internal standard; it exhibits the doublet signal A at about δ 1.5 ppm, singlet signal B at about δ 2.1 ppm, and singlet signal C at about δ 3.9 ppm, with the ratio of area strength of the signals A : B : C being 1 : 1 : 1.

Crystallinity It shows no crystallinity when tested.

Optical rotation $[\alpha]_D^{20}$: Between +41° and +47° (0.5 g, methanol, 50 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Cefuroxime Axetil as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Place 1.0 g of Cefuroxime Axetil in a crucible, add 10 mL of a solution of magnesium nitrate in ethanol(95) (1 in 10), and slowly heat to ash. If there is a residual carbide, wet it with a small amount of nitric acid and ignite to ash. After cooling, to the residuum, add 10

mL of dilute hydrochloric acid, and warm on a steam bath to dissolve. Use this solution as the test solution and perform the test (NMT 2 ppm).

(3) ***Related substances***—Dissolve 25 mg of Cefuroxime Axetil in 4 mL of methanol, add ammonium dihydrogen phosphate solution (23 in 1000) to make 10 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add 40 mL of methanol, add ammonium dihydrogen phosphate solution (23 in 1000) to make exactly 100 mL, and use this solution as the standard solution. Pipet 2 mL each of the test solution and the standard solution, perform the test with these solutions as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas from the respective solutions according to the automatic integration method; the peak areas other than cefuroxime axetil obtained from the test solution are not larger than 1.5 times the sum of the 2 peak areas of cefuroxime axetil from the standard solution, and the sum of peak areas other than cefuroxime axetil obtained from the test solution is not larger than 4 times the sum of the 2 peak areas of cefuroxime axetil from the standard solution.

Internal standard solution—A solution of acetanilide in methanol (27 in 5000).

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

Detection sensitivity: Pipet 1 mL of the standard solution, add 4 mL of methanol, and add ammonium dihydrogen phosphate solution (23 in 1000) to make exactly 10 mL. Proceed with 2 μL of this solution as directed under the Procedure. The obtained peak area of cefuroxime axetil is within the range between 7% and 13% of each peak obtained from 2 μL of the standard solution.

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the internal standard and cefuroxime axetil are eluted in this order with the resolution of the 2 peaks of cefuroxime axetil being NLT 1.5.

System repeatability: Repeat the test 6 times with 2 μL each of the standard solutions according to the above conditions; the relative standard deviation of the sum of the 2 peaks of cefuroxime axetil is NMT 2.0%.

Time span of measurement: About 3 times the retention time of cefuroxime axetil after the solvent peak

(4) ***Acetone***—Weigh accurately about 1 g of Cefuroxime Axetil, add exactly 0.2 mL of the internal standard solution, dissolve in dimethylsulfoxide to make 10 mL, and use this solution as the test solution. Separately, weigh accurately about 0.5 g of acetone, and add dimethylsulfoxide to make exactly 100 mL. Pipet 0.2 mL of this solution, add exactly 0.2 mL of the internal standard solution, add dimethylsulfoxide to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of acetone to the internal standard, respectively; the amount of acetone is NMT 1.3%.

$$\text{Content (\%) of acetone} = \frac{W_T}{W_S} \times \frac{Q_T}{Q_S} \times 0.2$$

W_S: Taken amount (g) of acetone
W_T: Taken amount (g) of Cefuroxime Axetil

Internal standard solution—A solution of 1-propanol in dimethylsulfoxide (1 in 200).

Operating conditions

Detector: A flame ionization detector

Column: A glass column, about 3 mm in inside diameter and about 2 m in length, packed with diatomaceous earth for gas chromatography (between 125 μm and 150 μm in particle diameter) that is coated at 20% with a mixture of polyethylene glycol 600 for gas chromatography and polyethylene glycol 1500 for gas chromatography in the ratio of 1 : 1.

Column temperature: A constant temperature of about 90 °C.

Sample injection port temperature: A constant temperature of about 115 °C.

Carrier gas: Nitrogen

Flow rate: Adjust the flow rate so that the retention time of the internal standard is about 4 minutes.

System suitability

System performance: Proceed with 1 μL of the standard solution according to the above conditions; acetone and the internal standard are eluted in this order with the resolution being NLT 5.

System repeatability: Repeat the test 6 times with 1 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of acetone with respect to the peak area of the internal standard is NMT 5.0%.

Water NMT 2.0% (0.4 g, volumetric titration, direct titration).

Residue on ignition NMT 0.2% (0.5 g).

Isomer ratio Perform the test as directed under the Assay and determine the content ratio of isomer A according to the following equation (between 0.48 and 0.55).

$$\text{Content ratio of isomer A in Cefuroxime Axetil} = \frac{Peak\ area\ of\ isomer\ A}{Peak\ area\ of\ isomer\ A + peak\ area\ of\ isomer\ B}$$

Assay Weigh accurately about 50 mg (potency) each of

Cefuroxime Axetil and cefuroxime axetil RS, and add methanol to each to make exactly 50 mL. Pipet 10 mL each of these solutions, add exactly 5 mL of the internal standard solution and 5 mL of methanol to ac, add ammonium dihydrogen phosphate solution (23 in 1000) to each to make exactly 50 mL, and use the resulting solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the sum of the 2 peak areas of cefuroxime axetil to the peak area of the internal standard, respectively.

$$\text{Potency (μg) of cefuroxime } (C_{16}H_{16}N_4O_8S) = \text{Potency (μg) of cefuroxime axetil RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of acetanilide in methanol (27 in 5000).

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 278 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and about 20 cm in length, packed with trimethylsilyl silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of ammonium dihydrogen phosphate solution (23 in 1000) and methanol (5 : 3).

Flow rate: Adjust the flow rate so that the retention time of the first eluted one of the 2 peaks of cefuroxime axetil is about 8 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the internal standard and cefuroxime axetil are eluted in this order with the resolution of the two peaks of cefuroxime axetil being NLT 1.5.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the ratio of the sum of the 2 peak areas of cefuroxime axetil to the peak area of the internal standard is NMT 1.0%.

Relative retention time: The relative retention time of isomer B and the relative retention time of isomer A with respect to the internal standard are about 2 and about 2.25, respectively.

Packaging and storage Preserve in light-resistant, tight containers.

Cefuroxime Axetil for Syrup
시럽용 세푸록심악세틸

Cefuroxime Axetil for Syrup is a preparation for syrup, which is suspended before use, and contains NLT 90.0% and NMT 120.0% of the labeled amount of cefuroxime ($C_{16}H_{16}N_4O_8S$: 424.39).

Method of preparation Prepare as directed under Syrups, with Cefuroxime Axetil.

Identification (1) Dissolve an amount of each Cefuroxime Axetil for Syrup and cefuroxime axetil RS in methanol so that each solution contains 15.8 μg (potency) per mL and measure the absorption spectra of the solutions in the range from 230 nm to 320 nm as directed under the Ultraviolet-visible Spectroscopy; both solutions exhibit a maximum at around 276 nm.

(2) The retention times of the major peaks obtained from the test solution and the standard solution prepared as directed under the Assay are the same.

pH Dissolve Cefuroxime Axetil for Syrup according to the label; the pH of the resulting solution is between 3.5 and 7.0.

Water NMT 6.0% (0.2 g, volumetric titration, direct titration).

Dissolution Weigh accurately an amount of Cefuroxime Axetil for Syrup, equivalent to about 0.15 g (potency) according to the labeled amount, suspend according to the label, and perform the test with the suspension at 100 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of phosphate buffer solution (pH 7.0) as the dissolution medium. Take NLT 20 mL of the dissolved solution 30 minutes after starting the test and filter through a membrane filter with a pore size not exceeding 0.5 μm. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add phosphate buffer solution (pH 7.0) to make exactly *V'* mL so that Each mL of the solution contains about 20 μg (potency) of cefuroxime ($C_{16}H_{16}N_4O_8S$) according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 0.15 g (potency) of cefuroxime axetil RS, add 25 mL of methanol, add phosphate buffer solution (pH 7.0) so that each mL contains 20 μg (potency), and use the solution as the standard solution. Determine the absorbances of the test solution and the standard solution at the absorbance maximum wavelength, around 278 nm, as directed under the Ultraviolet-visible Spectroscopy. Meets the requirements if the dissolution rate of Cefuroxime Axetil for Syrup in 30 minutes is NLT 65%.

$$\text{Dissolution rate (\%) with respect to the labeled amount of cefuroxime } (C_{16}H_{16}N_4O_8S) = \frac{C_S}{Amount\ (g)\ of\ \text{Cefuroxime Axetil for Syrup taken}} \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 90000$$

C_S: Concentration [mg (potency)/mL] of the standard solution

C: Labeled amount [mg (potency)] of cefuroxime ($C_{16}H_{16}N_4O_8S$) per g

Uniformity of dosage units (distribution) Meets the requirements.

Assay Proceed as directed under the Assay under Cefuroxime Axetil. Weigh accurately an amount of Cefuroxime Axetil for Syrup, equivalent to about 0.15 g (potency) according to the labeled potency, add 2 mL of water, shake the flask vigorously until dispersed, add 10.0 mL of the internal standard solution and methanol to make exactly 200 mL, and filter. Take exactly 20 mL of the filtrate, add water to make exactly 50 mL, and use the solution as the test solution. Separately, weigh accurately about 15 mg (potency) of cefuroxime axetil RS, dissolve in 1.0 mL of the internal standard solution, add water to make exactly 50 mL, and use the solution as the standard solution. Perform the test with each 20 μL of the test solution and the standard solution.

Packaging and storage Preserve in tight containers.

Cefuroxime Axetil Tablets
세푸록심악세틸 정

Cefuroxime Axetil Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of cefuroxime ($C_{16}H_{16}N_4O_8$ S: 424.39).

Method of preparation Prepare as directed under Tablets, with Cefuroxime Axetil.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Water NMT 6.0% (0.2 g, volumetric titration, direct titration).

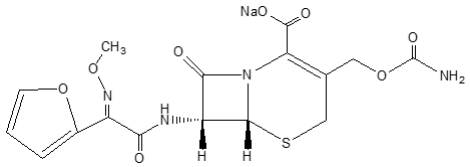
Dissolution Perform the test with 1 tablet of Cefuroxime Axetil Tablets at 55 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of 0.07 mol/L hydrochloric acid solution, appropriately deaerated, as the dissolution medium. Take a certain volume of the dissolved solution after 15 minutes from the start of the dissolution test, and carefully add the same volume of the dissolution medium, previously warmed to 37±0.5 °C. Filter the dissolved solution taken through a membrane filter with a pore size NMT 0.5 μm, pipet a certain amount of the filtrate, dilute it with 0.07 mol/L hydrochloric acid solution so that it contains about 20 μg (potency) of cefuroxime ($C_{16}H_{16}N_4O_8S$) per mL, and use this solution as the test solution for dissolution test (15 minutes). Repeat this procedure after 45 minutes from the start of the dissolution test, and use the resulting solution as the test solution for the dissolution test (45 minutes). Separately, weigh accurately about 60 mg (potency) of cefuroxime axetil RS, dissolve with 5 mL of methanol, add 0.07 mol/L hydrochloric acid solution so that it contains 20 μg (potency) per mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength of around 278 nm as directed under the Ultraviolet-visible Spectroscopy, and calculate the dissolution rate; it meets requirements if the dissolution rate of Cefpodoxime Axetil Tablets in 15 minutes is NLT 65%, and the dissolution rate of Cefpodoxime Axetil Tablets in 45 minutes is NLT 80%.

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay of Cefuroxime Axetil. However, weigh accurately the mass of NLT 20 tablets of Cefpodoxime Axetil Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 50 mg (potency) according to the labeled potency, and dissolve in methanol to make exactly 50 mL. Pipet 10 mL of the resulting solution, add 5 mL of the internal standard solution and 5 mL of methanol, add ammonium dihydrogen phosphate solution (23 in 1000) to make exactly 50 mL, and use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Cefuroxime Sodium
세푸록심나트륨



$C_{16}H_{15}N_4NaO_8S$: 446.37

Sodium (6*R*,7*R*)-7-[(2*E*)-2-(furan-2-yl)-2-methoxyiminoacetamido]-3-carbamoyloxymethyl-3,4-didehydrocepham-4-carboxylate [*56238-63-2*]

Cefuroxime Sodium contains NLT 875 μg (potency) of cefuroxime ($C_{16}H_{16}N_4O_8S$: 424.39) per mg, calculated on the anhydrous basis.

Description Cefuroxime Sodium occurs as white to pale yellowish white crystals or a crystalline powder.
It is freely soluble in water, sparingly soluble in methanol, and very slightly soluble in ethanol(95).

Identification (1) Determine the absorption spectra of

respective aqueous solutions of Cefuroxime Sodium and cefuroxime sodium RS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cefuroxime Sodium and cefuroxime sodium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Determine ^1H of a solution of Cefuroxime Sodium in deuterium oxide for nuclear magnetic resonance spectroscopy (1 in 10) as directed under the Nuclear Magnetic Resonance Spectroscopy, using sodium 3-trimethylsilylpropanesulfonate for nuclear magnetic resonance spectroscopy as the internal standard; it exhibits the singlet signal A at about δ 4.0 ppm, quartet signal B at about δ 6.6 ppm, and doublet signals C and D at about δ 6.9 ppm and δ 7.7 ppm, respectively, with the ratio of area of the signals A : B : C : D being 3 : 1 : 1 : 1.

(4) Cefuroxime Sodium responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between +59° and +66° (0.5 g, calculated on the anhydrous basis, water, 100 mL, 100 mm).

pH Dissolve 1 g of Cefuroxime Sodium in 10 mL of water; the pH of this solution is between 6.0 and 8.5.

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Cefuroxime Sodium in 10 mL of water; the solution is clear. Determine the absorbance of this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at a wavelength of 450 nm is NMT 0.25.

(2) ***Heavy metals*—**Proceed with 1.0 g of Cefuroxime Sodium as directed under Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(3) ***Arsenic*—**Proceed with 1.0 g of Ceftriaxone Sodium according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances*—**Dissolve 25 mg of Cefuroxime Sodium in 25 mL of water, and use this solution as the test solution. Pipet 1 mL of the test solution, add water to make exactly 100 mL, and use this solution as the standard solution. Pipet 20 μL each of the test solution and the standard solution, perform the test with these solutions as directed under the Liquid Chromatography according to the following operating conditions, and determine individual peak areas in each solution according to the automatic integration method; each peak area other than cefuroxime obtained from the test solution is not larger than the peak area of cefuroxime from the standard solution. Also, the sum of peak areas other than cefuroxime in the test solution is not larger than 3 times the peak area of cefuroxime in the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

System performance: Proceed as directed under the system suitability under the Assay.

Test for required detectability: Pipet 1 mL of the standard solution and add water to make exactly 10 mL. Confirm that the peak area of cefuroxime obtained from 20 μL of this solution is within the range between 7% and 13% of the peak area of cefuroxime obtained from the standard solution.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of cefuroxime is NMT 2.0%.

Time span of measurement: About 4 times the retention time of cefuroxime after the solvent peak.

(5) ***Dimethylaniline*—**Weigh accurately about 1.0 g of Cefuroxime Sodium, add 5 mL of 1 mol/L sodium hydroxide TS and 1 mL of the internal standard solution, and if necessary, centrifuge. Use the clear supernatant as the test solution. Separately, weigh accurately about 50 mg of dimethylaniline, add 2.0 mL of hydrochloric acid, and add water to make 50 mL. Pipet 5.0 mL of this solution and add water to make exactly 250 mL. Pipet 1.0 mL of this solution, add 5.0 mL of 1 mol/L sodium hydroxide TS and 1.0 mL of the internal standard solution, and if necessary, centrifuge. Use the supernatant as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of dimethylaniline to that of the internal standard, respectively (NMT 20 ppm).

$$\text{Content (ppm) of dimethylaniline} = \text{Amount (mg) of dimethylaniline taken} \times \frac{Q_T}{Q_S} \times \frac{Purity\ (\%)\ of\ dimethylaniline}{Taken\ amount\ (mg)\ of\ Cefuroxime\ Sodium} \times 4$$

Internal standard solution—Dissolve 50.0 mg of naphthalene in cyclohexane to make 50 mL. To 5.0 mL of this solution, add cyclohexane to make 100 mL, and use this solution as the internal standard solution.

Operating conditions

Detector: A flame ionization detector

Column: A column about 2 mm in internal diameter and about 2 m in length, packed with diatomaceous earth for gas chromatography coated with 50% phenyl-50% methylpolysiloxane for gas chromatography in 3% of its mass.

Column temperature: 120 °C

Temperatures of the sample injection port and the detector: 150 °C

Carrier gas: Nitrogen

Flow rate: 30 mL/min

Water NMT 4.0% (0.4 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in a sterile preparation. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of a sterile preparation.

Bacterial endotoxins It is less than 0.10 EU per mg (potency) of cefuroxime when used in a sterile preparation.

Assay Weigh accurately about 25 mg (potency) each of Cefuroxime Sodium and cefuroxime sodium RS, add water to each to make exactly 25 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of cefuroxime, respectively.

$$\text{Potency (μg) of cefuroxime } (C_{16}H_{16}N_4O_8S) = \text{Potency (μg) of cefuroxime sodium RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 273 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and about 125 mm in length, packed with hexasilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 0.68 g of sodium acetate trihydrate in 900 mL of water, add acetic acid(100) to adjust the pH to 3.4, and add water to make 1000 mL. To 990 mL of this solution, add 10 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of cefuroxime is about 8 minutes.

System suitability

System performance: Allow the test solution to stand at 60 ℃ for 10 minutes and cool. Quickly proceed with 20 μL of this solution according to the above conditions; the resolution between the peak of cefuroxime and the peak with the relative retention time with respect to cefuroxime of about 0.7 is NLT 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of cefuroxime is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Cefuroxime Sodium for Injection
주사용 세푸록심나트륨

Cefuroxime Sodium for Injection, as an injection that is dissolved upon use, contains NLT 90.0% and NMT 120.0% of the labeled amount of cefuroxime ($C_{16}H_{16}N_4O_8S$: 424.39).

Method of preparation Prepare as directed under Injections, with Cefuroxime Sodium.

Description Cefuroxime Sodium for Injection occurs as a white to pale yellowish white powder.

Identification Perform the test as directed under the Identification (1) and (2) under Cefuroxime Sodium.

pH Dissolve an amount of Cefuroxime Sodium for Injection equivalent to 1.0 g (potency) of cefuroxime in 10 mL of water; the pH of this solution is between 6.0 and 8.5.

Water NMT 3.5% (0.2 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.10 EU per mg (potency) of cefuroxime.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately about 50 mg (potency) according to the labeled potency of Cefuroxime Sodium for Injection, and dissolve in water to make exactly 250 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg (potency) of cefuroxime sodium RS, and dissolve in water to make 50 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak areas of cefuroxime sodium, A_T and A_S, in the test solution and the standard solution, respectively.

$$\text{Potency (μg) of cefuroxime } (C_{16}H_{16}N_4O_8S) = \text{Potency (μg) of cefuroxime sodium RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with hexyl silyl silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of a solution obtained by adding 0.1 mol/L acetic acid to 50 mL of 0.1 mol/L sodium acetate solution (acetate buffer solution, pH 3.4) and acetonitrile (10 : 1).

Flow rate: 2.0 mL/min

Packaging and storage Preserve in hermetic containers.

Cellulase
셀룰라제

Cellulase is an enzyme with cellulose digestive activity, from a useful strain of the genus *Aspergillus*, and contains NLT 90.0% of the cellulose digestive unit of the labeled amount.

Description Cellulase occurs as a pale yellow to pale yellowish brown power and has a characteristic odor.

Identification Perform the test as directed under the Assay; it exhibits positive response.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Cellulase according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic*—**Proceed with 1.0 g of Cellulase according to Method 3 and perform the test (NMT 2 ppm).

Loss on drying NMT 5.0% (1 g, 105℃, 4 hours).

Residue on ignition NMT 8. 0% (1 g).

Assay Weigh accurately about 0.5 g of Cellulase and dissolve in water to make exactly 200 mL. Take 1 mL of Cellulase, add water to make 100 mL, and use this solution as the test solution. Take 4 mL of sodium carboxymethyl cellulose solution, allow to stand at 37 ± 0.5 ℃ for 10 minutes, add 1 mL of the test solution, shake to mix, and allow to react at 37 ± 0.5 ℃ for 30 minutes. Add 2 mL of Fehling's alkaline copper TS, shake to mix, heat on a steam bath for 30 minutes, and cool with running water. Add 2 mL of arsenic molybdate TS, shake well to mix, add 3 mL of 0.5 mol/L sodium hydroxide. Shake again to mix, dissolve the precipitate, allow to stand for 20 minutes, and add acetic acid-sodium acetate buffer solution, pH 4.5, to make 25 mL. Take 1.0 mL of this solution, add 9 mL of acetic acid-sodium acetate buffer solution, pH 4.5, shake well to mix, perform the test as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance A_T at the wavelength of 750 nm. Take 1 mL of the test solution, add 2 mL of Fehling's alkaline copper TS and then 4 mL of sodium carboxymethyl cellulose solution, and shake to mix. Proceed according to the above conditions to determine absorbance A_B. Calculate the amount (mg) of glucose, G_T and G_B, corresponding to A_T and A_B, respectively, from the calibration curve of the standard glucose solution.

$$\text{Cellulose digestive activity (unit/g)} = (G_T - G_B) / 30 \times 1 / 0.18 \times 1 / W$$

W: Amount (g) of the sample per mL of the test solution.

Definition of potency: Under the conditions specified above, one cellulose saccharifying activity unit is the amount of enzyme that catalyzes the increase of reducing activity equivalent to 1 μmole of glucose per minute.

Glucose calibration curve: Weigh accurately about 50 mg of the glucose RS, previously dried at 105 ℃ for 6 hours, and dissolve in water to make exactly 50 mL. Pipet 1, 2, 3, 4, and 5 mL of this solution, add water to make exactly 10 mL, respectively, and use these solutions as the standard solutions for the calibration curve. Pipet 1 mL each of water and the standard solution for the calibration curve, add 4 mL of sodium carboxymethyl cellulose solution and 2 mL of Fehling's alkaline copper TS, shake to mix, and heat on a steam bath for 30 minutes. After cooling with water, add 2 mL of arsenic molybdate TS, and shake to mix. Add 3 mL of 0.5 mol/L sodium hydroxide, dissolve the precipitate, allow to stand for 20 minutes, and add acetic acid-sodium acetate buffer solution, pH 4.5, to make 25 mL. Take 1 mL each of these solutions, add 9 mL of acetic acid-sodium acetate buffer solution, pH 4.5, shake to mix, and perform the test as directed under the Ultraviolet-visible Spectroscopy to determine the absorbances A_0, A_1, A_2, A_3, A_4 and A_5 at the wavelength of 750 nm. Construct a calibration curve by plotting the absorbances, $A_1 - A_0$, $A_2 - A_0$, $A_3 - A_0$, $A_4 - A_0$ and $A_5 - A_0$, versus the amount (mg) of glucose.

Packaging and storage Preserve in tight containers.

Cellulase II
셀룰라제II

Cellulase II is a cellulose digestive enzyme extracted and purified from the enzyme obtained by culturing filamentous fungi of the genus *Aspergillus*. About 1 g of Cellulase II, when dried, contains NLT 2000 units of cellulose digestive activity.

Description Cellulase II occurs as a pale brown fine powder and has a characteristic odor. It is freely soluble in water.

Identification Perform the test with Cellulase II as direct under the Assay; it exhibits a positive response.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Cellulase II in 100 mL of water; the resulting solution is clear.

(2) ***Heavy metals***—Proceed with 0.1 g of Cellulase II according to Method 2, and perform the test. Prepare the control solution with 0.5 mL of lead standard solution (NMT 50 ppm).

(3) ***Arsenic—***Proceed with 0.1 g of Cellulase II according to Method 3, and perform the test (NMT 2 ppm).

Loss on drying NMT 5% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 20% (1 g).

Assay ***Cellulose digestive activity***—Weigh accurately about 20.0 mg of Cellulase II, transfer to a 100-mL volumetric flask, add water to make 1000 mL, filter, and use this solution as the test solution. Add 4.0 mL of sodium carboxymethyl cellulose solution in a 50-mL volumetric flask, heat on a steam bath at 40 ℃ for 5 minutes, add 1 mL of the test solution, and heat on a steam bath at 40 ℃ for 30 minutes. Add 2.0 mL of alkaline copper solution of Fehling's TS, heat in a hot water bath for 20 minutes, and cool with running water. Add 1.0 mL of arsenic molybdate TS, shake to mix, allow to stand at room temperature for 20 minutes, and add water to make exactly 50 mL. Determine absorbance at a wavelength of 500 nm using water as the control solution. With the difference in absorbance between the test solution and blank test solution, determine the amount of glucose using the glucose calibration curve, and calculate the cellulose digestive activity.

$$\text{Cellulose digestive activity (unit/g)} = \frac{\text{Amount (mg) of glucose produced}}{30} \times 100$$

Definition of potency: Under the conditions specified above, 100 cellulose digestive activity unit is the amount that creates reducing sugar equivalent to 1 mg of glucose per minute.

Glucose calibration curve: Weigh accurately about 1.0 g of glucose RS, previously dried at 80 ℃ for 5 hours, dissolve in water to make 100 mL, and use this solution as the standard solution for calibration curve. Pipet accurately 5.0 mL of water with 1 mL, 2 mL, 4 mL, 6 mL, 8 mL and 10 mL each of the standard solution for calibration curve, and add water to make 100 mL. Pipet accurately 5.0 mL each of these solutions to a 50-mL volumetric flask, add 2.0 mL each of alkaline copper solution of Fehling's TS, and heat for 20 minutes in a hot water bath. Cool with running water, add 1.0 mL of arsenic molybdate TS, shake well to mix, allow to stand for 20 minutes at room temperature, and add water to make exactly 50 mL. With these solutions, determine the absorbances A_0, A_1, A_2, A_3, A_4, A_5 and A_6 at the wavelength of 500nm as directed under the Ultraviolet-visible Spectroscopy. Construct a calibration curve by plotting the differences in absorbances $A_1 - A_0$, $A_2 - A_0$, $A_3 - A_0$, $A_4 - A_0$, $A_5 - A_0$ and $A_6 - A_0$ versus the amounts (mg) of glucose.

Packaging and storage Preserve in tight containers.

Cellulase AP_3 I
셀룰라제AP_3I

Cellulase AP_3 I is digestive enzyme extracted and purified from the enzyme obtained by culturing filamentous fungi belonging to the genus *Aspergillus*. Cellulase AP_3 I contains between 1200 and 1800 units of cellulose digestive activities per g when tested as directed under the Digestive Power.

Description Cellulase AP_3 I occurs as a pale yellow to pale yellowish brown powder and has a characteristic odor.
It is soluble in water and practically insoluble in ethanol.

Identification Dissolve about 0.5 g of Cellulase AP_3 I in water to make 50 mL, take 1 mL of this solution, add 10 mL of sodium carboxymethyl cellulose solution heated to 37 ± 0.5 ℃, and shake well to mix. Allow this solution to stand at 37 ± 0.5 ℃ for 10 minutes, add 4 mL of Fehling's TS, and heat; a reddish brown precipitate is formed.

Purity (1) ***Heavy metals—***Proceed with 1.0 g of Cellulase AP_3 I according to Method 2 and perform the test. Prepare the control solution with 5.0 mL of lead standard solution (NMT 50 ppm).

(2) ***Arsenic—***Proceed with 1.0 g of Cellulase AP_3 I according to Method 3 and perform the test (NMT 2 ppm).

Loss on drying NMT 10.0% (1 g, 105 °C, 4 hours).

Residue on ignition NMT 15.0% (1 g).

Assay ***Cellulose saccharifying activity***—Weigh accurately about 0.5 g of Cellulase AP_3 I, and add water to make 200 mL. Pipet 1.0 mL of this solution, add 100 mL of water, and use this solution as the test solution. Pipet accurately 1.0 mL of the test solution and 1.0 mL of water, add 2 mL of alkaline copper solution of Fehling's TS, and shake well to mix. Add 4 mL of sodium carboxymethyl cellulose solution, shake to mix, heat on a steam bath for 30 minutes, and cool immediately with running water. Add 2 mL of arsenic molybdate TS, shake to mix, add 3 mL of 0.5 mol/L sodium hydroxide TS, and shake to mix. Dissolve the precipitate, allow to stand at room temperature for 20 minutes, and add acetic acid-sodium acetate buffer solution, pH 4.5 to make 25 mL. Pipet 1.0 mL of

each of these solutions, add 9 mL of acetic acid-sodium acetate buffer solution, pH 4.5, shake to mix, and determine the absorbance, A_T and A_B at the wavelength of 750 nm as directed under the Ultraviolet-visible Spectroscopy. Separately, determine the amount of glucose, G_T and G, corresponding to A_T and A_B using the glucose calibration curve.

$$\text{Cellulose saccharifying activity (unit/g)} = \frac{(G_T - G_B)}{30} \times \frac{1}{0.18} \times n$$

n: Dilution factor of the test solution

Definition of potency: Under the conditions specified above, one cellulose saccharifying activity unit is the amount of enzyme that catalyzes the increases of reducing activity equivalent to 1 μmole of glucose per minute.

Glucose calibration curve: Weigh accurately about 1 g of glucose RS, previously dried at 105 ℃ for 6 hours, and calculate the loss in weight. Weigh accurately 1.0 g of dried weight equivalent to glucose, and dissolve in water to make 1000 mL. Pipet 1.0, 2.0, 3.0, 4.0 and 5.0 mL of this solution separately, and add water to make 10 mL, respectively (0.1, 0.2, 0.3, 0.4, and 0.5 mL of glucose in each 1 mL of the solution). Pipet 1.0 mL of each of the solutions, add 4.0 mL of sodium carboxymethyl cellulose solution and 2.0 mL of alkaline copper TS to a 50-mL Nessler tube, and shake to mix. Insert stopper to the Nessler tube, heat on a steam bath for 30 minutes, and cool with water. Add 2 mL of arsenic molybdate TS, shake to mix, add 3 mL of 0.5 mol/L sodium hydroxide TS into each tube, and shake to dissolve the precipitate. Allow the mixture to stand for 20 minutes, add acetate-sodium acetate buffer solution, pH 4.5 to make 25 mL. Pipet 1.0 mL of this solution and add 9.0 mL of acetate-sodium acetate buffer solution, pH 4.5, and shake to mix. Determine the absorbances A_1, A_2, A_3, A_4, and A_5 at the wavelength of 750 nm. Separately, pipet 1.0 mL of water instead of 1.0 mL of glucose solution, proceed in the same manner, and determine absorbance A_0. Construct a calibration curve by plotting the difference of absorbance (A_1-A_0, A_2-A_0, A_3-A_0, A_4-A_0, and A_5-A_0) versus the amount of glucose (mg).

Packaging and storage Preserve in tight containers.

Centella Titrated Extract, Hydrocortisone Acetate and Neomycin Sulfate Ointment
센텔라정량추출물·히드로코르티손아세테이트·네오마이신황산염 연고

Centella Titrated Extract, Hydrocortisone Acetate and Neomycin Sulfate Ointment contains NLT 36.0% and NMT 44.0% of asioticoside ($C_{48}H_{78}O_{19}$: 959.12), NLT 90.0% and NMT 110.0% of hydrocortisone acetate ($C_{23}H_{32}O_6$: 404.50), and NLT 90.0% and NMT 120.0% of neomycin sulfate ($C_{23}H_{46}N_6O_{13}\cdot 3H_2SO_4$: 908.88) according to the labeled amount of centella titrated extract.

Method of preparation Prepare as directed under Ointments, with Centella Titrated Extract, Hydrocortisone Acetate and Neomycin Sulfate.

Identification (1) ***Centella titrated extract and hydrocortisone acetate—***Take 3 g of Centella Titrated Extract, Hydrocortisone Acetate and Neomycin Sulfate Ointment, add 10 mL of methanol, shake to mix on a steam bath, then cool in a cold place, and filter. Take 5 mL of the filtrate, add methanol to make 10 mL, and use this solution as the test solution. Weigh appropriate amounts of asiaticoside RS, madecassic acid RS and asiatic acid RS and dissolve in methanol to make 0.5%. Separately weigh hydrocortisone acetate RS, dissolve in methanol to make 0.2%, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, ethanol(95), water and ammonia water (12 : 8 : 2 : 1) as the developing solvent, and air-dry the plate. Spray the plate with a mixture of acetic anhydride and sulfuric acid (9 : 1); the spots from the test solution and the standard solution have the same R_f value and color.

(2) ***Neomycin sulfate—***Weigh an appropriate amount of Centella Titrated Extract, Hydrocortisone Acetate and Neomycin Sulfate Ointment, place in a separatory funnel, add 50 mL of ether, shake vigorously to mix, and extract with an appropriate amount of 0.1 mol/L phosphate buffer solution (pH 8.0). Add 1 mL of ninhydrin TS and 0.5 mL of pyridine to 5 mL of an aqueous solution (1 in 1000) of Centella Titrated Extract, Hydrocortisone Acetate and Neomycin Sulfate Ointment and boil for 10 minutes; the solution exhibits a bluish purple color.

Assay (1) ***Asiaticoside in centella titrated extract—***Weigh a certain amount of centella titrated extract (equivalent to about 12 mg of asiaticoside ($C_{48}H_{78}O_{19}$)) according to the labeled amount of Centella Titrated Extract, Hydrocortisone Acetate and Neomycin Sulfate Ointment, add 20 mL of the mobile phase, dissolve by warming on a steam bath, cool, add the mobile phase to make exactly 50 mL, centrifuge, and use the clear supernatant as the test solution. Separately, weigh accurately about 12 mg of asiaticoside RS, proceed in the same manner with the test solution, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of each solution.

Amount (mg) of asiaticoside ($C_{48}H_{78}O_{19}$)
= Amount (mg) of asiaticoside RS × (A_T / A_S)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of water, methanol and acetonitrile (4 : 3 : 3).

Flow rate: 1.0 mL/min

(2) ***Hydrocortisone acetate***—Weigh accurately an amount of Centella Titrated Extract, Hydrocortisone Acetate and Neomycin Sulfate Ointment, equivalent to about 10 mg of hydrocortisone acetate ($C_{23}H_{32}O_6$) according to the labeled amount, add 30 mL of ethanol(95), shake to mix while warming on a steam bath, then cool and filter. Wash the residue 3 times with 20 mL of ethanol(95), combine the filtrate and washings, and add ethanol to make exactly 100 mL. Pipet 10 mL of this solution, add ethanol(95) to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg of hydrocortisone acetate RS, dissolve in ethanol(95) to make exactly 50 mL. Pipet 2 mL of this solution, add ethanol(95) to make exactly 100 mL, and use this solution as the standard solution. Pipet 20 mL each of the test solution and the standard solution, add 2 mL of 0.5% blue tetrazolium and 2 mL of tetramethylammonium hydroxide, seal, shake to mix, and let stand for 90 minutes in the dark. Separately, carry out the same procedure with ethanol and use the resulting solution as the blank test solution. Determine the absorbances of the test solution and the standard solution A_T and A_S at the wavelength of 525 nm, using the blank test solution as a control solution.

Amount (mg) of hydrocortisone acetate ($C_{23}H_{32}O_6$)
= Amount (mg) of hydrocortisone acetate RS × (A_T / A_S) × 0.4

(3) ***Neomycin sulfate***

Cylinder plate method and standard curve method (Prepare the test solution as follows.)

Method 1 Weigh accurately an amount of Centella Titrated Extract, Hydrocortisone Acetate and Neomycin Sulfate Ointment, equivalent to about 0.1 g (potency) according to the labeled potency, place in a separatory funnel, add 50 mL of ether and shake sufficiently to mix, extract 3 times with 25 mL each of 0.1 mol/L phosphate buffer solution (pH 8.0), combine the extracts, and prepare a solution of appropriate concentration using 0.1 mol/L phosphate buffer solution (pH 8.0).

Method 2 Weigh accurately an amount of Centella Titrated Extract, Hydrocortisone Acetate and Neomycin Sulfate Ointment, equivalent to about 10 mg (potency) of neomycin sulfate according to the labeled potency, place in a blender, add 60 mL of 0.1 mol/L phosphate buffer solution (pH 8.0) and grind at high speed for 3 minutes, then add 0.1 mol/L phosphate buffer solution (pH 8.0) to make exactly 100 mL of solution.

Method 3 Weigh accurately an amount of Centella Titrated Extract, Hydrocortisone Acetate and Neomycin Sulfate Ointment, equivalent to about 10 mg (potency) of neomycin sulfate according to the labeled potency, place in a glass centrifuge tube with a glass stopper, add exactly 50 mL of diluted hydrochloric acid (1 in 100), and shake thoroughly to mix while warming. Cool, add 50 mL of chloroform, shake well to mix, centrifuge, pipet 25 mL of the clear supernatant, adjust pH to 8.0 using sodium hydroxide solution (1 in 5), then add 0.1 mol/L phosphate buffer solution (pH 8.0) to make exactly 50 mL of solution.

Take appropriate amounts of the solutions from Method 1, Method 2 and Method 3 and dilute with 0.1 mol/L phosphate buffer solution (pH 8.0) to the concentrations of (A) ③ and (B) ③, and use these solutions as the test solutions.

(i) Cylinder plate method

① Medium: Agar medium for strata and base layer

Peptone	6.0 g
Yeast extract	3.0 g
Meat extract	1.5 g
Sodium chloride	2.5 g
Glucose	1.0 g
Agar	15.0 ~ 20.0 g

Weigh the above amount of substances, add purified water to make 1000 mL, and adjust the pH after sterilizing with sodium hydroxide TS to between 7.8 and 8.0.

② Test organism and test organism suspension Use *Staphylococcus aureus* ATCC 6538P as the test organism. However, make a test suspension so that the transmittance of the test suspension is 80% when measured using an absorbance photometer at a wavelength of 650 nm.

③ Weigh accurately an amount of Centella Titrated Extract, Hydrocortisone Acetate and Neomycin Sulfate Ointment equivalent to about 20 mg (potency) according to the labeled potency, dissolve in 0.1 mol/L phosphate buffer solution (pH 8.0) to make a solution containing 1 mg (potency) per mL, and use this solution as the test stock solution. Take appropriate amounts of this test stock solution and dilute with 0.1 mol/L phosphate buffer solution (pH 8.0) to contain 80 μg (potency) and 20 μg (potency) per mL, and use these solutions as the high-concentration and low-concentration test solu-

tions, respectively. Separately, take an appropriate amount of neomycin sulfate RS, dry for 3 hours at 0.7 kPa and 60 ℃, then weigh accurately an amount equivalent to 20 mg (potency), dissolve in 0.1 mol/L phosphate buffer solution (pH 8.0) to prepare a standard stock solution containing 1 mg (potency) per mL. Keep the standard stock solution below 5 ℃ and use it within 30 days. For the Assay, pipet an appropriate amount of the standard stock solution, dilute with 0.1 mol/L phosphate buffer (pH 8.0) to contain 80 μg (potency) and 20 μg (potency) per mL, and use these solutions as the high-concentration standard solution and the low-concentration standard solution, respectively. With these solutions, perform the test according to (A) ⑧ under the Microbial Assays for Antibiotics.

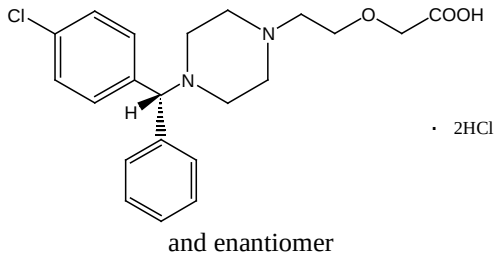
(ii) Standard curve method ① Medium : Follow (A) ① of the Assay.

② Test organism Use *Staphylococcus aureus* ATCC 6538 P as the test organism.

③ **Assay** Pipet an appropriate amount of the test stock solution of (A) ③, dilute with 0.1 mol/L phosphate buffer solution (pH 8.0) to contain 10.0 μg(potency) per mL, and use this solution as the test solution. Separately, pipet an appropriate amount of the standard stock solution of (A) ③ under the Assay, dilute with phosphate buffer solution (pH 8.0) to contain 6.4 μg(potency), 8.0 μg(potency), 10.0 μg(potency), 12.5 μg(potency) and 15.6 μg(potency) per mL, and use these solutions as the standard solutions, and use a solution containing 10.0 μg(potency) as the standard intermediate diluent. Perform the test as directed under the Microbial Assays for Antibiotics (B) ④ with the test solution, the standard solution and the standard intermediate diluent.

Packaging and storage Preserve in tight containers.

Cetirizine Dihydrochloride
세티리진염산염



and enantiomer

$C_{21}H_{25}N_2O_3Cl \cdot 2HCl$: 461.81

2-[2-{4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}ethoxy]acetic acid dihydrochloride [*83881-52-1*]

Cetirizine Dihydrochloride contains NLT 99.0% and NMT 100.5% of cetirizine dihydrochloride ($C_{21}H_{25}N_2O_3Cl \cdot 2HCl$), calculated on an anhydrous basis.

Description Cetirizine Dihydrochloride occurs as a white powder.

It is freely soluble in water and practically insoluble in dichloromethane or in acetone.

Identification (1) Weigh accurately 20.0 mg of Cetirizine Dihydrochloride and dissolve in 0.1 mol/L hydrochloric acid TS to make exactly 100 mL. Dilute 10.0 mL of this solution with 0.1 mol/L hydrochloric acid TS to make exactly 100 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at 231 nm and the specific absorbance at this wavelength is between 359 and 381.

(2) Determine the infrared spectra of Cetirizine Dihydrochloride and cetirizine dihydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 10 mg of Cetirizine Dihydrochloride in water to make 5 mL and use this solution as the test solution. Separately dissolve 10 mg of cetirizine dihydrochloride RS in water to make 5 mL and use this solution as the standard solution (1). Also, dissolve 10 mg of chlorphenamine maleate RS in water to make 5 mL. To 1 mL of the solution, add 1 mL of the standard solution (1) and use the resulting solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solutions (1) and (2) on the thin-layer chromatographic plate made of silica gel (mixed with a fluorescent indicator) for thin-layer chromatography. Next, develop the plate with a mixture of dichloromethane, methanol and ammonia water(28) (90 : 10 : 1) as the developing solvent to a distance of about 15 cm, and dry the plate in cool air. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values of the principal spots obtained from the test solution and the standard solution (1) are the same. However, this test is valid only when the two spots obtained from the standard solution (2) are clearly separated.

(4) An aqueous solution of Cetirizine Dihydrochloride (1 in 100) responds to the Qualitative Analysis for chloride.

pH Dissolve 1.0 g of Cetirizine Dihydrochloride in 20 mL of water; the pH of this solution is between 1.2 and 1.8.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Cetirizine Dihydrochloride in 20 mL of water; the solution is clear.

(2) ***Heavy metals***—Proceed with 2.0 g of Cetirizine Dihydrochloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances*—**Weigh accurately 20.0 mg of Cetirizine Dihydrochloride, dissolve in the mobile phase to make 100.0 mL, and use this solution as the test solution. Separately, dissolve 5.0 mg of cetirizine dihydrochloride RS and 5.0 mg of cetirizine related substance I RS [(RS)-1-[(4-chlorophenyl)phenylmethyl]piperazine} in the mobile phase to make exactly 25 mL. To 1.0 mL of this solution, add the mobile phase to make exactly 100 mL and use this solution as the standard solution (1). To 2.0 mL of the test solution, add the mobile phase to make exactly 50 mL. To 5.0 mL of this solution, add the mobile phase to make exactly 100 mL and use this solution as the standard solution (2). Perform the test with 20 μL each of the test solution and the standard solutions (1) and (2) as directed under the Liquid Chromatography, and determine the peak area from each solution by the automatic integration method. The area of any peak other than the major peak obtained from the test solution is not larger than that obtained from the standard solution (2) (0.2%), and the sum of the peak areas other than the major peak area obtained from the test solution is not larger than 1.5 times the peak area obtained from the standard solution (2) (0.3%). However, exclude any peak having an area smaller than 0.1 times the peak area obtained from the standard solution (2).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column : A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile, water and dilute sulfuric acid (93 : 6.6 : 0.4).

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution (1) according to the above conditions and adjust the sensitivity of the system so that the peak heights are about 50% of the full scale of the data collection device; the resolution between the peak of cetirizine and cetirizine related substance I is NLT 3 and the symmetry factor is NMT 2.0.

Loss on drying NMT 0.5% (1.0 g, 105 ºC, constant mass).

Residue on ignition NMT 0.2% (1.0 g).

Assay Weigh accurately about 0.1 g of Cetirizine Dihydrochloride, dissolve in a mixture of acetone and water (70: 30), and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 15.394 mg of $C_{21}H_{25}N_2O_3Cl \cdot 2HCl$

Packaging and storage Preserve in light-resistant, well-closed containers.

Cetirizine Dihydrochloride Solution
세티리진염산염 액

Cetirizine Dihydrochloride Solution contains NLT 95.0% and NMT 105.0% of cetirizine dihydrochloride ($C_{21}H_{25}ClN_2O_3 \cdot 2HCl$: 461.81) of the labeled amount.

Method of preparation Prepare as directed under Liquids, with Cetirizine Dihydrochloride.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

pH Between 4.0 and 6.5.

Assay Pipet a volume of Cetirizine Dihydrochloride Solution, equivalent to 10 mg of the labeled amount of cetirizine dihydrochloride ($C_{21}H_{25}ClN_2O_3 \cdot 2HCl$) and transfer it into a 100 mL-volumetric flask. Add 15 mL of water, sonicate for 10 minutes to dissolve, add 50% acetonitrile to make 100 mL, filter, and use this solution as the test solution. Separately, weigh accurately about 10 mg of cetirizine dihydrochloride RS, transfer it into a 100 mL-volumetric flask, then proceed in the same way as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and calculate the peak areas, A_T and A_S, of cetirizine dihydrochloride, respectively, from each solution.

Amount (mg) of cetirizine dihydrochloride ($C_{21}H_{25}ClN_2O_3 \cdot 2HCl$)
= Amount (mg) of cetirizine dihydrochloride RS $\times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

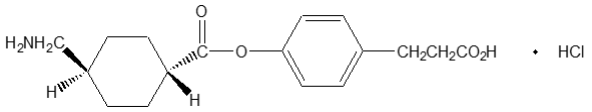
Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 - 10 μm in particle diameter).

Mobile phase: A mixture of phosphate buffer (pH 7.0) and acetonitrile (80 : 60).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Cetraxate Hydrochloride
세트락세이트염산염



$C_{17}H_{23}NO_4 \cdot HCl$: 341.83
3-[4-[4-(Aminomethyl)cyclohexanecarbonyl]oxyphenyl] propanoic acid hydrochloride [*27724-96-5*]

Cetraxate Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of cetraxate hydrochloride ($C_{17}H_{23}NO_4 \cdot HCl$).

Description Cetraxate Hydrochloride occurs as white crystals or a crystalline powder.
It is soluble in methanol, sparingly soluble in water or ethanol(95), and practically insoluble in ether.

Melting point—About 236 ℃ (with decomposition)

Identification (1) Determine the absorption spectra of solutions of Cetraxate Hydrochloride and cetraxate hydrochloride RS in methanol (1 in 2500) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Dissolve 0.5 g of Cetraxate Hydrochloride in 5 mL of a mixture of water and 2-propanol (1 : 1) by warming, cool to NMT 25 ℃, and filter the extracted crystals. Determine the infrared spectra of the crystals, dried in vacuum for 4 hours and then dried again at 105 ℃ for 1 hour, and cetraxate hydrochloride RS, previously dried, as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Cetraxate Hydrochloride (1 in 100) responds to the Qualitative Analysis (2) for chloride.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Cetraxate Hydrochloride as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Cetraxate Hydrochloride as directed under Method 3 and perform the test. Use a solution of magnesium nitrate in ethanol(95) (1 in 5) (NMT 2 ppm).

(3) ***Cis isomer***—Dissolve 0.10 g of Cetraxate Hydrochloride in 10 mL of water and use this solution as the test solution. Pipet 5 mL of this solution and add water to make exactly 100 mL. Pipet 2 mL of this solution, add water to make exactly 50 mL, and use this solution as the standard solution. With 10 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions and determine the peak areas from the respective solutions according to the automatic integration method; the peak area whose retention time is 1.3 to 1.6 times the retention time of cetraxate in the test solution is not greater than the peak area of cetraxate in the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: To a mixture of water, methanol and 0.5 mol/L ammonium acetate TS (15 : 10 : 4), add acetic acid to adjust the pH to 6.0.

Flow rate: Adjust the flow rate so that the retention time of cetraxate is about 10 minutes.

System suitability

Detection sensitivity: Adjust the sensitivity so that the peak height of cetraxate obtained from 10 μL of the standard solution is NLT 20 mm.

System performance: Dissolve 20 mg of Cetraxate Hydrochloride and 10 mg of phenol in 100 mL of water. Take 2 mL of this solution and add water to make 20 mL. Proceed with 10 μL of this solution according to the above conditions; cetraxate and phenol are eluted in this order with the resolution between these peaks being NLT 5.

(4) ***3-(p-hydroxyphenyl)propionic acid***—To 0.10 g of Cetraxate Hydrochloride, add exactly 2 mL of the internal standard solution, add methanol to make 10 mL, and use this solution as the test solution. Separately, to 25 mg of 3-(*p*-hydroxyphenyl)propionic acid, and dissolve in methanol to make exactly 100 mL. Pipet 2 mL of this solution, add exactly 2 mL of the internal standard solution, add methanol to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions and calculate the peak area ratios, Q_T and Q_S, of 3-(*p*-hydroxyphenyl)propionic acid to internal standard, respectively; Q_T is not greater than Q_S.

Internal standard solution—A solution of caffeine in methanol (1 in 4000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: To a mixture of water, methanol and 0.5 mol/L ammonium acetate TS (15 : 5 : 2), add acetic acid to adjust the pH to 5.5.

Flow rate: Adjust the flow rate so that the retention time of 3-(*p*-hydroxyphenyl)propionic acid is about 7 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; 3-(*p*-hydroxyphenyl)propionic acid and internal standard are eluted in this order with resolution between these peaks being NLT 5.

Detection sensitivity: Adjust the sensitivity so that the peak height of 3-(*p*-hydroxyphenyl)propionic acid from 10 μL of the standard solution is NLT 30 mm.

(5) ***Related substances*—**Dissolve 0.10 g of Cetraxate Hydrochloride in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, methanol and acetic acid(100) (20 : 4 : 3) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly ninhydrin TS on the plate and heat the plate at 90 ℃ for 10 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (0.5 g, 105 ℃, 3 hours).

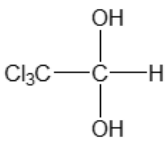
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Cetraxate Hydrochloride, previously dried, dissolve in 100 mL of water, and add dilute sodium hydroxide TS to adjust the pH to between 7.0 and 7.5. To this solution, add 10 mL of formaldehyde solution, stir for about 5 minutes to mix, and titrate with 0.1 mol/L sodium hydroxide VS over about 20 minutes (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 34.183 mg of $C_{17}H_{23}NO_4 \cdot HCl$

Packaging and storage Preserve in tight containers.

Chloral Hydrate
포수클로랄



$C_2H_3Cl_3O_2$: 165.40

2,2,2-Trichloroethane-1,1-diol [*25655-41-8*]

Chloral Hydrate contains NLT 99.5% and NMT 101.0% of chloral hydrate ($C_2H_3Cl_3O_2$).

Description Chloral Hydrate occurs as colorless crystals. It has an irritating odor and an irritating and slightly bitter taste.
It is very soluble in water and freely soluble in ethanol(95) or ether.
It slowly evaporates in the air.

Identification (1) Dissolve 0.2 g of Chloral Hydrate in 2 mL of water, and add 2 mL of sodium hydroxide TS; the resulting solution is turbid, and two clear layers form by warming.

(2) To 0.2 g of Chloral Hydrate, add 3 drops of aniline and 3 drops of sodium hydroxide TS, and heat; an unpleasant odor of phenyl isocyanide (toxic) is perceptible.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Chloral Hydrate in 2 mL of water; the resulting solution is clear and colorless.

(2) ***Acid***—Dissolve 0.20 g of Chloral Hydrate in 2 mL of water, and add 1 drop of methyl orange TS; the resulting solution exhibits a yellow color.

(3) ***Chloride*—**Perform the test with 1.0 g of Chloral Hydrate. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid TS (NMT 0.011%).

(4) ***Chloral alcoholate*—**Weigh 1.0 g of Chloral Hydrate, add 10 mL of sodium hydroxide TS, warm, and filter the clear supernatant. Add dropwise iodine TS until the filtrate becomes yellow, and allow to stand for 1 hour; a yellow precipitate does not form.

(5) ***Benzene*—**To the solution of (1), add 3 mL of water, and warm; it has no benzene odor.

(6) ***Heavy metals*—**Dissolve 3.0 g of Chloral Hydrate in freshly boiled and cooled water to make 30 mL. Pipet 10.0 mL of this solution, and add water to make 20 mL. Use this solution as the test solution and perform the test. Separately, proceed with 6.0 mL of the lead standard solution in the same manner as the test solution. To 10 mL of this solution, add 2 mL of the test solution, and use this solution as a control solution. Separately, add 2 mL of the test solution to 10 mL of water, and use this solution as the blank test solution. To 12 mL each of the test solution, the control solution and the blank test solution, add 2 mL of acetate buffer solution, pH 3.5, mix, add 1.2 mL of thioacetamide TS, and immediately mix. Allow to stand for 2 minutes; the color of the test solution is not more intense than that of the control solution (NMT 20 ppm).

Residue on ignition NMT 0.1% (1 g).

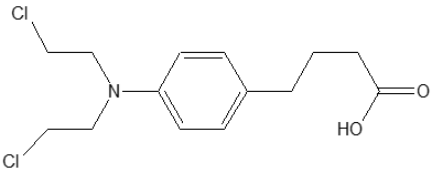
Assay Weigh accurately about 4 g of Chloral Hydrate in a stoppered flask, add 10 mL of water and 40 mL of 1

mol/L sodium hydroxide, allow to stand for exactly 2 minutes, and immediately titrate excess sodium hydroxide solution with 0.5 mol/L sulfuric acid VS (indicator: 2 drops of phenolphthalein TS). Perform a blank test in the same manner.

Each mL of 1 mol/L sodium hydroxide VS
= 165.40 mg of $C_2H_3Cl_3O_2$

Packaging and storage Preserve in tight containers.

Chlorambucil
클로람부실



$C_{14}H_{19}Cl_2NO_2$: 304.21
4-[4-[*bis*(2-Chloroethyl)amino]phenyl]butanoic acid
[*305-03-3*]

Chlorambucil contains NLT 98.0% and NMT 101.0% of chlorambucil ($C_{14}H_{19}NaO_2$: 2), calculated on the anhydrous basis.

Description Chlorambucil occurs as a milk white grain powder.
It is freely soluble in acetone and practically insoluble in water.
It dissolves in dilute sodium hydroxide TS.

Identification (1) Dissolve 50 mg of Chlorambucil in 5 mL of acetone and add water to make 10 mL. Add 1 drop of 1 mol/L sulfuric acid and then add 4 drops of silver nitrate TS; the solution does not become turbid immediately. Warm this solution on a steam bath; the resulting solution forms white turbidity.

(2) Determine the infrared spectra of solutions of Chlorambucil and Chlorambucil RS in carbon disulfide (1 to 125) as directed under the solution method under the Mid-infrared Spectroscopy, using solid cells with 1 mm in thickness; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 65 and 69 ºC.

Water NMT 0.5% (1 g, volumetric titration, direct titration).

Assay Weigh accurately about 0.2 g of Chlorambucil, dissolve in 10 mL of acetone, add 10 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 2 drops of phenolphthalein TS).

Each mL of 0.1 mol/L sodium hydroxide VS
= 30.421 mg of $C_{14}H_{19}Cl_2NO_2$

Packaging and storage Preserve in light-resistant, tight containers.

Chlorambucil Tablets
클로람부실 정

Chlorambucil Tablets contain NLT 85.0% and NMT 110.0% of the labeled amount of chlorambucil ($C_{14}H_{19}Cl_2NO_2$: 304.22).

Method of preparation Prepare as directed under Tablets, with Chlorambucil.

Identification Weigh an amount of Chlorambucil Tablets, previously powdered, equivalent to 16 mg of chlorambucil, add 20 mL of carbon disulfide, and shake to mix. Filter this solution, evaporate the filtrate to dryness, dissolve the residue in 2 mL of carbon disulfide, and perform the test as directed under the Identification (1) of Chlorambucil.

Disintegration Meets the requirements. However, in the case of coated tablets, precipitate it in water at room temperature for 5 minutes in advance, place it in an auxiliary container, and perform the test using Solution 1; disintegrate within 30 minutes. If it does not disintegrate, take out the auxiliary container, and continue the test at 37 ± 2 ℃ using Solution 2 as the test solution; disintegrate within a total of 45 minutes. If 1 or 2 tablets do not completely disintegrate, perform the test with 12 new tablets; NMT 2 tablets do not disintegrate out of a total of 18 tablets.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Chlorambucil Tablets, and powder. Weigh accurately an amount, equivalent to about 2 mg of chlorambucil ($C_{14}H_{19}Cl_2NO_2$), add 50 mL of ethanol(95), and shake gently. Add 5.0 mL of 0.1 mol/L hydrochloric acid and 2.0 mL of internal standard solution, sonicate for 5 minutes, and shake to mix. Add ethanol(95) to make exactly 100 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 20 mg of chlorambucil RS, previously dried in a silica gel desiccator for 24 hours, and dissolve in ethanol(95) to make exactly 20 mL. Pipet 2.0 mL of this solution, add about 50 mL of ethanol(95), shake gently, and add 5.0 mL of 0.1 mol/L hydrochloric acid and 2.0 mL of internal standard solution. Add ethanol(95) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the

peak area ratios, Q_T and Q_S of chlorambucil to the peak area of the internal standard, respectively.

$$\text{Amount (mg) of chlorambucil } (C_{14}H_{19}Cl_2NO_2) = \text{Amount (mg) of chlorambucil RS} \times \frac{Q_T}{Q_S} \times \frac{1}{10}$$

Internal standard solution—A solution ethanol of propyl p-hydroxybenzoate in ethanol (1 in 2500).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 2 mm in internal diameter and 25 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Add 1.0 mL of acetic acid(100) to 500 mL of ethanol(95), and add water to make 1000 mL.

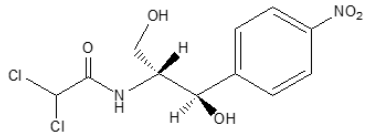
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; chlorambucil and the internal standard are with the resolution being NLT 2.0.

System reproducibility: Repeat the test 6 times with 10 μL each of the standard solution under the above operating conditions; the relative standard deviation of the ratios of the peak area of chlorambucil to that of the internal standard is NMT 2.0%.

Packaging and storage Preserve in well-closed containers (preserve in light-resistant, well-closed containers for uncoated tablets.).

Chloramphenicol
클로람페니콜



$C_{11}H_{12}Cl_2N_2O_5$: 323.13

2,2-Dichloro-*N*-[(1*R*,2*R*)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-yl]acetamide [*56-75-7*]

Chloramphenicol contains NLT 980 μg and NMT 1020 μg (potency) of chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$) per mg, calculated on the dried basis.

Description Chloramphenicol occurs as white to yellowish white crystals or a crystalline powder.
It is freely soluble in methanol or ethanol(99.5) and slightly soluble in water.

Identification (1) Using the test solution and the standard solution obtained from Chloramphenicol and chloramphenicol RS under the Assay, determine the absorption spectrum according to the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Chloramphenicol and chloramphenicol RS according to the potassium bromide disk method as directed under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between +18.5° and +21.5° (1.25 g, ethanol(99.5), 25 mL, 100 mm).

Melting point Between 150 and 155 ℃.

pH The pH of the saturated solution of Chloramphenicol is between 4.5 and 7.5.

Absorbance $E_{1cm}^{1\%}$ (278 nm): Between 289 and 307 (20 mg, water,1000 mL).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Chloramphenicol according to Method 2 and perform the test. Prepare the control solution with 2.5 mL of lead standard solution (NMT 25 ppm).

(2) ***Arsenic***—Prepare the test solution with 2.0 g of Chloramphenicol according to Method 4 and perform the test (NMT 1 ppm).

(3) ***Related substances***—Dissolve 0.10 g of Chloramphenicol in 10 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution, dissolve in methanol to make exactly 100 mL, and use this solution as the standard solution (1). Pipet 10 mL of the standard solution (1), add methanol to make exactly 20 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and standard solutions (1) and (2) on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator), develop the plate with a mixture of chloroform, methanol and acetic acid(100) (79 : 14 : 7) to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet rays (main wavelength: 254 nm); the spots other than the spots of the starting point and the principal spot from the test solution are not more intense than the spots from the standard solution (1). The sum of spots other than the spots of the starting point and the principal spot from the test solution is NMT 2.0%.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins It meets the requirements when used in the manufacturing of sterile preparations. Chloramphenicol is less than 0.2 EU per mg (potency) of chloramphenicol.

Assay Weigh accurately about 50 mg (potency) each of Chloramphenicol and chloramphenicol RS, dissolve in the mobile phase to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas A_T and A_S of chloramphenicol.

Potency (μg) of chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$)
= Potency (μg) of chloramphenicol RS × $\frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 250 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of water, methanol and acetic acid(31) (550 : 450 : 1).

Flow rate: 1.5 mL/min.

System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; the number of theoretical plates and symmetry factor of the peak of chloramphenicol are NLT 1800 and NMT 2.0, respectively.

System repeatability: Repeat the test 6 times according to the above conditions with 10 μL of the standard solution; the relative standard deviation of the peak area of chloramphenicol is NMT 1.0%

Packaging and storage Preserve in tight containers.

Chloramphenicol Ophthalmic Solution
클로람페니콜 점안액

Chloramphenicol Ophthalmic Solution contains NLT 90.0% and NMT 120.0% of the labeled amount of chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$: 323.13).

Method of preparation Prepare as directed under Ophthalmic Solutions, with Chloramphenicol.

Identification (1) Weigh an amount of Chloramphenicol Ophthalmic Solution, equivalent to 10 mg of chloramphenicol, dissolve in 1 mL of 50% ethanol(95), add 3 mL of calcium chloride solution (1 in 100) and 50 mg of zinc powder, and warm on a steam bath for 10 minutes. Pour the clear supernatant into a test tube, add 0.1 g of anhydrous sodium acetate and 2 drops of benzoyl chloride, shake for 1 minute, and add 10 drops of iron(III) chloride TS (add dilute hydrochloric acid if the liquid is not clear); the solution exhibits a reddish purple to violet color. Perform the test as above without adding zinc powder; the resulting solution is colorless.

(2) The retention times of the major peak obtained from the test solution and the standard solution in the Assay are the same.

pH Between 3.0 and 6.0. However, the pH is 7.0 to 7.5 with the buffer solution.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in ophthalmic solutions Meets the requirements.

Assay Proceed as directed under the Assay under Chloramphenicol. However, weigh accurately an amount of Chloramphenicol Ophthalmic Solution equivalent to about 40 mg (potency) according to the labeled potency to make exactly 100 mL with methanol. Pipet 5 mL of this solution to make 25 mL with the mobile phase, filter it through a membrane filter with a pore size of NMT 0.5 μm, and use the filtrate as the test solution. Weigh accurately an amount of chloramphenicol RS equivalent to about 40 mg (potency), make exactly 100 mL with methanol, and pipet 5 mL of this solution to make 25 mL with the mobile phase. Filter it through a membrane filter with a pore size of NMT 0.5 μm, and use the filtrate as the standard solution.

Packaging and storage Preserve in tight containers.

Chloramphenicol, Dexamethasone Disodium Phosphate and Tetrahydrozoline Hydrochloride Ophthalmic Solution
클로람페니콜·덱사메타손이나트륨인산염·테트라히드로졸린염산염 점안액

Chloramphenicol, Dexamethasone Disodium Phosphate and Tetrahydrozoline Hydrochloride Ophthalmic Solution contains NLT 90.0% and NMT 120.0% of the labeled amount of chloramphenicol ($C_{11}H_{12}C_{l2}N_2O_5$: 323.13); NLT 90.0% and NMT 110.0% of the labeled amount of dexamethasone disodium phosphate ($C_{22}H_{28}FNa_2O_8P$: 516.41) and tetrahydrozoline hydrochloride ($C_{13}H_{16}N_2 \cdot HCl$: 236.74).

Method of preparation Prepare as directed under Oph-

thalmic Solutions, with Chloramphenicol, Dexamethasone Disodium Phosphate and Tetrahydrozoline Hydrochloride.

Identification (1) ***Chloramphenicol***—The retention time of the peak obtained from the test solution and the standard solution from the Assay and the ultraviolet absorption spectrum between 200 and 400 nm are the same.

(2) ***Dexamethasone disodium phosphate***—The retention time of the peak obtained from the test solution and the standard solution from the Assay and the ultraviolet absorption spectrum between 200 and 400 nm are the same.

(3) ***Tetrahydrozoline hydrochloride***—Take an amount of Chloramphenicol, Dexamethasone Disodium Phosphate and Tetrahydrozoline Hydrochloride Ophthalmic Solution, equivalent to 10 mg of tetrahydrozoline hydrochloride, and add diluted hydrochloric acid (1 in 100) to make 100 mL. Take 1 mL of this solution, add diluted hydrochloric acid (1 in 100) to make 100 mL, and use this solution as the test solution. Take 1 mL of this solution, add diluted hydrochloric acid (1 in 100) to make 100 mL, and use this solution as the test solution. Separately, weigh about 10 mg of tetrahydrozoline hydrochloride RS, proceed in the same manner as in the preparation of the test solution with tetrahydrozoline hydrochloride RS, and use this solution as the standard solution. Determine the absorption spectra of the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelength.

pH Between 5.5 and 7.5.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Particulate matter in Ophthalmic solutions Meets the requirements.

Assay Pipet an amount of Chloramphenicol, Dexamethasone Disodium Phosphate and Tetrahydrozoline Hydrochloride Ophthalmic Solution, equivalent to about 100 mg of chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$), [about 20 mg of dexamethasone disodium phosphate ($C_{22}H_{28}FNa_2O_8P$) and about 5 mg of tetrahydrozoline hydrochloride ($C_{13}H_{16}N_2 \cdot HCl$)], according to the labeled amount, and add methanol to make 10 mL. Sonicate for about 30 minutes, filter through a membrane filter with a pore size of 0.45 μm, and use the filtrate as the test solution. Separately, weigh accurately about 100 mg of chloramphenicol RS, about 20 mg of dexamethasone disodium phosphate RS and about 5 mg of tetrahydrozoline hydrochloride RS, add 80% methanol to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of chloramphenicol, dexamethasone disodium phosphate and tetrahydrozoline hydrochloride, A_{T1}, A_{T2}, A_{T3}, A_{S1}, A_{S2} and A_{S3}.

$$\text{Amount (mg) of chloramphenicol } (C_{11}H_{12}Cl_2N_2O_5) = \text{Amount (mg) of chloramphenicol RS} \times \frac{A_{T1}}{A_{S1}}$$

$$\text{Amount (mg) of dexamethasone disodium phosphate } (C_{22}H_{28}FNa_2O_8P) = \text{Amount (mg) of dexamethasone disodium phosphate RS} \times \frac{A_{T2}}{A_{S2}}$$

$$\text{Amount (mg) of tetrahydrozoline hydrochloride } (C_{13}H_{16}N_2 \cdot HCl) = \text{Amount (mg) of tetrahydrozoline hydrochloride RS} \times \frac{A_{T3}}{A_{S3}}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm). However, proceed with a photodiode array detector (200 to 400 nm) for the Identification.

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Use mobile phases A and B to control a stepwise or gradient elution-wise as follows.

Mobile phase A: Dissolve 2.72 g of potassium dihydrogen phosphate in water to make 1000 mL, and add phosphoric acid to adjust the pH to 3. Add 100 mL of methanol to 900 mL of this solution.

Mobile phase B: Dissolve 2.72 g of potassium dihydrogen phosphate in water to make 1000 mL, and add phosphoric acid to adjust the pH to 3. Add 900 mL of methanol to 100 mL of this solution.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 2	80	20
2 - 15	80 → 10	20 → 90
15 - 20	10	90
20 - 30	80	20

Flow rate: 1.0 mL/min

System suitability

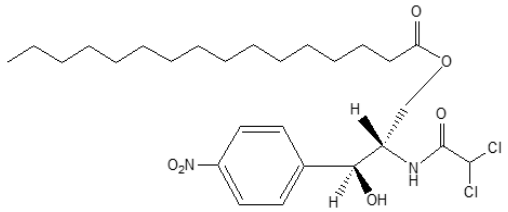
System performance: Proceed with 10 μL of the standard solution according to the above conditions; dexamethasone disodium, chloramphenicol, phosphate and tetrahydrozoline hydrochloride are eluted in this order with the resolution being NLT 11.0.

System repeatability: Repeat the test 6 times with

10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak areas of chloramphenicol, dexamethasone disodium phosphate and tetrahydrozoline hydrochloride is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Chloramphenicol Palmitate
클로람페니콜팔미테이트



$C_{27}H_{42}Cl_2N_2O_6$: 561.54

[(2*R*,3*R*)-2-[(2,2-Dichloroacetyl)amino]-3-hydroxy-3-(4-nitrophenyl)propyl]hexadecanoate [*530-43-8*]

Chloramphenicol Palmitate contains NLT 558 μg and NMT 587 μg (potency) of Chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$ 323.13) per mg, calculated on the dried basis.

Description Chloramphenicol Palmitate occurs as a white to grayish white crystalline powder.
It is freely soluble in acetone, sparingly soluble in methanol or ethanol(99.5) and practically insoluble in water.

Identification (1) Determine the absorption spectra of solutions of Chloramphenicol Palmitate and chloramphenicol palmitate RS in ethanol(99.5) (1 in 33000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Dissolve 5 mg of Chloramphenicol Palmitate and chloramphenicol palmitate RS in 1 mL of acetone and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Develop the plate with a mixture of acetone and cyclohexane (1: 1) to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f value of the principal spot obtained from the test solution and the spots from the standard solution are the same.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{25}$: Between +21° and +25° [1 g, calculated on the dried basis, ethanol(99.5), 20 mL, 100 mm].

Melting point Between 91 and 96 ℃.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Chloramphenicol Palmitate according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Chloramphenicol Palmitate according to Method 3 and perform the test (NMT 2 ppm).

(3) ***Related substances***—Weigh accurately 50 mg of Chloramphenicol Palmitate, dissolve in 50 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under Liquid Chromatography according to the following conditions, and determine each peak area of the respective solution by the automatic integration method; the sum of peak areas other than the peak of chloramphenicol palmitate from the test solution is not larger than 3.5 times the peak area of chloramphenicol palmitate from the standard solution. The peak areas of chloramphenicol and chloramphenicol palmitate, having a relative retention time of about 0.5 and about 5.0 with respect to chloramphenicol palmitate, are calculated by multiplying the area obtained by the automatic integration method by the sensitivity coefficients of 0.5 and 1.4, respectively.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column about 6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 20 °C.

Mobile phase: Methanol

Flow rate: Adjust the flow rate so that the retention time of chloramphenicol palmitate is about 5 minutes.

Time span of measurement: About 6 times of the retention time of chloramphenicol palmitate.

System suitability

Test for required detectability: Dissolve 50 mg of Chloramphenicol Palmitate in methanol to make 50 mL. Pipet 1 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the system suitability solution. Pipet 5 mL of the system suitability solution and add methanol to make exactly 50 mL. Confirm that the peak area of chloramphenicol palmitate obtained from 20 μL of this solution is equivalent to 7 to 13% of that from the system suitability solution.

System performance: Proceed with 20 μL of the system suitability solution under the above operating conditions; the number of theoretical plates for the peak of chloramphenicol palmitate is NLT 5000.

System reproducibility: Repeat the test 6 times with 20 μL each of the system suitability solutions under the above conditions; the relative standard deviation of the peak area of chloramphenicol palmitate is NMT 1.0%.

(4) ***Free chloramphenicol***—Weigh accurately about 1.0 g of Chloramphenicol Palmitate, and dissolve in xylene by heating to make exactly 80 mL. After cooling, extract with 15 mL volumes of water three times and discard the xylene. To the extract, add water to make exactly 50 mL. Add exactly 10 mL of toluene to this solution, mix, and extract the water layer. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance, *A*, at a wavelength of 278 nm is NMT 0.268. Perform a blank test in the same way and make necessary corrections(NMT 450 ppm).

$$\text{Free chloramphenicol (ppm)} = A \times \frac{10000}{5.96}$$

Loss on drying NMT 1.0% (1 g, NMT 0.67 kPa, 60 ℃, 3 hours).

Assay Weigh accurately about 37 mg (potency) each of Chloramphenicol Palmitate and chloramphenicol palmitate RS, dissolve each in 40 mL of methanol and 1 mL of acetic acid(100), and add methanol to make exactly 50 mL. Pipet 10 mL of this solution, add the mobile phase to make exactly 25 mL, and use them as the test solution and the standard solution, respectively. Take exactly 10 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas A_T and A_S of chloramphenicol palmitate for each solution.

$$\text{Potency (μg) of chloramphenicol } (C_{11}H_{12}Cl_2N_2O_5) = \text{Potency (μg) of chloramphenicol RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of methanol, water and acetic acid(100) (172: 27 : 1).

Flow rate: Adjust the flow rate so that the retention time of chloramphenicol palmitate is about 7 minutes.

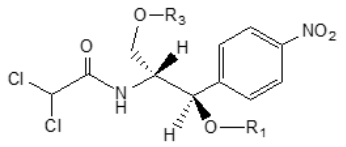
System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; the number of theoretical plates for the peak of chloramphenicol palmitate is NLT 2400.

System repeatability: Repeat the test 6 times according to the above conditions with 10 μL of the standard solution each time; the relative standard deviation of the peak area of chloramphenicol palmitate is NMT 1.0%

Packaging and storage Preserve in light-resistant, tight containers.

Chloramphenicol Sodium Succinate
클로람페니콜숙시네이트나트륨



$C_{15}H_{15}Cl_2N_2NaO_8$: 445.18

Sodium 4-[(2*R*,3*R*)-2-[(2,2-dichloroacetyl)amino]-3-hydroxy-3-(4-nitrophenyl)propoxy]-4-oxo-butanoate [*982-57-0*]

Chloramphenicol Sodium Succinate contains NLT 711 μg (potency) of chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$: 323.13) per mg, calculated on the anhydrous basis.

Description Chloramphenicol Sodium Succinate occurs as white to yellowish white crystals or a crystalline powder.

It is very soluble in water and freely soluble in methanol or ethanol(99.5).

It is hygroscopic.

Identification (1) Determine the absorption spectra of aqueous solutions of Chloramphenicol Sodium Succinate and chloramphenicol sodium succinate RS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelength.

(2) Determine the infrared spectra of Chloramphenicol Sodium Succinate and chloramphenicol sodium succinate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) This solution responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between +5 and +8° (1.25 g calculated on the anhydrous basis, 25 mL of water, 100 mm).

pH Dissolve 1.4 g of Chloramphenicol Sodium Succinate in 5 mL of water; the pH of this solution is between 6.0 and 7.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g

of Chloramphenicol Sodium Succinate in 10 mL of water; the resulting solution is clear, and colorless to yellow.

(2) ***Heavy metals***—Proceed with 1.0 g of Chloramphenicol Sodium Succinate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Chloramphenicol Sodium Succinate according to Method 1 and perform the test (NMT 2 ppm).

(4) ***Free chloramphenicol***—Weigh accurately about 33 mg of Chloramphenicol Sodium Succinate, dissolve in the mobile phase to make exactly 50 mL, filter through a filter with a pore size of not exceeding 0.5 μm, and use the filtrate as the test solution. Weigh accurately about 0.6 mg of chloramphenicol RS, dissolve in the mobile phase to make exactly 100 mL, filter through a filter with a pore size of not exceeding 0.5 μm, and use the filtrate as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, determine each peak area of the respective solution by the automatic integration method, and determine the peak areas, A_T and A_S, of chloramphenicol in each solution (NMT 2.0%).

$$\text{Content (\%) of free chloramphenicol } (C_{11}H_{12}Cl_2N_2O_5) = 5000 \times \frac{C}{W \times Q} \times \frac{A_T}{A_S}$$

C: Concentration (μg/mL) of chloramphenicol in the standard solution

Q: Amount (μg) of chloramphenicol in each mg of chloramphenicol sodium succinate in the test solution

W: Amount (mg) of sample taken

A_T: Peak area of chloramphenicol obtained from the test solution

As: Peak area of chloramphenicol obtained from the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 275 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of 0.05 mol/L ammonium dihydrogen phosphate TS (pH adjusted to 2.5 ± 0.1 with 10% phosphoric acid) and methanol (60 : 40).

Flow rate: 1 mL/min

System suitability

Column performance: Proceed with the test solution under the above operating conditions; the resolution between the two major peaks, chloramphenicol-1-succinate and chloramphenicol-3-succinate, is NLT 2.0, and the number of theoretical plates and symmetry factor are NLT 1750 and NMT 1.2, respectively.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above operating conditions; the relative standard deviation of the peak areas of the two major peaks, chloramphenicol-1-succinate and chloramphenicol-3-succinate, is NMT 2.0%.

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins It is less than 0.2 EU per mg of chloramphenicol when used in the manufacturing of sterile preparations.

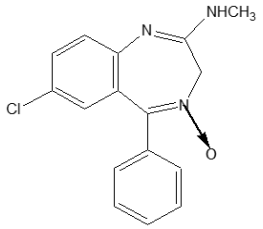
Water NMT 2.0% (1.0 g, volumetric titration, direct titration).

Assay Weigh accurately about 20 mg (potency) of Chloramphenicol Sodium Succinate, dissolve in water to make exactly 1000 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg (potency) of Chloramphenicol Succinate RS, and add exactly 50 mL of water to suspend. Add slowly 7 mL of 0.01 mol/L sodium hydroxide TS while stirring, and adjust the pH to 7.0. To this solution, add water to make exactly 1000 mL, and use this solution as the standard solution. Measure the absorbances of the test solution (A_T) and the standard solution (A_S) at the wavelength of 276 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Potency (μg) of chloramphenicol } (C_{11}H_{12}Cl_2N_2O_5) = \text{Potency (μg) of Chloramphenicol Sodium Succinate RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in hermetic containers.

Chlordiazepoxide
클로르디아제폭시드



$C_{16}H_{14}ClN_3O$: 299.76

7-Chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine-4-oxide [*58-25-3*]

Chlordiazepoxide, when dried, contains NLT 98.5% and NMT 101.0% of chlordiazepoxide ($C_{16}H_{14}ClN_3O$).

Description Chlordiazepoxide occurs as white to pale yellow crystals or a crystalline powder.
It is freely soluble in acetic acid(100), sparingly soluble

in ethanol(95), very slightly soluble in ether and practically insoluble in water.
It is soluble in dilute hydrochloric acid.
It is gradually affected by light.

Melting point—About 240 °C (with decomposition).

Identification (1) Determine the absorption spectra of solutions of Chlordiazepoxide and chlordiazepoxide RS in 0.1 mol/L hydrochloric acid TS (1 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the absorption spectra of Chlordiazepoxide and chlordiazepoxide RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Perform the test with Chlordiazepoxide as directed under the Flame Coloration (2); a green color is observed.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Chlordiazepoxide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Perform the test using light-resistant containers. Weigh 0.20 g of Chlordiazepoxide, dissolve in exactly 10 mL of a mixture of ethanol and ammonia TS (97:3), and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of methanol and ammonia TS (97 : 3) to make exactly 200 mL, and use this solution as the standard solution (1). Separately, weigh 10 mg of 2-amino-5-chlorobenzophenone RS, add methanol to make exactly 200 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 25 μL of the test solution and 5 μL each of the standard solutions (1) and (2) on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate and ethanol(99.5) (19: 1) to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution (1). Spray evenly a solution of sodium nitrite in 1 mol/L hydrochloric acid TS (1 in 100) on the plate, allow to stand for 1 minute, and spray evenly oxalic acid N-(1-naphthyl)-N'-diethylethylenediamine and acetone TS on the plate: the spots from the test solution are not more intense than the spots from the standard solution (2).

Loss on drying NMT 0.5% (1 g, in vacuum, phosphorus pentoxide, 60 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.6 g of Chlordiazepoxide, previously dried, dissolve in 50 mL of acetic acid, and titrate with 0.1 mol/L perchloric acid VS (indicator: 3 drops of methylosaniline chloride TS). However, the endpoint of the titration is when the color of the clear supernatant changes from purple through bluish purple to blue. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 29.976 mg of $C_{16}H_{14}ClN_3O$

Packaging and storage Preserve in light-resistant, tight containers.

Chlordiazepoxide Powder
클로르디아제폭시드 산

Chlordiazepoxide Powder contains NLT 93.0% and NMT 107.0% of the labeled amount of chlordiazepoxide ($C_{16}H_{14}ClN_3O$: 299.76).

Method of preparation Prepare as directed under Powders, with Chlordiazepoxide.

Identification (1) Weigh a portion of Chlordiazepoxide Powder, equivalent to 10 mg of chlordiazepoxide according to the labeled amount, add 100 mL of 0.1 mol/L hydrochloric acid TS, shake to mix, and filter. Add 0.1 mol/L hydrochloric acid TS to 5 mL of the filtrate to make 100 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 244 nm and 248 nm and between 306 nm and 310, and a minimum between 288 nm and 292 nm.

(2) Weigh a portion of Chlordiazepoxide Powder, equivalent to 20 mg of chlordiazepoxide according to the labeled amount, add 10 mL of methanol, and shake for 5 minutes to mix. Then, filter by suction through a glass filter, and evaporate the filtrate with the aid of a current of nitrogen to dryness. Dry the residue in vacuum at 60 ºC for 1 hour and determine the absorption spectrum of the residue as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy: it exhibits absorption at the wave numbers of about 1625 cm^{-1}, 1465 cm^{-1} 1265 cm^{-1}, 850 cm^{-1} and 765 cm^{-1}.

Purity ***Related substances***—Perform the test using light-resistant containers. Weigh an amount, equivalent to 50 mg of chlordiazepoxide, according to the labeled amount of Chlordiazepoxide Powder, add exactly 5 mL of a mixture of methanol and ammonia TS (97 : 3), shake to mix, centrifuge, and use the clear supernatant as the test solution Separately, weigh 50.0 mg of chlordiazepoxide RS, dissolve in a mixture of methanol and ammonia TS (97 : 3) to make exactly 50 mL, and use this solution as the standard solution (1). Weigh 5.0 mg of 2-amino-5-chlorobenzophenone RS, dissolve in methanol

to make exactly 200 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 25 μL of the test solution and 10 μL each of the standard solutions (1) and (2) on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Proceed as directed under the Purity (2) under Chlordiazepoxide.

Particle size distribution estimation by analytical sieving Meets the requirements.

Uniformity of dosage units (divided) Meets the requirements.

Assay Perform the test using light-resistant containers. Weigh accurately an amount of Chlordiazepoxide Powder, equivalent to about 0.1 g of chlordiazepoxide ($C_{16}H_{14}ClN_3O$), transfer into a stoppered flask, and add exactly 10 mL of water to wet. Then add exactly 90 mL of methanol, stopper, shake vigorously for 15 minutes, and centrifuge. Pipet 10 mL of the clear supernatant, add exactly 5 mL of the internal standard solution, add methanol again to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of chlordiazepoxide RS (previously dried in a phosphorus pentoxide desiccator in vacuum at 60 ºC for 4 hours), and dissolve in exactly 10 mL of water and 90 mL of methanol. Pipet 10 mL of this solution, put exactly 5 mL of the internal standard solution, add methanol again to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios of the peak area, Q_T and Q_S, of chlordiazepoxide to that of the internal standard for the test solution and the standard solution, respectably.

$$\text{Amount (mg) of chlordiazepoxide } (C_{16}H_{14}ClN_3O) = \text{Amount (mg) of chlordiazepoxide RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of isobutyl salicylate in methanol (1 in 20).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 25 to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of methanol and 0.02 mol/L ammonium dihydrogenphosphate TS (7:3).

Flow rate: Adjust the flow rate so that the retention time of chlordiazepoxide is about 5 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution under the above conditions; Chlordiazepoxide and the internal standard are eluted in this order with the resolution being NLT 9.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak area of chlordiazepoxide to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Chlordiazepoxide Tablets
클로르디아제폭시드 정

Chlordiazepoxide Tablets contain NLT 93.0% and NMT 107.0% of chlordiazepoxide ($C_{16}H_{14}ClN_3O$: 299.76) of the labeled amount.

Method of preparation Prepare as directed under Tablets, with Chlordiazepoxide.

Identification (1) Weigh the amount, equivalent to 10 mg of chlordiazepoxide according to the labeled amount of Chlordiazepoxide Tablets, previously powdered, add 100 mL of 0.1 mol/L hydrochloric acid TS, shake to mix, and filter. Add 0.1 mol/L hydrochloric acid TS to 5 mL of the filtrate to make 100 mL. Determine the absorption spectrum of the solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 244 nm and 248 nm and between 306 nm and 310 nm; it exhibits a minimum between 288 nm and 292 nm.

(2) Weigh the amount, equivalent to 10 mg of chlordiazepoxide according to the labeled amount of Chlordiazepoxide Tablets, previously powdered, add 10 mL of ether to shake vigorously, and centrifuge. Pipet 5 mL of the clear supernatant, and evaporate ether by heating in the water bath.

(3) Determine the infrared spectra of the residues as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; it exhibits absorption at the wavenumbers of about 1625 cm^{-1}, 1465 cm^{-1}, 1265 cm^{-1}, 850 cm^{-1} and 765 cm^{-1}.

Purity ***Related substances***—Perform the test, using light-resistant containers. Weigh the amount, equivalent to 50 mg of chlordiazepoxide according to the labeled amount of Chlordiazepoxide Tablets, previously powdered, add exactly 5 mL of a mixture of methanol and ammonia TS (97 : 3), shake to mix, centrifuge, and use the clear supernatant as the test solution. Separately, weigh 50 mg of chlordiazepoxide RS, and dissolve in a mixture of methanol and ammonia RS (97 : 3) to make exactly 50 mL, and use this solution as the standard solution (1). Again, weigh 5.0 mg of 2-amino-5-

chlorobenzophenone RS, dissolve in methanol to make exactly 200 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 25 μL of the test solution and 10 μL each of the standard solution (1) and (2) on the plate made of silica gel with fluorescent indicator for thin-layer chromatography. Perform the test as directed under the Purity (2) of Chlordiazepoxide.

Dissolution Perform the test with 1 tablet of Chlordiazepoxide Tablets at 100 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of Solution 2 as the dissolution solution. Take NLT 30 mL of the dissolved solution after 60 minutes from the start of the Dissolution, and filter through a membrane filter with a pore size of NMT 0.8 μm. Discard the first 10 mL of the filtrate, pipet V mL of the subsequent filtrate, and add Solution 2 for the Dissolution to obtain exactly V′ mL of a solution containing about 3.7 μg of chlordiazepoxide ($C_{16}H_{14}ClN_3O$) per mL according to the labeled amount, and use the clear supernatant as the test solution. Separately, weigh accurately about 12 mg of chlordiazepoxide for Assay (previously dried in a phosphorus pentoxide desiccator in vacuum at 60 ºC for 4 hours), and dissolve in Solution 2 for the Dissolution to make exactly 200 mL. Pipet 3 mL of this solution, add Solution 2 for the Dissolution to make exactly 50 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 260 nm as directed under the Ultraviolet-visible Spectroscopy.
Meets the requirements if the dissolution rate of Chlordiazepoxide Tablets in 60 minutes is NLT 70%.

Dissolution rate (%) with respect to the labeled amount of chlordiazepoxide ($C_{16}H_{14}ClN_3O$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 10$$

W_S: Amount (mg) of chlordiazepoxide RS
C: Labeled amount (mg) of chlordiazepoxide ($C_{16}H_{14}ClN_3O$) in 1 tablet

Uniformity of dosage units Meets the requirements.

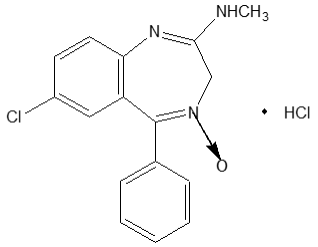
Assay Perform this procedure, using light-resistant containers. Take the number of tablets equivalent to 0.1 g of chlordiazepoxide ($C_{16}H_{14}ClN_3O$) of Chlordiazepoxide Tablets, add 10 mL of water, and shake well to disintegrate. Next, add 60 mL of methanol to shake well, add again methanol to make exactly 100 mL, and centrifuge. Take exactly 10 mL of the clear supernatant, add exactly 5 mL of the internal standard solution, add methanol to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of chlordiazepoxide RS (previously dried in a phosphorus pentoxide desiccator in vacuum at 60 ºC for 4 hours), dissolve in 1 mL of water and methanol, add exactly 5 mL of the internal standard solution, add methanol to make 100 mL, and use this solution as the standard solution. Perform the test as directed under the Assay of Chlordiazepoxide Acid.

Amount (mg) of chlordiazepoxide ($C_{16}H_{14}ClN_3O$)
= Amount (mg) of chlordiazepoxide RS $\times \frac{Q_T}{Q_S} \times 10$

Internal standard solution—A solution of Isobutyl salicylate in methanol (1 in 20).

Packaging and storage Preserve in light-resistant, tight containers.

Chlordiazepoxide Hydrochloride
클로르디아제폭시드염산염



$C_{16}H_{14}ClN_3O \cdot HCl$: 336.22
7-Chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine-4-oxide monohydrochloride [*438-41-5*]

Chlordiazepoxide Hydrochloride contains NLT 98.0% and NMT 102.0% of chlordiazepoxide hydrochloride ($C_{16}H_{14}ClN_3O \cdot HCl$), calculated on the dried basis.

Description Chlordiazepoxide Hydrochloride occurs as a white, crystalline powder and is odorless.
It is soluble in water or ethanol(95) and practically insoluble in hexane.
It is affected by light.

Identification (1) To about 20 mg of Chlordiazepoxide Hydrochloride, add 5 mL of hydrochloric acid and 10 mL of water, and heat to hydrolyze. After cooling, add 2 mL of sodium nitrite solution (1 in 1000), 1 mL of ammonium sulfamate solution (1 in 200) and 1 mL of N-1-naphthylethylenediamine dihydrochloride solution (1 in 1000); the solution exhibits a purple color.

(2) The retention times of the major peaks obtained from the test solution and the standard solution under the Assay are the same.

(3) Determine the infrared spectra of Chlordiazepoxide Hydrochloride and chlordiazepoxide hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 212 and 218 ℃ (with decompo-

sition).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Chlordiazepoxide Hydrochloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Weigh about 50 mg of Chlordiazepoxide Hydrochloride, transfer into an Erlenmeyer flask, and add 2.5 mL of acetone, and shake to mix. Allow to stand until insoluble substances settle and use the clear supernatant as the test solution. Separately, weigh an appropriate amount 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one-4-oxide RS, dissolve in acetone to prepare a solution containing 100 μg per mL, and use this solution as the standard solution (1). Weigh an appropriate amount of 2-amino-5-chlorobenzophenone RS, dissolve in acetone to prepare a solution containing 10 μg per mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 50 μL of the test solution and 10 μL each of the standard solutions (1) and (2) on a plate made of silica gel for the Thin-layer chromatography. Develop the plate in a developing chamber, previously not equilibrated with the developing solvent, with ethyl acetate to about three-fourths of the plate, and air-dry the plate. Spray evenly 1 mol/L sulfuric acid in the plate, dry the plate at 105 ºC for 15 minutes, and then spray evenly sodium nitrite (1 in 1000), ammonium sulfamate (1 in 200) and N-(1-naphthyl)ethylenediamine hydrochloric acid (1 in 1000) ; the spots from the test solution, equivalent to those from the standard solutions, are not greater or more intense than the spots from the standard solutions (1) and (2).

Loss on drying NMT 0.5% (1 g, in vacuum, phosphorus pentoxide, 60 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Perform the procedure, protected from direct sunlight. Weigh about 0.1 g of Chlordiazepoxide Hydrochloride, add the mobile phase, sonicate for 5 minutes to dissolve, and make exactly 50 mL. Take exactly 10 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the test solution Separately, weigh accurately an amount of chlordiazepoxide hydrochloride RS, dissolve in the mobile phase to make a solution containing 2 mg per mL. Pipet 10 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under Liquid Chromatography according to the following conditions. Measure the peak areas, A_T and A_S, of Chlordiazepoxide Hydrochloride, for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of Chlordiazepoxide Hydrochloride} = 0.5 \times C \times \frac{A_T}{A_S}$$

C: Concentration (μg/mL) of the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of methanol and water (60:40).

Flow rate: 1 mL/min

System suitability

System performance: Proceed with 5 μL of the standard solution under the above operating conditions; the number of theoretical plates and symmetry factor are NLT 3600 and NMT 2.0, respectively.

System repeatability: Repeat the test 5 times with 5 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area for chlordiazepoxide hydrochloride is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Chlordiazepoxide Hydrochloride Capsules
클로르디아제폭시드염산염 캡슐

Chlordiazepoxide Hydrochloride Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of chlordiazepoxide hydrochloride ($C_{16}H_{14}ClN_3$: 336.22).

Method of preparation Chlordiazepoxide Hydrochloride Capsules are prepared as directed under Tablets, with Chlordiazepoxide Hydrochloride.

Identification (1) Determine the absorption spectrum of the test solution obtained from the Assay as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima at the wavelengths of 245 ± 2 nm and 311 ± 2 nm, and absorbance ratio is 2.90 to 3.45.

(2) Take an appreciate amount of the contents of Chlordiazepoxide Hydrochloride Capsules, and perform the test as directed under the Identification (1) of Chlordiazepoxide Hydrochloride.

Purity ***Related substances***—Weigh an amount of Chlordiazepoxide Hydrochloride Capsules equivalent to 25 mg of Chlordiazepoxide Hydrochloride according to the labeled amount, and perform the test as directed under the Purity (2) of Chlordiazepoxide Hydrochloride. Use 15 μL of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one-4-oxide in acetone (1 in 1000) and 10 μL

of 2-amino-5-chloro-benzophenone in acetone (1 in 20000).

Dissolution Take 1 capsule of Chlordiazepoxide Hydrochloride Capsules, proceed with 900 mL of water as the dissolution medium at 100 revolutions per minute according to Method 1, and perform the test. Take the dissolved solution after 30 minutes from the start of the test, and pass through a membrane filter with a pore size of NMT 0.8 μm. Pipet *V mL* of the filtrate, add water to prepare exactly *V′* mL of a solution having known concentration of about 6 μg of Chlordiazepoxide Hydrochloride per mL, and use this solution as the test solution. Separately, weigh accurately about 30 mg of chlordiazepoxide hydrochloride RS, and dissolve in water acid to make exactly 100 mL. Pipet 2 mL of the resulting solution, and add water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength of about 245 nm, using water as the blank, as directed under Ultraviolet-visible Spectrophotometry. Remove the contents of 12 Chlordiazepoxide Hydrochloride Capsules as completely as possible with the aid of a current of air, determine the absorbance at the same dilution and in the same manner as for the Capsules and make any necessary modifications.

It meets the requirements if the dissolution rate of Chlordiazepoxide Hydrochloride Capsules for 30 minutes is NLT 85%.

Dissolution rate (%) of the labeled amount of Chlordiazepoxide Hydrochloride Capsules ($C_{16}H_{14}ClN_3O \cdot HCl$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{90}{C} \times \frac{1}{5}$$

W_S: Amount (mg) of chlordiazepoxide hydrochloride RS

C: Labeled amount (mg) of chlordiazepoxide hydrochloride ($C_{16}H_{14}ClN_3O \cdot HCl$) per tablet

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to following method.

Perform the test using a light-resistant container. Transfer the contents of 1 capsule to a 200-mL volumetric flask, dissolve in and dilute with water to volume, and filter, discarding the first 20 mL of the filtrate. Dilute a portion of the filtrate quantitatively and step-wise with 0.1N hydrochloric acid to obtain a solution having a concentration of about 6 μg of Chlordiazepoxide Hydrochloride per mL. Dissolve a suitable quantity of Chlordiszeposide Hydrocholride RS, accurately weighed, in 0.1 N hydrochloric acid to obtain a standard solution having a known concentration of about 6 μg per mL. Concomitantly determine the absorbances A_T and A_S of the test solution and the standard solution at the absorbance maximum wavelength of about 245nm, with a suitable spectrophotometer, using 0.1 mol/L hydrochloric acid as the blank.

Amount (mg) of chlordiazepoxide hydrochloride ($C_{16}H_{14}ClN_3O \cdot HCl$) in 1 capsule of Chlordiazepoxide Hydrochloride Capsules

$$= \frac{T}{D} \times C \times \frac{A_T}{A_S}$$

T: Labeled amount (mg) of chlordiazepoxide hydrochloride in 1 capsule

D: Concentration (μg/mL) of chlordiazepoxide hydrochloride in the test solution calculated according to the labeled amount

C: Concentration (μg/mL) of the standard solution

Assay Perform the test using light-resistant containers. Weigh accurately the contents of NLT about 20 Chlordiazepoxide Hydrochloride Capsules and determine the average weight per capsule. Mix the combined contents and transfer an accurately weighed portion of the powder, equivalent to about 60 mg of chlordiazepoxide hydrochloride (C16H14ClN3O·HCl), to a volumetric flask. Add methanol to make 100 mL, mix and filter and discard the first 15 mL of the filtrate. Pipet 5 mL of the clear filtrate into a volumetric flask and add sulfuric acid in ethanol (1 in 360) to make 100 mL. Pipet 10 mL of this solution into a volumetric flask and dilute with sulfuric acid in ethanol (1 in 360) to make 50 mL and use this solution as the test solution. Dissolve an accurately a portion of Chlordiazepoxide Hydrochloride in methanol to obtain a solution having a known concentration of about 60 mg per mL. Dilute this solution quantitatively and step-wise with sulfuric acid in ethanol (1 in 360) to obtain a standard solution having a known concentration of about 6 μg per mL. Concomitantly determine the absorbances of the test solution and the standard solution at the absorbance maximum wavelength at about 245 nm, as directed under Ultraviolet-visible Spectrophotometry, using sulfuric acid in ethanol (1 in 360) as the blank. Calculate the absorbances, A_T and A_S, for the test solution and the standard solution, respectively.

Amount (mg) of chlordiazepoxide hydrochloride ($C_{16}H_{14}ClN_3O \cdot HCl$)

$$= 10 \times C \times \frac{A_T}{A_S}$$

C: Concentration (μg/mL) of the standard solution

Packaging and storage Preserve in light-resistant, tight containers.

Chlordiazepoxide Hydrochloride for Injection
주사용 클로르디아제폭시드염산염

Chlordiazepoxide Hydrochloride for Injection is a preparation for injection, which is dissolved before use. It

contains NLT 93.0% and NMT 107.0% of the labeled amount of chlordiazepoxide hydrochloride ($C_{16}H_{14}ClN_3O \cdot HCl$: 336.22).

Method of preparation Prepare as directed under Injections, with Chlordiazepoxide Hydrochloride.

Description Lincomycin Hydrochloride Hydrate occurs as a white crystalline powder and is odorless.
It is soluble in water and ethanol(95) and practically insoluble in hexane.
It is affected by light.

Identification Perform the test as directed under the Identification under Chlordiazepoxide Hydrochloride.

pH Dissolve 1.0 g of Chlordiazepoxide Hydrochloride for Injection in 100 mL of water; the pH of the solution is between 2.5 and 3.5.

Purity ***Heavy metals and related substances***—Perform the tests as directed under the Purity (1) and (2) under Chlordiazepoxide Hydrochloride.

Loss on drying NMT 0.5% (1 g, in vacuum, phosphorus pentoxide, 60 ℃, 4 hours).

Sterility Meets the requirements.

Bacterial endotoxins Less than 3.57 EU per mg of chlordiazepoxide hydrochloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay under Chlordiazepoxide Hydrochloride.

Packaging and storage Preserve in light-resistant, hermetic containers.

Chlorhexidine Gluconate Solution
클로르헥시딘글루콘산염 액

Chlorhexidine Gluconate Solution is an aqueous solution of 2-gluconate of chlorhexidine.

Chlorhexidine Gluconate Solution contains NLT 19.0 w/v% and NMT 21.0 w/v% of chlorhexidine gluconate ($C_{22}H_{30}Cl_2N_1 \cdot 2C_6H_{12}O_7$: 897.76).

Description Chlorhexidine Gluconate Solution occurs as a clear, colorless to pale yellow liquid, is odorless, and has a bitter taste.
It is miscible with acetic acid(100) or water.
1 mL of Chlorhexidine Gluconate Solution is miscible with NMT 5 mL of ethanol(99.5) or NMT 3 mL of acetone, but a white turbidity is formed with the addition of these solvents.
It is gradually colored by light.

Specific gravity—d_{20}^{20}: Between 1.06 and 1.07.

Identification (1) To 0.05 mL of Chlorhexidine Gluconate Solution, add 5 mL of methanol, 1 mL of bromine TS and 1 mL of 8 mol/L sodium hydroxide TS; the solution exhibits a deep red color.

(2) To 0.5 mL of Chlorhexidine Gluconate Solution, add 10 mL of water and 0.5 mL of copper(II) sulfate TS; a white precipitate is formed. Heat to boiling; the precipitate changes to pale violet.

(3) To 10 mL of Chlorhexidine Gluconate Solution, add 5 mL of water, cool in iced water, and slowly add 5 mL of sodium hydroxide TS while stirring to mix; a white precipitate is formed. Filter this solution, wash the residue with water, and recrystallize from diluted ethanol (7 in 10), and dry at 105℃ for 30 minutes; the crystals obtained melt between 130 and 134 ℃.

(4) Neutralize the filtrate in (3) using 5 mol/L hydrochloric acid TS. To 5 mL of the resulting solution, add 0.65 mL of acetic acid(100) and 1 mL of freshly distilled phenylhydrazine, heat on a steam bath for 30 minutes and cool, and scratch the inner wall with a glass rod; crystals are formed. Collect the crystals, dissolve in 10 mL of hot water, add a small amount of activated charcoal, and filter. After cooling, scratch the inner wall with a glass rod, collect the formed crystals, and dry; the crystals obtained melt at about 195℃ (with decomposition).

pH Dissolve about 5.0 mL of Chlorhexidine Gluconate Solution in 100 mL of water; the pH of this solution is between 5.5 and 7.0.

Purity (1) **4-*Chloroaniline***—Dissolve 2.0 mL of Chlorhexidine Gluconate Solution in water to make exactly 100 mL. Take exactly 5 mL of this solution, add 20 mL of water, 5 mL of 1 mol/L hydrochloric acid TS and 0.3 mL of sodium nitrite TS, shake to mix, and allow to stand for 2 minutes. Next, add 4 mL of ammonium sulfamate TS, and allow to stand for 1 minute. Next, add 5 mL of oxalic acid *N*-(1-naphthyl)-*N'*-diethylethylenediamine-acetone TS, allow to stand for 10 minutes, and add 1 mL of ethanol(95) and water to make 50 mL; the color of the resulting solution is not more intense than the following control solution.

Control solution—Dissolve 20 mg of 4-chloroaniline in 10 mL of 1 mol/L hydrochloric acid TS, and add water to make exactly 100 mL. Pipet 5 mL of this solution and add water to make exactly 100 mL. To 5 mL of this solution, add 20 mL of water and 5 mL of 1 mol/L hydrochloric acid TS, and proceed in the same manner as the above.

(2) ***Related substances***—Pipet 5.0 mL of Chlorhexidine Gluconate Solution and add water to make 100 mL. Take exactly 5 mL of this solution, transfer to a 25 mL volumetric flask, and add diluent to make a solution containing about 2 mg of chlorhexidine gluconate per mL, use this solution as the test solution. Pipet 3.0 mL of the test solution, add diluent to make 100 mL, and use this solution as the standard solution (1). Pipet 2.0 mL of the standard solution (1), add diluent to make 100 mL, and use this solution as the standard solution (2). Perform the test with 20 μL each of the test solution, the standard solutions (1) and (2) as directed under the Liquid Chromatography according to the following operating conditions. Determine the peak area of each solution by the automatic integration method; the total area of peaks other than chlorhexidine obtained from the test solution is not larger than the peak area of chlorhexidine from the standard solution (1) (3.0%). However, disregard any peak having an area smaller than the peak area of chlorhexidine from the standard solution (2).

Diluent—Dissolve 27.6 g of sodium dihydrogen phosphate dihydrate in 1500 mL of water, adjust the pH to 3.0 with phosphoric acid, and add water to make 2000 mL.

Operating conditions

Proceed as directed under the operating conditions under the Assay.

Residue on ignition NMT 0.1% (0.2 g, after evaporation).

Assay Pipet 5.0 mL of Chlorhexidine Gluconate Solution, and add water to make exactly 250 mL. Pipet 5 mL of this resulting solution, add diluent to make exactly 250 mL, and use this solution as the test solution. Separately, weigh accurately 100 mg of chlorhexidine acetate RS, and dissolve in water to make 100 mL. Pipet 5 mL of this solution, add diluent to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak areas, A_T and A_S, of chlorhexidine from the test solution and the standard solution, respectively.

The amount (w/v%) of chlorhexidine gluconate ($C_{22}H_{30}Cl_2N_1 \cdot 2C_6H_{12}O_7$) in Chlorhexidine Gluconate Solution

$$= \frac{897.76}{625.55} \times 0.25 \times C \times \frac{A_T}{A_S}$$

899.76: Molecular weight of chlorhexidine gluconate

625.55: Molecular weight of chlorhexidine acetate

C: Concentration (μg/mL) of chlorhexidine acetate in standard solution

Diluent—Dissolve 27.6 g of sodium dihydrogen phosphate dihydrate in 1500 mL of water, adjust the pH to 3.0 with phosphoric acid, and add water to make 2000 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 239 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: A mixture of a solution, prepared by dissolving 27.6 g of sodium dihydrogen phosphate dihydrate and 10 mL of triethylamine in 1500 mL of water, adjusting the pH to 3.0 with phosphoric acid, and adding water to make 2000 mL, and acetonitrile (70:30).

Mobile phase B: Acetonitrile

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 9	100	0
9 - 10	100 → 45	0 → 55
10 - 15	45	55
15 - 16	45 → 100	55 → 0
16 - 21	100	0

Flow rate: 1.5 mL/min

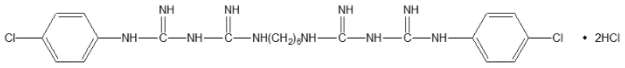
System suitability

System performance: Dissolve 0.1 mg of chlorhexidine acetate RS and 0.1 mg of 4-chloroaniline in 100 mL of diluent, and use this solution as the system suitability solution Proceed with 50 μL of system suitability solution according to the above conditions; the resolution between chlorhexidine and 4-chloroaniline is NLT 3.

System repeatability: Repeat the test 6 times with 50 μL of the system suitability solution according to the above operating conditions; the relative standard deviations of the peak areas of chlorhexidine and 4-chloroaniline are NMT 2.0% and 5.0%, respectively.

Packaging and storage Preserve in light-resistant, tight containers.

Chlorhexidine Hydrochloride
클로르헥시딘염산염



$C_{22}H_{30}Cl_2N_{10}\cdot 2HCl$: 578.37

N-(4-Chlorophenyl)-1-3-(6-{*N*-[3-(4-chlorophenyl)carbamimidamidomethanimidoyl]amino}hexyl)carbamimidamido-methanimidamide hydrochloride [*3697-42-5*]

Chlorhexidine Hydrochloride, when dried, contains NLT 98.0% and NMT 101.0% of chlorhexidine hydrochloride ($C_{22}H_{30}Cl_2N_{10}\cdot 2HCl$).

Description Chlorhexidine Hydrochloride occurs as a white, crystalline powder, which is odorless and has a bitter taste.
It is soluble in formic acid, slightly soluble in methanol or warm methanol, and practically insoluble in water, ethanol(95) or ether.
It is gradually colored by light.

Identification (1) Dissolve 10 mg of Chlorhexidine Hydrochloride in 5 mL of methanol by warming, and add 1 mL of bromine TS and 1 mL of 8 mol/L sodium hydroxide TS; the solution exhibits a deep red color.

(2) Dissolve 0.3 g of Chlorhexidine Hydrochloride in 10 mL of 6 mol/L hydrochloric acid TS, cool in iced water, and slowly add 10 mL of 8 mol/L sodium hydroxide TS while stirring to mix; a white precipitate develops. Filter the precipitate, wash the residue with water, and recrystallize from diluted ethanol (7 in 10), and dry at 105℃ for 30 minutes; the crystals obtained melt between 130 and 134 ℃.

(3) Dissolve 0.1 g of Chlorhexidine Hydrochloride in 50 mL of dilute nitric acid; the resulting solution responds to the Qualitative Analysis for chloride.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Chlorhexidine Hydrochloride according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Put 1.0 g of Chlorhexidine Hydrochloride into a crucible, add 10 mL of a solution of magnesium nitrate in ethanol(95) (1 in 10), fire ethanol to combust, and heat gradually to incinerate. If a carbonized substance remains, moisten with a small amount of nitric acid, and ignite again to incinerate. After cooling, add 10 mL of dilute hydrochloric acid to the residue, warm on a steam bath to dissolve, use this solution as the test solution, and perform the test (NMT 2 ppm).

(3) ***Related substances***—Weigh accurately about 0.2 g of Chlorhexidine Hydrochloride, dissolve in the mobile phase A to make 100 mL, and use this solution as the test solution. Separately, pipet 3.0 mL of the test solution, add the mobile phase A to make exactly 100 mL, and use this solution as the standard solution (1). Pipet 2 mL of this solution, add the mobile phase A to make exactly 100 mL, and use this solution as the standard solution (2). Perform the test with 20 μL each of the test solution, the standard solution (1) and the standard solution (2) as directed under the Liquid Chromatography according to the following conditions; the total amount of related substances is NMT 3.0%. However, disregard any peak with an area less than that of the major peak from the standard solution (2).

$$\text{Content (\%) of each related substance} = 100 \times \frac{A_T}{A_S} \times \frac{C_S}{C_T}$$

C_S: Concentration (mg/mL) of chlorhexidine hydrochloride in the standard solution (1)

C_T: Concentration (mg/mL) of chlorhexidine hydrochloride in the test solution

A_T: Peak area of individual related substance in the test solution

A_S: Peak area of chlorhexidine in the standard solution (1)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 239 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: Dissolve 27.6 g of sodium dihydrogen phosphate dihydrate and 10 mL of triethylamine in 1500 mL of water, adjust the pH to 3.0 with phosphoric acid, and add water to make 2000 mL. Add 300 mL of acetonitrile to 700 mL of this solution.

Mobile phase B: Acetonitrile

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0	100	0
0 - 15	100	0
15 - 16	100 → 45	0 → 55
16 - 21	45	55
21 - 22	45 → 100	55 → 0
22 - 27	100	0

Flow rate: 1.5 mL/min

(4) ***4-Chloroaniline***—Dissolve 0.1 g of Chlorhexidine Hydrochloride in 2 mL of formic acid, immediately add 15 mL of 1 mol/L hydrochloric acid TS and 20 mL of water, add 0.3 mL of sodium nitrite TS, shake to mix, and allow to stand for 2 minutes. Next, add 4 mL of ammonium sulfamate TS, allow to stand for 1 minute, add 5 mL of oxalic acid *N*-(1-naphthyl)-*N'*-diethylethylenediamine-acetone TS, allow to stand for 10 minutes, and add 1 mL

of ethanol(95) and water to make 50 mL; the color of the resulting solution is not more intense than the following control solution.

Control solution—Dissolve 20 mg of 4-chloroaniline in 10 mL of 1 mol/L hydrochloric acid TS, and add water to make exactly 100 mL. Pipet 5 mL of this solution and add water to make exactly 100 mL. To 2.0 mL of this solution, add 2 mL of formic acid, 15 mL of 1 mol/L hydrochloric acid TS and 20 mL of water, and proceed in the same manner as the above.

Loss on drying NMT 2.0% (1 g, 130 ℃, 2 hours).

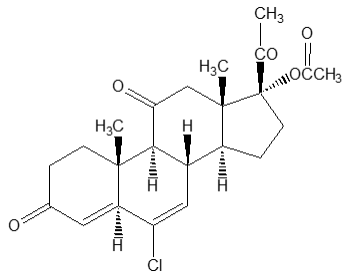
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Chlorhexidine Hydrochloride, previously dried, dissolve in 2.0 mL of formic acid, add 60 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 14.459 mg of $C_{22}H_{30}Cl_2N_{10}\cdot 2HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Chlormadinone Acetate
클로르마디논아세테이트



$C_{23}H_{29}ClO_4$: 404.93

[(8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-Acetyl-6-chloro-10,13-dimethyl-3-oxo-2,8,9,11,12,14,15,16-octahydro-1*H*-cyclopenta[a]phenanthren-17-yl]acetate [*302-22-7*]

Chlormadinone Acetate, when dried, contains NLT 98.0% and NMT 101.0% of chlormadinone acetate ($C_{23}H_{29}ClO_4$).

Description Chlormadinone Acetate occurs as white to pale yellow crystals or a crystalline powder and is odorless.

It is freely soluble in chloroform, soluble in acetonitrile (95), slightly soluble in ethanol(95) or ether and practically insoluble in water.

Identification (1) Dissolve 2 mg of Chlormadinone Acetate in 1 mL of ethanol(95) and add 1 mL of 1,3-dinitrobenzene TS and 1 mL of potassium hydroxide solution (1 in 5); the resulting solution exhibits a purple color.

(2) Add 2 mL of potassium hydroxide-ethanol TS to 50 mg of Chlormadinone Acetate and boil on a steam bath for 5 minutes. After cooling, add 2 mL of diluted sulfuric acid (2 in 7) and boil gently for 1 minute; the odor of ethyl acetate is perceptible.

(3) Determine the infrared spectra of Chlormadinone Acetate and chlormadinone acetate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) Perform the Flame Coloration (2) with Chlormadinone Acetate; it exhibits a green color.

Optical rotation $[\alpha]_D^{20}$: Between -10.0° and -14.0° (0.2 g after drying, acetonitrile, 10 mL, 100 mm).

Melting point Between 211 and 215 ºC.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Chlormadinone Acetate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Prepare the test solution with 1.0 g of Chlormadinone Acetate according to Method 3 and perform the test (NMT 2 ppm).

(3) ***Related substances***—Dissolve 20 mg of Chlormadinone Acetate in 10 mL of acetonitrile and use this solution as the test solution. Pipet 1 mL of this solution, add acetonitrile to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of each solution according to the automatic integration method; the total area of peaks other than the peak of Chlormadinone Acetate from the test solution is not larger than the peak area of Chlormadinone Acetate from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 236 nm).

Column: A stainless steel column about 6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of acetonitrile and water (13 : 7).

Flow rate: Adjust the flow rate so that the retention time of Chlormadinone Acetate is about 10 minutes.

System suitability

Test for required detectability: Pipet 5 mL of the standard solution and add acetonitrile to make exactly 50 mL. Confirm that the peak area of Chlormadinone Acetate obtained from 10 mL of this solution is within the range of 7 to 13% of the peak area of Chlormadinone Acetate obtained from the standard solution.

System performance: Dissolve 8 mg of Chlormadinone Acetate and 2 mg of butyl p-hydroxybenzoate in 100 mL of acetonitrile. Proceed with 10 μL of this solution under the above operating conditions; butyl p-hydroxybenzoate and Chlormadinone Acetate are eluted in this order with the resolution being NLT 8.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of Chlormadinone Acetate is NMT 1.0%.

Time span of measurement: About 1.5 times the retention time of Chlormadinone Acetate after the solvent peak.

Loss on drying NMT 0.5% (0.5 g, in vacuum, phosphorus pentoxide, 4 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately about 20 mg each of Chlormadinone Acetate and chlormadinone acetate RS and dissolve in ethanol(95) to make exactly 100 mL. Pipet 5 mL each of these solutions, add ethanol(95) to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively at 285 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of chlormadinone acetate ($C_{23}H_{29}ClO_4$)
= Amount (mg) of chlormadinone acetate RS$\times \frac{A_T}{A_S}$

Packaging and storage Preserve in light-resistant, tight containers.

Chlorophyllin Copper Complex Sodium
클로로필린구리나트륨착염

Chlorophyllin Copper Complex Sodium is a sodium salt of chlorophyllin, obtained from chlorophyll by copper substitution.

Description Chlorophyllin Copper Complex Sodium is a bluish green to blackish green powder, and is odorless or has a slightly characteristic odor.
It is freely soluble in water and practically insoluble in ethanol or ether.
The pH of an aqueous solution of Chlorophyllin Copper Complex Sodium (1 in 100) is between 9.5 and 11.0.
It is hygroscopic.

Identification (1) Wet 1.0 g of Chlorophyllin Copper Complex Sodium with a small amount of sulfuric acid and slowly heat at a low temperature as much as possible to nearly ash. After cooling, wet it with a small amount of sulfuric acid and slowly heat until no white fumes appear. Then, ignite at 450 to 500 ℃ to make the residue completely ash. After cooling, put 10 mL of dilute hydrochloric acid and heat on a steam bath to dissolve, and filter, if necessary. Add water to make 10 mL and use this solution as the test solution. To 5 mL of the test solution, add 0.5 mL of sodium diethyldithiocarbamate TS; the resulting solution produces a brown precipitate.

(2) Take the test solution from (1) and perform the test according to the flame coloration of metal salt under the Flame Coloration; it exhibits a green color at first, and then a yellow color.

(3) With the test solution in the absorbance, determine the absorption spectrum according to the Ultraviolet-visible Spectroscopy; it exhibits absorption maxima, A_1 and A_2, between 403 nm and 407 nm and between 627 nm and 633 nm, respectively. And A_1/A_2 is 3.2 to 4.0 at the absorbance maximum wavelength.

Absorbance Weigh accurately about 0.1 g of Chlorophyllin Copper Complex Sodium and dissolve by adding water to make 100.0 mL. Take 1.0 mL of this solution, add phosphate buffer solution, pH 7.5, to make 100.0 mL, and gently shake to mix. Use this solution as the test solution. Measure the absorbance at the absorbance maximum wavelength at around 405 nm as quickly as possible, and calculate $E_{1cm}^{1\%}$ on the dried basis; it is beween 508 and 650.

Purity (1) ***Free copper ion***—Dissovle 1.0 g of Chlorophyllin Copper Complex Sodium in 50 mL of water, and use this solution as the test solution. With this solution, spot 2 μL each of the test solutions and the copper standard solution on a plate made of silica gel for thin-layer chromatography according to the Thin Layer Chromatography. Develop the plate with a mixture of *n*-butanol, water and acetic acid(100) (4 : 2 : 1) to a distance of about 10 cm, and dry the plate at 105 °C for 10 minutes. Spray evenly sodium diethyldithiocarbamate TS (1 in 1000); the spots from the standard solution and the test solution have the same R_f value and the spot from the test solution is not more intense than that from the standard solution.

Copper standard solution—Weigh exactly 0.393 g of copper sulfate, put in 100-mL volumetric flask, and dissolve in 60 mL of diluted hydrochloric acid (1 in 100). Add 2 to 3 drops of diluted sulfuric acid (1 in 20), shake well to mix, and then add diluted hydrochloric acid (1 in 100) to make 100 mL. Each mL of this solution contains 1 mg of copper (Cu).

(2) ***Arsenic***—Proceed with 0.5 g of Chlorophyllin Copper Complex Sodium according to Method 3 and

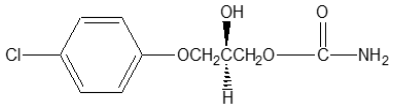
perform the test (NMT 4 ppm).

(3) ***Alkaline tar pigment***—Add 1 mL of sodium hydroxide (1 in 50) and 50 mL of ether to an aqueous solution (1 in 200) of Chlorophyllin Copper Complex Sodium, and shake to mix. Take the ether layer, wash twice with 15 mL of sodium hydroxide solution (1 in 50), add 5 mL of acetic acid(100) (1 in 10) diluted in ether, and shake to mix; the water layer is colorless.

Loss on drying NMT 5.0% (1 g, 105 °C, 2 hours).

Packaging and storage Preserve in tight containers.

Chlorphenesin Carbamate
클로르페네신카르바메이트



and enantiomer

$C_{10}H_{12}ClNO_4$: 245.66

[3-(4-Chlorophenoxy)-2-hydroxypropyl]carbamate [*886-74-8*]

Chlorphenesin Carbamate, when dried, contains NLT 98.0% and NMT 102.0% of chlorphenesin carbamate ($C_{10}H_{12}ClNO_4$).

Description Chlorphenesin Carbamate occurs as white crystals or a crystalline powder.
It is freely soluble in methanol, ethanol(95), or pyridine, and slightly soluble in water.
A solution of Chlorphenesin Carbamate in ethanol(95) (1 in 20) shows no optical rotation.

Identification (1) Determine the absorption spectra of solutions of Chlorphenesin Carbamate and chlorphenesin carbamate RS in ethanol(95) (3 in 200000) as directed under the Ultraviolet-visible spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Chlorphenesin Carbamate and chlorphenesin carbamate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Perform the Flame Coloration (2) with Chlorphenesin Carbamate; it exhibits a green color.

Melting point Between 88 and 91 ºC.

Purity (1) ***Heavy metals***—Weigh 2.0 g of Chlorphenesin Carbamate, dissolve in 20 mL of ethanol(95), and add 2 mL of dilute acetic acid and water to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution by adding 20 mL of ethanol(95), 2 mL of dilute acetic acid, and water to 2.0 mL of lead standard solution to make 50 mL (NMT 10 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Chlorphenesin Carbamate according to Method 3 and perform the test (NMT 2 ppm).

(3) ***Chlorphenesin-2-carbamate***—Dissolve 0.10 g of Chlorphenesin Carbamate in 20 mL of a mixture of hexane for liquid chromatography and 2-propanol (7 : 3), and use this solution as the test solution. With 10 μL of the test solution, perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the peak area, A_a, of chlorphenesin carbamate and the peak area, A_b, of chlorphenesin-2-carbamate as directed in the automatic integration method; the ratio, $A_b/(A_a + A_b)$, is not greater than 0.007.

Operating conditions

Detector: An ultraviolet photometer (wavelength: 280 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of hexane, 2-propanol, and acetic acid(100) (700 : 100 : 1).

Flow rate: Adjust the flow rate so that the retention time of chlorphenesin carbamate is about 9 minutes.

System suitability

Test for required detectability: Weigh 1 mL of the test solution, add a mixture of hexane for liquid chromatography and 2-propanol (7 : 3) to make 100 mL, and use this solution as the system suitability solution. Take 5 mL of the system suitability solution and add a mixture of hexane for liquid chromatography and 2-propanol (7 : 3) to make 10 mL. Confirm that the peak area of chlorphenesin carbamate obtained from 10 μL of this solution is between 40% and 60% of the peak area of chlorphenesin carbamate from the system suitability solution.

System performance: Dissolve 0.1 g of Chlorphenesin Carbamate in 50 mL of methanol. To 25 mL of this solution, add 25 mL of dilute sodium hydroxide TS and warm at 60 °C for 20 minutes. To 20 mL of this solution, add 5 mL of 1 mol/L hydrochloric acid TS, put 20 mL of ethyl acetate, and shake well to mix. Allow it to stand, and take the ethyl acetate layer separately. Proceed with 10 μL of this solution according to the above conditions; chlorphenesin, chlorphenesin carbamate and chlorphenesin-2-carbamate are eluted in this order with the relative retention times of chlorphenesin and chlorphenesin-2-carbamate to the retention time of chlorphenesin carbamate being about 0.7 and 1.2, respectively, and with the resolution of chlorphenesin and chlorphenesin carbamate being NLT 2.0.

System repeatability: Repeat the test 6 times with 10 μL of the system suitability solution according to the

above conditions; the relative standard deviation of the peak area of chlorphenesin carbamate is NMT 2.0%.

(4) ***Other related substances***—Dissolve 0.10 g of Chlorphenesin Carbamate in 10 mL of ethanol(95), and use this solution as the test solution. Pipet 1 mL of this solution, and add ethanol(95) to make exactly 20 mL. Pipet 2 mL of this solution, add ethanol(95) to make exactly 20 mL, and use this solution as the standard solution. With the test solution and the standard solution, perform the test as directed under the Thin Layer Chromatography. Spot 50 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, methanol, and ammonia water(28) (17 : 2 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Allow it to stand in iodine vapor for 20 minutes; the spot other than the principal spot obtained from the test solution is NMT 1, and not more intense than the spot from the standard solution.

Loss on drying NMT 0.2% (1 g, in vacuum, silica gel, 4 hours).

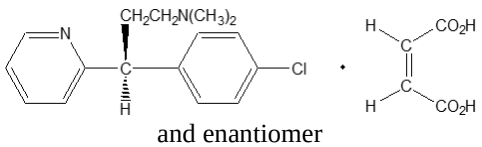
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Chlorphenesin Carbamate, previously dried, dissolve in 20 mL of pyridine, add exactly 50 mL of 0.1 mol/L potassium hydroxide-ethanol solution, and warm at 70 °C for 40 minutes. After cooling, add 100 mL of ethanol(95) and titrate an excessive amount of potassium hydroxide with 0.1 mol/L hydrochloric acid VS (indicator: 1 mL of thymol blue TS). The endpoint of the titration is when the color of the solution changes from blue through bluish green to yellow. Perform a blank test in the same manner.

Each mL of 0.1 mol/L potassium hydroxide-ethanol VS
= 24.566 mg of $C_{10}H_{12}ClNO_4$

Packaging and storage Preserve in tight containers.

Chlorpheniramine Maleate
클로르페니라민말레산염



and enantiomer

$C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$: 390.86
(*Z*)-but-2-Enedioic acid; [3-(4-chlorophenyl)-3-(pyridin-2-yl)propyl]dimethylamine [*113-92-8*]

Chlorpheniramine Maleate, when dried, contains NLT 98.0% and NMT 101.0% of *d*-chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$).

Description Chlorpheniramine Maleate occurs as white fine crystals.
It is very soluble in acetic acid(100), freely soluble in water or methanol, and sparingly soluble in ethanol(95).
It dissolves in dilute hydrochloric acid.
An aqueous solution of Chlorpheniramine Maleate (1 in 20) shows no optical rotation.

Identification (1) Determine the absorption spectra of the solutions of Chlorpheniramine Maleate and chlorpheniramine maleate RS in 0.1 mol/L hydrochloric acid TS (3 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Chlorpheniramine Maleate and chlorpheniramine maleate RS, previously dried, as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 0.1 g of Chlorpheniramine Maleate in 5 mL of methanol, and use this solution as the test solution. Separately, dissolve 56 mg of maleic acid in 10 mL of methanol, use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of ether, methanol, acetic acid(100) and water (70 : 20 : 7 : 3) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); of the two spots obtained from the test solution, one spot shows the same intensity as the spot obtained from the standard solution, and their R_f values are the same.

Melting point Between 130 and 135 °C.

pH Dissolve 1.0 g of Chlorpheniramine Maleate in 100 mL of newly boiled and cooled water; the pH of this solution is between 4.0 and 5.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Chlorpheniramine Maleate in 50 mL of water; the resulting solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Chlorpheniramine Maleate as directed under Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve 0.10 g of Chlorpheniramine Maleate in 100 mL of the mobile phase, and use this solution as the test solution. Pipet 3 mL of this solution, and add the mobile phase to make exactly 100 mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following con-

ditions. Determine the peak area of each solution by the automatic integration method; the peak area other than maleic acid and chlopheniramine obtained from the test solution is not greater than two thirds times the peak area of chlopheniramine from the standard solution. Also, the total area of peaks other than maleic acid and chlorpheniramine obtained from the test solution is not larger than the peak area of chlorpheniramine from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column 3.9 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 8.57 g of ammonium dihydrogen phosphate and 1 mL of phosphoric acid in water to make 1000 mL. To 800 mL of this solution, add 200 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of chlopheniramine is about 11 minutes.

System suitability

Test for required detectability: Weigh accurately 2.5 mL of the standard solution and add the mobile phase to make exactly 25 mL. Verify that the peak area of chlopheniramine obtained from 20 μL of this solution is equivalent to 7% - 13% of the peak area of chlopheniramine obtained from the standard solution.

System performance: Proceed with 20 μL of the standard solution under the above operating conditions; the number of theoretical plates and the symmetry factor of the peak of chlopheniramine are NLT 4000 plates and NMT 2.0, respectively.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of chlopheniramine is NMT 4.0%.

Time span of measurement: About 4 times -the retention time of chlopheniramine after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 °C, 3 hours).

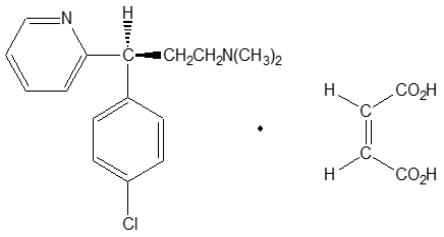
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Chlorpheniramine Maleate, previously dried, dissolve in 20 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of methylrosanilinium chloride TS). However, the endpoint of the titration is when the violet color of the solution turns to bluish green and then finally to green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 19.543 mg of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$

Packaging and storage Preserve in light-resistant, tight containers.

d-Chlorpheniramine Maleate
d-클로르페니라민말레산염



$C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$: 390.86

(*Z*)-but-2-Enedioic acid; (3*S*)-[3-(4-chlorophenyl)-3-(pyridin-2-yl)propyl]dimethylamine [*2438-32-6*]

d-Chlorpheniramine Maleate, when dried, contains NLT 99.0% and NMT 101.0% of *d*-chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$).

Description *d*-Chlorpheniramine Maleate occurs as a white crystalline powder.
It is odorless and has a bitter taste.
It is very soluble in methanol or acetic acid(100) and is freely soluble in dimethylformamide or ethanol(95).
It dissolves in dilute hydrochloric acid.

Identification (1) Determine the absorption spectra of the solutions of *d*-Chlorpheniramine Maleate and *d*-chlorpheniramine maleate RS in 0.1 mol/L hydrochloric acid TS (3 in 100000) as directed under the Ultraviolet-visible spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of *d*-Chlorpheniramine Maleate and *d*-chlorpheniramine maleate RS, previously dried, as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 0.1 g of *d*-Chlorpheniramine Maleate in 5 mL of methanol, and use this solution as the test solution. Separately, dissolve about 56 mg of maleic acid in 10 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of ether, methanol, acetic acid(100) and water (70 : 20 : 7 : 3) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); of the two spots obtained from the test solution, one spot shows the same intensity to the spot obtained from the standard solution,

and their R_f values are the same.

Optical rotation $[\alpha]_D^{20}$: Between +39.5° and +43.0° (0.5 g after drying, dimethylformamide, 10 mL, 100 mm).

Melting point Between 111 and 115 ℃.

pH Dissolve 1.0 g of *d*-Chlorpheniramine Maleate in 100 mL of newly boiled and cooled water; the pH of this solution is between 4.0 and 5.0.

Absorbance $E_{1cm}^{1\%}$ (265 nm): Between 210 nm and 220 nm (5 mg after drying, 0.25 mol/L sulfuric acid TS, 250 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of *d*-Chlorpheniramine Maleate in 50 mL of water; the resulting solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of *d*-Chlorpheniramine Maleate according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve about 0.10 g of *d*-Chlorpheniramine Maleate in 100 mL of the mobile phase and use this solution as the test solution. Pipet 3 mL of this solution, and add the mobile phase to make exactly 100 mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 20 mL, and use this solution as the standard solution. Pipet 20 μL each of the test solution and the standard solution, and perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the peak area other than maleic acid and *d*-chlopheniramine obtained from the test solution is not greater than two thirds times the peak area of *d*-chlopheniramine from the standard solution. Also, the total area of peaks other than maleic acid and *d*-chlorpheniramine obtained from the test solution is not larger than the peak area of *d*-chlorpheniramine from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless-steel column about 3.9 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μ*m* in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 8.57 g of ammonium dihydrogen phosphate and 1 mL of phosphoric acid in water to make 1000 mL. To 800 mL of this solution, add 200 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of *d*-chlopheniramine is about 11 minutes.

System suitability

Test for required detectability: Weigh accurately 2.5 mL of the standard solution and add the mobile phase to make exactly 25 mL. Verify that the peak area of *d*-chlopheniramine obtained from 20 μL of this solution is equivalent to 7 to 13% of the peak area of *d*-chlopheniramine obtained from the standard solution.

System performance: Proceed with 20 μL of the standard solution according to the above operating conditions; the number of theoretical plates of *d*-chlopheniramine peak is NLT 4000 plates with the symmetry factor being NMT 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of *d*-chlopheniramine is NMT 4.0%.

Time span of measurement: About 4 times the retention time of *d*-chlopheniramine after the solvent peak

Loss on drying NMT 0.5% (1 g, 65 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of *d*-Chlorpheniramine Maleate, previously dried, dissolve in 20 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of methylosaniline chloride TS). However, the endpoint of the titration is when the violet color of the solution turns to bluish green and then finally to green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 19.543 mg of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$

Packaging and storage Preserve in light-resistant, tight containers.

Chlorpheniramine Maleate Injection
클로르페니라민말레산염 주사액

Chlorpheniramine Maleate Injection is an aqueous solution for injection, which contains NLT 95.0% and NMT 105.0% of the labeled amount of dl-chlorpheniramine maleate (C16H19FO2·C4H4O4 : 390.86).

Method of preparation Prepare as directed under Injections, with Chlorpheniramine Maleate.

Description Chlorpheniramine Maleate Injection occurs as a clear, colorless liquid.

pH— Between 4.5 and 7.0.

Identification Weigh an amount of Chlorpheniramine Maleate Injection, equivalent to 25 mg of chlorpheniramine maleate, according to the labeled amount, add 5 mL of sodium hydroxide TS, and extract with 10 mL of hex-

ane. Wash the hexane layer with 10 mL of water, shake with 0.5 g of anhydrous sodium sulfate for several minutes to mix, and filter. Evaporate the solution on a steam bath at about 50 ºC in vacuum, and determine the Mid-infrared spectrum of the residue as directed under the liquid film method under the Mid-infrared spectrophotometry: it exhibits absorption at the wavenumbers of about 2940 cm^{-1}, 2810 cm^{-1}, 2770 cm^{-1}, 1589 cm^{-1}, 1491 cm^{-1}, 1470 cm^{-1}, 1434 cm^{-1}, 1091 cm^{-1} and 1015 cm^{-1}.

Sterility Meets the requirements.

Bacterial endotoxins Less than 8.8 EU per mg of Chlorpheniramine Maleate Injection.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Take exactly an amount of Chlorpheniramine Maleate Injection, equivalent to about 3 mg of chlorpheniramine maleate, put into a 100-mL separatory funnel, add 20 mL of water and 2 mL of sodium hydroxide TS, and extract twice with 50 mL each of ether. Combine the ether extracts, wash with 20 mL of water, and then extract with 20 mL, 20 mL and 5 mL of 0.25 mol/L sulfuric acid TS successively. Combine all the extracts, and add 0.25 mol/L sulfuric acid TS to make exactly 50 mL. Pipet 10 mL of this solution, add 0.25 mol/L sulfuric acid TS to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 30 mg of chlorpheniramine maleate RS, previously dried at 105 ℃ for 3 hours, and dissolve in water to make exactly 200 mL. Pipet 20 mL of this solution, put into a 100-mL separatory funnel, add 2 mL of sodium hydroxide TS, and extract twice with 50 mL each of ether. Proceed in the same manner as the test solution and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy and determine the absorbances, A_T and A_S, at 265 nm.

Amount (mg) of chlorpheniramine maleate ($C_{20}H_{38}N_4O_4$)
= Amount (mg) of chlorpheniramine maleate RS
$$\times \frac{A_T}{A_S} \times \frac{1}{10}$$

Packaging and storage Preserve in light-resistant, hermetic containers.

Chlorpheniramine Maleate Powder
클로르페니라민말레산염 산

Chlorpheniramine Maleate Powder contains NLT 93.0% and NMT 107.0% of the labeled amount of *d*-chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$: 390.86)

Method of preparation Prepare as directed under Powders, with Chlorpheniramine Maleate.

Identification Weigh an amount of Chlorpheniramine Maleate Powder, equivalent to 50 mg of chlorpheniramine maleate according to the labeled amount, add 40 mL of 0.1 mol/L hydrochloric acid TS, shake to mix, and filter. Put the filtrate into a separatory funnel and wash with 40 mL of hexane. Add 10 mL of sodium hydroxide TS and extract with 20 mL of hexane. Wash the hexane layer by adding 5 mL of water. If necessary, centrifuge, add 0.5 g of anhydrous sodium sulfate to the hexane extract, shake for several minutes to mix, and filter. Evaporate this solution in vacuum on a steam bath at about 50 °C, and determine the absorption of the residue as directed under the liquid film method under the Mid-infrared spectrophotometry; it exhibits absorption at the wavenumbers of about 2940 cm^{-1}, 2810 cm^{-1}, 2770 cm^{-1}, 1589 cm^{-1}, 1491 cm^{-1}, 1470 cm^{-1}, 1434 cm^{-1}, 1091 cm^{-1} and 1015 cm^{-1}.

Particle size distribution estimation by analytical sieving Meets the requirements.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Weigh accurately an amount of Chlorpheniramine Maleate Powder, equivalent to about 4 mg of chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$), add 70 mL of the internal standard solution, and shake to mix for 15 minutes. Add internal standard solution again to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of chlorpheniramine maleate RS, previously dried at 105 ℃ for 3 hours, and add internal standard solution to make exactly 100 mL. Pipet 20 mL of the resulting solution, add the internal standard solution to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 30 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of chlopheniramine to that of the internal standard.

Amount (mg) of chlorpheniramine maleate ($C_{20}H_{38}N_4O_4$)
= Amount (mg) of chlorpheniramine maleate RS$\times \frac{Q_T}{Q_S} \times \frac{1}{5}$

Internal standard solution—Add water to 7 mL of a solution of methyl *p*-hydroxybenzoate in methanol (1 in

1000) to make 1000 mL.

Operating conditions

Detector: An ultraviolet photometer (wavelength: 265 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 15 cm in length with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 1 g of sodium 1-heptanesulfonate in 900 mL of water, add 10 mL of acetic acid(100), and then add water to make 1000 mL. To 650 mL of this solution, add 350 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of chlopheniramine is about 8 minutes.

System suitability

System performance: Proceed with 30 μL of the standard solution according to the above conditions; internal standard solution and chlopheniramine are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 30 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area ratios of chlopheniramine to that of the internal standard is NMT 1.0%.

Time span of measurement: About 4 times the retention time of chlopheniramine after the solvent peak.

Packaging and storage Preserve in tight containers.

Chlorpheniramine Maleate Tablets
클로르페니라민말레산염 정

Chlorpheniramine Maleate Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$: 390.86).

Method of preparation Prepare as directed under Tablets, with Chlorpheniramine Maleate Tablets.

Identification Weigh an amount of Chlorpheniramine Maleate Tablets, previously powdered, equivalent to 50 mg of chlorpheniramine maleate, according to the labeled amount, add 40 mL of 0.1 mol/L hydrochloric acid TS, shake to mix, and filter. Place the filtrate in a separatory funnel, and wash with 40 mL of hexane. Next, add 10 mL of sodium hydroxide TS, and extract with 20 mL of hexane. Add 5 mL of water to the hexane layer, and wash with water. Centrifuge, if necessary, add 0.5 g of anhydrous sodium sulfate to the hexane extract, shake for several minutes to mix, and filter. Filter this solution under reduced pressure on a steam bath at about 50 °C to evaporate, and determine the infrared spectra of the residue as directed under the liquid film method under the Mid-infrared Spectroscopy; it exhibits absorptions at the wavenumbers of about 2940 cm^{-1}, 2810 cm^{-1}, 2770 cm^{-1}, 1589 cm^{-1}, 1491 cm^{-1}, 1470 cm^{-1}, 1434 cm^{-1}, 1091 cm^{-1} and 1015 cm^{-1}.

Dissolution Perform the test with 1 tablet of Chlorpheniramine Maleate Tablets at 50 revolutions per minute according to Method 2, using 500 mL of 0.01 mol/L hydrochloric acid TS as the dissolution medium. Take the dissolved solution after 30 minutes from the start of the test and filter. Discard the first 10 mL of the filtrate, pipet V mL of the subsequent filtrate, add the dissolution medium to make exactly V' mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of chlorpheniramine maleate RS, dissolve in the dissolution medium to obtain the same concentration as the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength of about 265 nm as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as a control solution. It meets the requirements when the dissolution rate in 30 minutes is NLT 80% (Q).

Dissolution rate (%) with respect to the labeled amount of chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$)

$$= C_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 50000$$

C_S: Concentration (mg/mL) of the standard solution

C: Labeled amount (mg) of chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$) in 1 tablet

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following method.

Take 1 of Chlorpheniramine Maleate Tablets, add 10 mL of water, and shake well to disintegrate. Add water to make exactly V mL of a solution containing about 80 μg of chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$) per mL, and filter through a membrane filter with a pore size of NMT 0.5 μm. Weigh accurately 5 mL of the filtrate, add exactly 2.5 mL of the internal standard solution, and add water to make exactly 10 mL. Use this solution as the test solution. Separately, dry the chlorpheniramine maleate RS at 105 °C for 3 hours, weigh accurately about 20 mg, and add water to make exactly 100 mL. Weigh accurately 20 mL of this solution, add accurately 25 mL of internal standard solution and water to make 100 mL, and use this solution as the standard solution. Perform the test with 30 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, of chlorpheniramine maleate to that of the internal standard.

Amount (mg) of chlorpheniramine maleate ($C_{20}H_{38}N_4O_4$)
= Amount (mg) of chlorpheniramine maleate RS

$$\times \frac{Q_T}{Q_S} \times \frac{V}{250}$$

Internal standard solution—add water to 7 mL of a solution of butyl p-hydroxybenzoate in methanol (1 in 250) to make 1000 mL.

Assay Weigh accurately the mass of NLT 20 Chlorpheniramine Maleate Tablets, and powder. Weigh accurately an amount, equivalent to about 4 mg of chlorpheniramine maleate ($C_{20}H_{38}N_4O_4$), add 70 mL of the internal standard solution, and shake for 15 minutes to mix. Add the internal standard solution again to make exactly 100 mL, filter through a membrane filter with a pore size of NMT 0.5 μm, and use the filtrate as the test solution. Separately, dry chlorpheniramine maleate RS at 105 °C for 3 hours, weigh accurately about 20 mg, and add the internal standard solution to make exactly 100 mL. Pipet 20 mL of this solution, add the internal standard solution to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 30 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak area ratios, Q_T and Q_S, of chlorpheniramine to that of the internal standard for the test solution and the standard solution, respectively.

Amount (mg) of chlorpheniramine maleate ($C_{20}H_{38}N_4O_4$)
= Amount (mg) of chlorpheniramine maleate RS
$$\times \frac{Q_T}{Q_S} \times \frac{1}{5}$$

Internal standard solution—Add water to 7 mL of a solution of butyl p-hydroxybenzoate in methanol (1 in 1000) to make 1000 mL.

Operating conditions

Detector: An ultraviolet photometer (wavelength: 265 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 1 g of sodium 1-heptanesulfonate in 900 mL of water, add 10 mL of acetic acid(100), and add water again to make 1000 mL. To 650 mL of this solution, add 350 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of chlorpheniramine is about 8 minutes.

System suitability

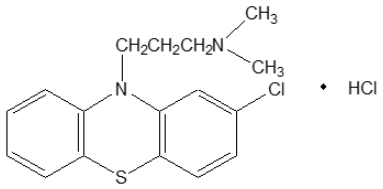
System performance: Proceed with 30 μL of the standard solution under the above operating conditions; the internal standard and chlorpheniramine are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 30 μL each of the standard solution as directed under the above conditions; the relative standard deviation of the peak area ratios of chlorpheniramine to that of the internal standard is NMT 1.0%.

Time span of measurement: About 4 times the retention time of chlorpheniramine after the solvent peak.

Packaging and storage Preserve in tight containers.

Chlorpromazine Hydrochloride
클로르프로마진염산염



$C_{17}H_{19}ClN_2S \cdot HCl$: 355.33

3-(2-Chlorophenothiazin-10-yl)-*N*,*N*-dimethylpropan-1-amine hydrochloride [*69-09-0*]

Chlorpromazine Hydrochloride, when dried, contains NLT 99.0% and NMT 101.0% of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2 S \cdot HCl$).

Description Chlorpromazine Hydrochloride occurs as a white to pale yellow, crystalline powder and has no odor or a faint, characteristic odor.

It is very soluble in water, freely soluble in acetic acid(100) or ethanol(95), sparingly soluble in acetic anhydride, and practically insoluble in ether.

It is gradually colored by light.

Identification (1) Determine the infrared spectra of Chlorpromazine Hydrochloride and chlorpromazine hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve 0.5 g of Chlorpromazine Hydrochloride in 5 mL of water, add 2 mL of ammonia TS, heat on a steam bath for 5 minutes, cool, and filter. Acidify the filtrate with dilute nitric acid; the resulting solution responds to the Qualitative Analysis (2) for chloride.

Melting point Between 194 and 198 ℃.

pH Dissolve 1.0 g of Chlorpromazine Hydrochloride in 20 mL of freshly boiled and cooled water; the pH of this solution is between 4.0 and 5.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Chlorpromazine Hydrochloride in 20 mL of water; the solution is clear and colorless to pale yellow.

(2) ***Heavy metals***—Proceed with 1.0 g of Chlorpromazine Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL

of lead standard solution (NMT 20 ppm).

(3) ***Related substances (other alkylated phenothiazine)***—Weigh accurately about 50 mg of Chlorpromazine Hydrochloride, previously dried, dissolve in methanol to make exactly 10 mL, shake to mix, and use this solution as the test solution. Separately, weigh accurately about 50 mg of chlorpromazine hydrochloride RS, dissolve in methanol to make a 10 mL solution with a concentration of 5 mg per mL, and use this solution as the standard stock solution. Pipet 1 mL of this solution, add the methanol to make 20 mL, then pipet 1 mL of this solution, add methanol to make a 10 mL solution with a concentration of 25 μ*g* per mL, and use this solution as the standard solution. Spot 10 μL each of the test solution, the standard stock solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography under the Thin Layer Chromatography. Next, develop the plate with a mixture of ether and ethyl acetate saturated with ammonia water(28) (1:1) as a developing solvent to a distance of about 10 cm, and air-dry the plate for 20 minutes. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are neither larger nor more intense than the spots from the diluted standard solution (NMT 0.5%).

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh exactly about 0.7 g of Chlorpromazine Hydrochloride, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 35.533 mg of $C_{17}H_{19}ClN_2S{\cdot}HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Chlorpromazine Hydrochloride Injection
클로르프로마진염산염 주사액

Chlorpromazine Hydrochloride Injection is an aqueous solution for injection and contains NLT 95.0% and NMT 105.0% of the labeled amount of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S{\cdot}HCl$: 355.33).

Method of preparation Prepare as directed under Injections, with Chlorpromazine Hydrochloride.

Description Chlorpromazine Hydrochloride Injection occurs a clear, colorless to pale yellow liquid.

pH—Between 4.0 and 6.5.

Identification (1) Perform the test with a volume of Chlorpromazine Hydrochloride Injection, equivalent to 5 mg of Chlorpromazine Hydrochloride according to the labeled amount, as directed under the Identification (1) under Chlorpromazine Hydrochloride.

(2) Perform the test with a volume of Chlorpromazine Hydrochloride Injection, equivalent to 0.1 g of Chlorpromazine Hydrochloride according to the labeled amount, as directed under the Identification (2) under Chlorpromazine Hydrochloride.

Sterility Meets the requirements

Bacterial endotoxins Less than 6.9 EU per mg of Chlorpromazine Hydrochloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Take exactly a volume of Chlorpromazine Hydrochloride Injection, equivalent to about 0.15 g of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S{\cdot}HCl$), add 30 mL of water and 10 mL of a solution of sodium hydroxide (1 in 5), and extract twice with 30 mL each of ether and three times with 20 mL each of ether. Wash with 10 mL each of water until the washings of all ether extracts combined do not exhibit a red color. Concentrate the ether extracts on a steam bath to about 20 mL, add 5 g of anhydrous sodium sulfate, allow to stand for 20 minutes, and filter through absorbent cotton. Wash with ether, combine the washings with the filtrate, and evaporate the ether on a steam bath. Dissolve the residue in 50 mL of acetone for non-aqueous titration and 5 mL of acetic acid(100) and titrate with 0.05 mol/L perchloric acid VS (indicator: 3 drops of bromocresol green-methylrosaniline chloride TS). The endpoint of titration is when the color of the solution changes from purple to bluish purple. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L perchloric acid VS
= 17.767 mg of $C_{17}H_{19}ClN_2S{\cdot}HCl$

Packaging and storage Preserve in light-resistant, hermetic containers. Colored containers may be used.

Chlorpromazine Hydrochloride Tablets
클로르프로마진염산염 정

Chlorpromazine Hydrochloride Tablets contain NLT 93.0% and NMT 107.0% of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S \cdot HCl$: 355.33).

Method of preparation Prepare as directed under Tablets, with Chlorpromazine Hydrochloride.

Identification The retention time of the major peak obtained from the test solution and the standard solution under the Assay and the ultraviolet absorption spectrum at 200 to 400 nm are the same.

Purity ***Related substances (other related alkylation of phenothiazine)***—Weigh accurately NLT 20 Chlorpromazine Hydrochloride Tablets, and powder. Weigh accurately an amount, equivalent to about 50 g according to the labeled amount, and transfer to a stoppered centrifuge tube, add 10 mL of methanol, shake vigorously to mix, and centrifuge. Use this solution as the test solution. In the case of sugar-coated tablets, wash the coated sugar with water in advance to remove the sugarcoating. Separately, weigh accurately 50 mg of chlorpromazine hydrochloride RS, dissolve in methanol to make 10 mL to obtain a solution containing about 5 mg per mL, and use this solution as the standard stock solution. Take exactly 1 mL of this solution and add methanol to make 20 mL. Then, take again exactly 1 mL of this solution, add methanol to make 10 mL, prepare a solution containing 25 μg in 1 mL, and use this solution as the standard solution. Spot 10 μL each of the test solution, the standard stock solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography as directed under the Thin Layer Chromatography. Next, develop the plate with a mixture of ethyl acetate (1:1) saturated with ether and ammonia water(28) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not larger or not more intense than the spots from the standard solution (NMT 0.5%).

Dissolution Perform the test with 1 tablet of Chlorpromazine Hydrochloride Tablets at 75 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of Solution 2 as the dissolution medium. Take more than 20 mL of the dissolution medium 60 minutes after starting the test, and filter by membrane filter with a pore size of NMT 0.8 μm. Discard the first 10 mL of the filtrate, take exactly V mL of the subsequent filtrate, and add Solution 2 according to the labeled amount to obtain a solution containing about 5.6 μg of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S \cdot HCl$), and make it exactly V' mL. Use the clear supernatant as the test solution. Separately, dry chlorpromazine hydrochloride RS at 105 °C for 2 hours, weigh accurately about 90 mg, and dissolve in Solution 2 to make exactly 200 mL. Pipet 5 mL of this solution, and add Solution 2 to make exactly 100 mL. Pipet again 5 mL of this solution, add Solution 2 to make exactly 20 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 254 nm as directed under the Ultraviolet-visible Spectroscopy.
NLT 75% of the labeled amount of Chlorpromazine Hydrochloride is dissolved in 60 minutes.

Dissolution rate (%) with respect to the labeled amount of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S \cdot HCl$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 2$$

W_S: Amount (mg) of chlorpromazine hydrochloride RS

C: Labeled amount (mg) of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S \cdot HCl$) in 1 tablet

Uniformity of dosage units Meets the requirements.

Assay Perform this test using a light-resistant container, protected from direct sunlight. Weigh accurately the mass of NLT 20 Chlorpromazine Hydrochloride Tablets, and powder. Weigh accurately an amount, equivalent to about 50 mg of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S \cdot HCl$), add 60 mL of a mixture of diluted phosphoric acid (1 in 500) and ethanol(99.5) (7 : 3), and sonicate for 5 minutes. Shake vigorously for 20 minutes to mix, add a mixture of diluted phosphoric acid (1 in 500) and ethanol(99.5) (1 : 1) to make exactly 100 mL, and filter through a membrane filter with a pore size of NMT 0.45 μm. Discard 3 mL of the first filtrate, take exactly 2.5 mL of the subsequent filtrate, add exactly 5 mL of the internal standard solution, and add a mixture of diluted phosphoric acid (1 in 500) and ethanol(99.5) (1:1) to make exactly 25 mL, and use this solution as the test solution. Separately, dry the chlorpromazine hydrochloride RS at 105 °C for 2 hours, weigh accurately about 25 mg, and dissolve in a mixture of diluted phosphoric acid (1 in 500) and ethanol(99.5) (1 : 1) to make exactly 100 mL. Take exactly 5 mL of this solution, add exactly 5 mL of the internal standard solution and then a mixture of diluted phosphoric acid (1 in 500) and ethanol(99.5) (1 : 1) to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, of chlorpromazine hydrochloride to that of the internal standard.

Amount (mg) of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S \cdot HCl$)
= Amount (mg) of chlorpromazine hydrochloride RS

$$\times \frac{Q_T}{Q_S} \times 2$$

Internal standard solution—A solution of ethylparaben in a mixture of diluted phosphoric acid (1 in

500) and ethanol(99.5) (1 : 1) (1 in 4500).

Operating conditions

Detector: An ultraviolet absorbance photometer (wavelength: 256 nm). However, use a photo-diode array detector (200 to 400 nm) when the Identification is performed.

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of diluted 0.05 mol/L sodium dihydrogen phosphate TS (1 in 2) and acetonitrile (27 : 13).

Flow rate: Adjust the flow rate so that the retention time of chlorpromazine is about 15 minutes.

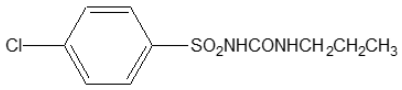
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the internal standard and chlorpromazine are eluted in this order with the resolution being NLT 10.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area ratios of chlorpromazine to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Chlorpropamide
클로르프로파미드



$C_{10}H_{13}ClN_2O_3S$: 276.74

1-[(4-Chlorobenzene)sulfonyl]-3-propylurea [*94-20-2*]

Chlorpropamide, when dried, contains NLT 98.0% and NMT 101.0% of chlorpropamide ($C_{10}H_{13}ClN_2O_3S$).

Description Chlorpropamide occurs as white crystals or a crystalline powder, and is odorless.

It is freely soluble in acetone, soluble in ethanol(95), slightly soluble in ether, and practically insoluble in water.

Identification (1) Dissolve 80 mg of Chlorpropamide and chlorpropamide RS each in 50 mL of methanol. Pipet 1 mL each of these solutions and add 0.01 mol/L hydrochloric acid TS to make 200 mL. Determine the absorption spectra of the resulting solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Chlorpropamide and chlorpropamide RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Perform the test with Chlorpropamide as directed under the Flame Coloration (2); a green color is observed.

Melting point Between 127 and 131 °C.

Purity (1) ***Acid***—Add 150 mL of water to 3.0 g of Chlorpropamide, warm at 70 °C for 5 minutes, allow to stand in iced water for 1 hour, and filter. To 25 mL of the filtrate, add 2 drops of methyl red TS and 0.30 mL of 0.1 mol/L sodium hydroxide TS; the solution exhibits a yellow color.

(2) ***Chloride***—To 40 mL of the filtrate obtained in (1), add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid (NMT 0.011%).

(3) ***Sulfate***—To 40 mL of the filtrate obtained in (1), add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid (NMT 0.021%).

(4) ***Heavy metals***—Proceed with 2.0g of Chlorpropamide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Selenium***—Weigh about 0.2 g of Chlorpropamide and combust as directed under the Oxygen Flask Combustion, using 25 mL of diluted nitric acid (1 in 30) as an absorbent. Use the combustion flask with a volume of 1 L. After burning, wash the stopper and the inner wall of the flask with 10 mL of water, and use 20 mL of water to move the solution in the combustion flask into a 150-mL beaker. Heat lightly until it boils, boil for 10 minutes, allow to cool to the room temperature, and use this solution as the test solution. Separately, pipet 6.0 mL of standard selenium stock solution, add 25 mL of diluted nitric acid (1 in 30) and 25 mL of water, and use this solution as the standard solution. To each of the test and standard solutions, add diluted ammonia water(28) (1 in 2) to adjust the pH to 2.0 ± 0.2, add water to dilute exactly to 60 mL, and use 10.0 mL of water to move the diluted solution to a separatory funnel. Then, wash the separatory funnel with 10 mL of water. Add 0.2 g of hydroxylamine hydrochloride, and stir to dissolve. Then, immediately add 5.0 mL of 2,3-diaminonaphthalene TS, put a stopper, stir to mix, and allow to stand at the room temperature for 100 minutes. To the resulting mixture, add 5.0 mL of cyclohexane, shake hard for two minutes, and allow to stand. If layers are separated, remove the water layer, centrifuge cyclohexane extracts, remove water, and take the cyclohexane layer. With these solutions and a control solution prepared with 25 mL of water added to 25 mL of diluted nitric acid (1 in 30) in the same way,

perform the test as directed under the Ultraviolet-visible Spectroscopy. Determine the absorption at the absorption maximum wavelength around 380 nm; the absorption of the solution from the test solution is not larger than the absorption from the standard solution (NMT 30 ppm).

(6) ***Related substances***—Weigh 0.60 g of Chlorpropamide, dissolve in acetone to make exactly 10 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add acetone to make exactly 300 mL, and use this solution as the standard solution (1). Separately, dissolve 60 mg of 4-chlorobenzenesulfonamide RS in acetone to make exactly 300 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution, the standard solution (1), and the standard solution (2) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of cyclohexane, 3-methyl-1-butanol, methanol and ammonia water(28) (15: 10 : 5 : 1) as the developing solvent to a distance of about 10 cm and air-dry the plate. Dry the plate at 100℃ for 1 hour, sprinkle sodium hypochlorite TS evenly, and then air-dry for 15 minutes. Sprinkle potassium iodide starch TS evenly; the spot obtained from the test solution, of which location corresponds to that of the spot from the standard solution (2), is not more intense than the spot obtained from the standard solution (2). The spots other than the principal spot from the test solution and the above spot are not more intense than those from the standard solution (1).

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

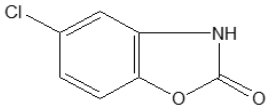
Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.5 g of Chlorpropamide, previously dried, dissolve in 30 mL of neutralized ethanol, add 20 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of phenolphthalein TS).

Each mL of 0.1 mol/L sodium hydroxide VS
= 27.674 mg of $C_{10}H_{13}ClN_2O_3S$

Packaging and storage Preserve in well-closed containers.

Chlorzoxazone
클로르족사존



$C_7H_4ClNO_2$: 169.57
5-Chloro-2,3-dihydro-1,3-benzoxazol-2-one [*95-25-0*]

Chlorzoxazone contains NLT 98.0% and NMT 102.0% of chlorzoxazone ($C_7H_4ClNO_2$), calculated on the dried basis.

Description Chlorzoxazone occurs as white to pale yellow crystals or a crystalline powder. It is odorless, tasteless and a little irritant.
It is freely soluble in *N*,*N*-Dimethylformamide, soluble in methanol, ethanol(95) or acetone, slightly soluble in ether, and practically insoluble in water.

Identification (1) Determine the absorption spectra of solutions of Chlorzoxazone and chlorzoxazone RS in methanol (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit a maximum and a minimum of absorption at the same wavelengths.

(2) Determine the infrared spectrum of Chlorzoxazone and chlorzoxazone RS as directed in the potassium bromide disk method under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 189 and 194 ℃.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Chlorzoxazone according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Weigh accurately an appropriate amount of Chlorzoxazone, dissolve in methanol to prepare a solution containing 20 mg in 1 mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of 2-amino-4-chlorophenol RS (previously dried at 105 ℃ for 2 hours), dissolve in methanol to prepare a solution containing 100 μg in 1 mL, and use this solution as the standard solution (1). Also, dissolve in methanol to prepare a solution containing 50 μg in 1 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution, the standard solution (1), and the standard solution (2) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of cyclohexane and acetone (2 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spot from the standard solution (1) (NMT 0.5%). Also, allow to stand in iodine vapor; the spots other than the principal spot obtained from the test solution are not greater and not more intense than the spot from the standard solution (2) (NMT 0.25%).

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

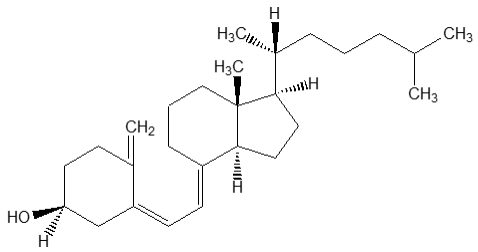
Residue on ignition NMT 0.15% (1 g).

Assay Weigh accurately about 50 mg of Chlorzoxazone and chlorzoxazone RS, (previously dried at 105 ºC for 2 hours), dissolve in methanol to make exactly 100 mL, respectively. Pipet 4 mL each of these solutions, add methanol to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using methanol as a control solution, and determine the absorbances, A_T and A_S, at the wavelength of 282 nm.

$$\text{Amount (mg) of chlorzoxazone } (C_7H_4ClNO_2) = \text{Amount (mg) of chlorzoxazone RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers.

Cholecalciferol
콜레칼시페롤



Vitamin D_3 $C_{27}H_{44}O$: 384.64

(1*S*,3*Z*)-3-[(2*E*)-2-[(1*R*,3a*S*,7a*R*)-7a-Methyl-1-[(2R)-6-methylheptan-2-yl]-2,3,3a,5,6,7-hexa-hydro-1*H*-inden-4-ylidene]ethylidene]-4-methylidenecyclohexan-1-ol [*67-97-0*]

Cholecalciferol contains NLT 97.0% and NMT 103.0% of cholecalciferol ($C_{27}H_{44}O$).

Description Cholecalciferol occurs as a white crystalline powder and is odorless.
It is freely soluble in ethanol(95), chloroform, ether or isooctane, and practically insoluble in water.
It is affected by air or light.

Melting point— Between 84 and 88 ℃.
Transfer Cholecalciferol into a capillary tube, dry for 3 hours using a desiccator (in vacuum, NMT 2.67 kPa), seal the capillary tube, and put in a bath heated to a temperature of about 10 ℃ lower than the predicted melting point. Then heat at a rate of 3 ℃ per minute, and measure the melting point.

Identification (1) Dissolve 0.5 mg of cholecalciferol in 5 mL of chloroform, and add 0.3 mL of acetic anhydride and 0.1 mL of sulfuric acid and shake to mix; the solution exhibits a red color, then immediately changes to violet, then blue, then finally green.

(2) Determine the infrared spectra of cholecalciferol and cholecalciferol RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

Optical rotation $[\alpha]_D^{20}$: Between +103° and +112° (50 mg, ethanol(95), 10 mL, 100 mm) For this test, dissolve within 30 minutes after opening, and measure within 30 minutes of preparing the solution.

Absorbance $E_{1cm}^{1\%}$ (265 nm): Between 450 and 490 (10 mg, ethanol(95), 1000 mL).

Purity ***7-Dehydrocholesterol***—Dissolve 10 mg of cholecalciferol in 2.0 mL of diluted ethanol (9 in 10), then add a solution of 20 mg digitonin dissolved in 2.0 mL of diluted ethanol (9 in 10) and let stand for 18 hours; no precipitate forms.

Assay Weigh accurately about 30 mg each of cholecalciferol and cholecalciferol RS and add isooctane to each to make exactly 50 mL. Pipet 10 mL each of these solutions, add exactly 3 mL of internal standard solution to each solution, and add the mobile phase to make 50 mL. Use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak area of cholecalciferol to that of the internal standard Q_T and Q_S. Perform the test using light-resistant containers, avoiding contact with air or oxidizing agents.

$$\text{Amount (mg) of cholecalciferol } (C_{27}H_{44}O) = \text{Amount (mg) of cholecalciferol RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of dimethyl phthalate in isooctane (1 in 100).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 10 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Mobile phase: A mixture of hexane and *n*-amyl alcohol (997 : 3).

Flow rate: Adjust the flow rate so that the retention time of cholecalciferol is about 25 minutes.

Selection of column: Dissolve 15 mg of cholecalciferol RS in 25 mL of isooctane. Transfer the solution to a flask, heat for 2 hours in an oil bath with a reflux condenser, and quickly chill to room temperature. Transfer the solution to a quartz test tube and irradiate for 3 hours under a short-wavelength lamp (main wavelength: 254 nm) and a long-wavelength lamp (main wavelength: 365 nm). Pipet 10 mL of this solution and add the mobile

phase to make 50 mL. Proceed with 10 μL of this solution according to the above conditions; the ratios of the retention times of previtamin D_3, transvitamin D_3 and tachysterol $_3$ are about 0.5, about 0.6 and about 1.1, respectively, and the resolutions between previtamin D_3 and transvitamin D_3 and between cholecalciferol and tachysterolD_3 NLT 1.0, respectively.

Packaging and storage Place in light-resistant, well-closed containers, substituting air with nitrogen, and store in a cold place.

Cholecalciferol and Calcium Carbonate Capsules
콜레칼시페롤·탄산칼슘 캡슐

Cholecalciferol and Calcium Carbonate Capsules contain NLT 90.0% and NMT 150.0% of the labeled amount of cholecalciferol ($C_{27}H_{44}O$: 384.64) and NLT 90.0% and NMT 110.0% of the labeled amount calcium carbonate ($CaCO_3$: 100.09).

Method of preparation Prepare as directed under Capsules, with Cholecalciferol and Calcium Carbonate.

Identification (1) ***Cholecalciferol***—Perform the test with Cholecalciferol and Calcium Carbonate Capsules as directed under the Analysis for Vitamins.

(2) ***Calcium in calcium carbonate***—Dissolve the contents of Cholecalciferol and Calcium Carbonate Capsules equivalent to 0.5 g of calcium carbonate in 10 mL of dilute hydrochloric acid, boil and cool. Neutralize by adding ammonia TS; the solution responds to the Qualitative Analysis (3) for calcium salt.

(3) ***Carbonate in calcium carbonate***—Cholecalciferol and Calcium Carbonate Capsules respond to the Qualitative Analysis (1) for carbonate.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Cholecalciferol***—Weigh accurately the contents of NLT 20 capsules of Cholecalciferol and Calcium Carbonate Capsules. Weigh accurately an amount equivalent to about 30 mg of cholecalciferol ($C_{27}H_{44}O$) and about 30 mg of cholecalciferol RS, and add isooctane to make 50 mL. Pipet 10.0 mL each of these solutions, add 3.0 mL of the internal standard solution to each, add the mobile phase to make 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios Q_T and Q_S, of the peak area of cholecalciferol, to that of the internal standard. However, perform the test with light-resistant containers, avoiding contact with air or other oxidizing agents as much as possible.

$$\text{Amount (mg) of cholecalciferol } (C_{27}H_{44}O) = \text{Amount (mg) of cholecalciferol RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of dimethyl phthalate in isooctane (1 in 100).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column with about 4 mm in internal diameter and 10 to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of hexane and n-amyl alcohol (997 : 3).

Flow rate: Adjust the flow rate so that the retention time of cholecalciferol is about 25 minutes.

Selection of column: Dissolve 15 mg of cholecalciferol RS in 25 mL of isooctane. Put this solution to a flask with a reflex condenser, heat in an oil bath for 2 hours, and cool to room temperature quickly. Transfer this solution to a quartz test tube, expose to ultraviolet rays (main wavelength: 254 nm and 365 nm), and combine 10 mL of this solution and the mobile phase to make 50 mL. Proceed with 10 μL of this solution under the above operating conditions; the ratio of the retention times of previtamin D_3, transvitamin D_3 and tachysterol D_3 to that of cholecalciferol are about 0.5, 0.6 and 1.1, respectively. Resolutions of previtamin D_3 and transvitamin D_3, and cholecalciferol and tachysterol D_3 are NLT 1.0, respectively.

(2) ***Calcium carbonate***—Weigh accurately the contents of NLT 20 capsules of Cholecalciferol and Calcium Carbonate Capsules. Weigh an amount equivalent to 200 mg of calcium carbonate ($CaCO_3$), put in a crucible, ignite at 800 ℃ to incinerate, and cool. Dissolve this residue in 10 mL of water and 3 mL of 3 mol/L hydrochloric acid, and add water to make 150 mL. Add 15 mL of 1 mol/L sodium hydroxide TS to this solution, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS until the color changes from reddish purple to blue (indicator: 300 mg of hydroxynaphthol blue). Prepare the blank test solution by adding 15 mL of 1 mol/L sodium hydroxide TS to 150 mL of water, perform a blank test in the same manner and make any necessary correction.

$$\text{Each mL of 0.05 mol/L disodium ethylenediaminetetraacetate VS} = 5.004 \text{ mg of } CaCO_3$$

Packaging and storage Preserve in well-closed containers.

Cholecalciferol and Calcium Carbonate Tablets
콜레칼시페롤·탄산칼슘 정

Cholecalciferol and Calcium Carbonate Tablets contain NLT 90.0% and NMT 150.0% of the labeled amount of cholecalciferol ($C_{27}H_{44}O$: 384.64) and NLT 90.0% and NMT 110.0% of the labeled amount of calcium carbonate ($CaCO_3$: 100.09).

Method of preparation Prepare as directed under Tablets, with Cholecalciferol and Calcium Carbonate.

Identification (1) ***Cholecalciferol***—Perform the test with Cholecalciferol and Calcium Carbonate Tablets as directed under the Analysis for Vitamins.

(2) ***Calcium of calcium carbonate***—Dissolve an amount of Cholecalciferol and Calcium Carbonate Tablets equivalent to 0.5 g of calcium carbonate in 10 mL of dilute hydrochloric acid, and boil. After cooling, neutralize by adding ammonia TS; this solution responds to the Qualitative Analysis (3) for calcium salt.

(3) ***Carbonate of calcium carbonate***—Cholecalciferol and Calcium Carbonate Tablets responds to the Qualitative Analysis (1) for carbonate.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

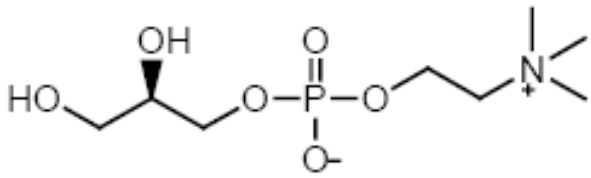
Assay (1) ***Cholecalciferol***—Weigh accurately the mass of NLT 20 tablets of Cholecalciferol and Calcium Carbonate Tablets, powder, and perform the test as directed under the Analysis for Vitamins.

(2) ***Calcium carbonate***—Weigh accurately the mass of NLT 20 tablets of Cholecalciferol and Calcium Carbonate Tablets, and powder. Weigh accurately an amount, equivalent to about 200 mg of calcium carbonate ($CaCO_3$), put in a crucible, ignite at 800℃ to incinerate, and cool. Dissolve this residue in 10 mL of water and 3 mL of 3 mol/L hydrochloric acid, and add water to make 150 mL. Add 15 mL of 1 mol/L sodium hydroxide TS to this solution, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS until the color changes from reddish purple to blue (indicator: 300 mg of hydroxynaphthol blue). Add 15 mL of 1 mol/L sodium hydroxide TS to 150 mL of water, perform a blank test in the same manner, and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 5.004mg of $CaCO_3$

Packaging and storage Preserve in well-closed containers.

Choline Alphoscerate
콜린알포세레이트



$C_8H_{20}NO_6P$: 257.20

(*R*)-2-[[(2,3-Dihydroxypropoxy)hydroxyphosphinyl]oxy]-*N*,*N*,*N*-trimethyl-ethanaminium, inner salt, [*28319-77-9*]

Choline Alphoscerate contains NLT 98.0% and NMT 102.0% of choline alphoscerate ($C_8H_{20}NO_6 \cdot HCl$: 257.20), calculated on the anhydrous basis.

Method of preparation If there is any possibility of glycidol or chloropropanediol to be mixed according to the manufacturing process of Choline Alphoscerate, take caution with starting material, manufacturing process, and intermediate material control to minimize the residue of impurities in consideration of risk assessment results. If necessary, the manufacturing process may be verified by the test data proving that no quality risk exists in the final drug substance.

Description Choline Alphoscerate occurs as a clear, colorless and viscous fluid.
It is freely soluble in water, methanol and ethanol, sparingly soluble in 1-butanol, and insoluble in acetone, ethyl acetate and ether.

Identification Weigh 0.2 g each of Choline Alphoscerate and choline alphoscerate RS, dissolve in 1 mL of methanol, and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of acetone, methanol, water and acetic acid(100) (30 : 24 : 12 : 12) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Evenly spray the plate with a solution of 1.25 g of potassium permanganate and 12 g of sodium hydroxide dissolved in 300 mL of water as a coloring agent; the R_f values of the spots from the test solution and the standard solution are the same.

Optical rotation $[\alpha]_D^{20}$: Between -2.40° and -2.80° (2.5 g, calculated on the anhydrous basis, water, 25 mL, 100 mm).

pH Between 5.0 and 7.0 (10% aqueous solution).

Purity (1) ***Chloride***—Perform the test with 1 g of Cho-

line Alphoscerate as directed under the Chloride. Prepare the control solution with 0.53 mL of 0.01 mol/L hydrochloric acid (NMT 0.02%).

(2) ***Sulfate***—Perform the test with 1 g of Choline Alphoscerate as directed under the Sulfate. Prepare the control solution with 0.4 mL of 0.005 mol/L sulfuric acid (NMT 0.02%).

(3) ***Phosphoric acid ion***—Weigh 1 g of Choline Alphoscerate, dissolve in 10 mL of water, add 5 mL of a mixture of ammonium molybdate-sulfuric acid TS and ammonium metavanadate TS (1 : 1) and allow to stand for 5 minutes; the yellow color that appears is not more intense than the color of the control solution. For the control solution, add 5 mL of a mixture of ammonium molybdate-sulfuric acid TS and ammonium metavanadate TS (1 : 1) to 10 mL of standard phosphate solution.

Ammonium metavanadate TS—Add water to 0.2 g of ammonium vanadate (NH_4VO_3, 116.98) to make 400 mL.

(4) ***Heavy metals***—Proceed with 2.0 g of Choline Alphoscerate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Related substances***—Dissolve 1.0 g of Choline Alphoscerate in 10 mL of methanol and use this solution as the test solution. Pipet 0.5 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of acetone, methanol, water and acetic acid(100) (30 : 24 : 12 : 12) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Evenly spray the plate with a solution of 1.25 g of potassium permanganate and 12 g of sodium hydroxide dissolved in 300 mL of water as a coloring agent; the spots other than the principal spot from the test solution are not greater or more intense than the spots from the standard solution (0.5%). Also, the sum of the spots other than the principal spot from the test solution is NMT 2.0%.

Water NLT 14.0% and NMT 16.0% (volumetric titration, direct titration).

Assay Weigh accurately an amount of Choline Alphoscerate equivalent to about 0.3 g of choline alphoscerate, calculated on the anhydrous basis, dissolve in 5 mL of mercuric acetate TS, dissolve in 50 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS

= 25.72 mg of $C_8H_{20}NO_6P$

Packaging and storage Preserve in light-resistant, tight containers.

Choline Alphoscerate Capsules
콜린알포세레이트 캡슐

Choline Alphoscerate Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of choline alphoscerate ($C_8H_{20}NO_6P$: 257.20).

Method of preparation Prepared as directed under Capsules, with Choline Alphoscerate.

Identification (1) Weigh the contents of Choline Alphoscerate Capsules equivalent to 0.4 g of choline alphoscerate, add methanol to make 2 mL, and use this solution as the test solution. Separately, weigh about 0.2 g of choline alphoscerate RS, dissolve in 1 mL of methanol, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of acetone, methanol, water and acetic acid(100) (30 : 24 : 12 : 12) (as the developing solvent) to a distance of about 15 cm, and air-dry the plate. Evenly spray the plate with a solution of 1.25 g of potassium permanganate and 12 g of sodium hydroxide dissolved in 300 mL of water as a coloring agent; the R_f values of the spots of the test solution exhibits an R_f value corresponding to that of the standard solution.

(2) The retention times of the major peaks of the test solution correspond to those of the standard solution, as obtained in the Assay.

Dissolution Take 1 capsule of Choline Alphoscerate Capsules, proceed with 900 mL of water as the dissolution medium at 50 revolutions per minute according to Method 2 under the Dissolution, and perform the test. Take the dissolved solution 45 minutes after starting the test, filter and use the filtrate as the test solution. Separately, weigh accurately about 111.1 mg of choline alphoscerate RS, and dissolve in water to make exactly 25 mL. Filter the resulting solution, pipet 5 mL of the filtrate, add water to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of choline alphoscerate, A_T and A_S, in each solution. Meets the requirements if the dissolution rate of Choline Alphoscerate Capsules for 45 minutes is NLT 85%.

Dissolution rate (%) of the labeled amount of choline

$$\text{alphoscerate } (C_8H_{20}NO_6P) = W_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 360$$

W_S: Amount (mg) of choline alphoscerate RS

C: Labeled amount (mg) of choline alphoscerate ($C_8H_{20}NO_6P$) in 1 tablet

Operating conditions

Detector: A differential refractometer

Column: A stainless steel column with about 4.6 mm in internal diameter and about 25.0 cm in length, packed with aminopropylsilyl silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 38 °C.

Mobile phase: 60% acetonitrile.

Flow rate: 1.5 mL/min

System suitability

System repeatability: Repeat the test 6 times with 50 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area for choline alphoscerate is NMT 2.0%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the contents of NLT 20 capsules of Choline Alphoscerate Capsules. Weight accurately an amount equivalent to about 4 g of Choline Alphoscerate Capsules, add 500 mL of water, crush with ultrasonic waves, add water to make exactly 1000 mL with shaking and stirring. Pipet 20 mL of this solution, add water to make 50 mL, filter through a membrane filter (0.45 μm), and use the filtrate as the test solution. Separately, weigh accurately about 0.4 g of choline alphoscerate RS, add water to make exactly 250 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of choline alphoscerate, A_T and A_S, in each solution.

$$\text{Amount (mg) of choline alphoscerate} = \text{Amount (mg) of choline alphoscerate RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: A differential refractometer

Column: A stainless steel column about 4.6 mm in internal diameter and about 25.0 cm in length, packed with aminopropyl sylilated silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: 60% acetonitrile.

Temperature: A constant temperature of about 38 °C.

Flow rate: 1.5 mL/min

Packaging and storage Preserve in tight containers.

Chorionic Gonadotropin
태반성성선자극호르몬

Gonadotropin, chorionic [*9002-61-3*]

Chorionic Gonadotropin is a dried form of gonadotropin obtained from the urine of healthy pregnant women through a process of virus removal or inactivation.

Each mg of Chorionic Gonadotropin contains NLT 2500 chorionic gonadotropin units. Also, each mg of protein contains NLT 3000 chorionic gonadotropin units.

Chorionic Gonadotropin contains NLT 80.0% and NMT 125.0% of the labeling unit.

Description Chorionic Gonadotropin occurs as a white to pale yellowish brown powder and is odorless.
It is freely soluble in water and practically insoluble in ether.

Identification With Y_3 and Y_4 obtained from the Assay, calculate b using the following equation; b is NMT 120.

$$b = \frac{E}{I}$$
$$E = \frac{Y_3 - Y_4}{f}$$
$$I = \log \frac{T_H}{T_L}$$

f: The number of test animals in one group

Purity (1) ***Clarity and color of solution***—Dissolve 50 mg of Chorionic Gonadotropin in 5 mL of Isotonic Sodium Chloride Injection; the resulting solution is colorless to pale yellow and clear.

(2) ***Estrogen***—Weigh accurately an amount equivalent to 100 units based on the labeled units, dissolve in 0.5 mL of isotonic sodium chloride injection, and use this as the injection. Inject subcutaneously to 3 female white rats or mice that have been at least 2 weeks after castration. After injection, collect vaginal secretions twice a day for three consecutive days, on the 3rd, 4th, and 5th days, and spread a thin layer of these secretions onto a glass slide. After drying, stain with Giemsa TS, wash with water, dry, and examine under a microscope; any sign of estrus does not appear.

Loss on drying NMT 5.0% (0.1 g, in vacuum, phosphorus pentoxide, 4 hours).

Bacterial endotoxins Less than 0.03 EU per unit of Chorionic Gonadotropin.

Abnormal toxicity Take an appropriate amount of Chorionic Gonadotropin, make the solution containing 120 units per mL, and use this solution as the test solution. Use at least two healthy and well-nourished marmots

weighing about 350 g each. Administer an intraperitoneal injection of 5.0 mL of the test solution per marmot, and observe them for at least 7 days; none of the marmots exhibit abnormalities.

Inactivity Perform the Assay and the following test with Chorionic Gonadotropin; Chorionic Gonadotropin contains NLT 3000 units of placental chorionic gonadotropin per mg of protein.

(1) ***Test solution***—Prepare a solution by adding an appropriate amount of water according to the labeled amount of Chorionic Gonadotropin so that 1 mL of the solution contains about 500 units.

(2) ***Standard solution***—Weigh accurately 10 mg of bovine serum albumin, and dissolve in water to make exactly 20 mL. To this solution, add water to make four different standard solutions containing exactly 300, 200, 100, and 50 μg of each bovine serum albumin per mL.

(3) **Procedure**—Pipet 0.5 mL each of the four standard solutions and 0.5 mL of the test solution, transfer into glass test tubes with a internal diameter of about 18 mm and a length of about 130 mm, add exactly 5 mL of alkaline copper TS to each tube, and shake to mix. Warm it on a steam bath for 10 minutes, add exactly 0.5 mL of diluted Folin TS (1 in 2), shake to mix, and warm it on a steam bath for 20 minutes. To these solutions, proceed in the same manner by using 0.5 mL of water, and use this solution as the control solution. Perform the test as directed under the Ultraviolet-visible Spectroscopy to measure the absorbances at the wavelength of 750 nm.
Using the absorbance obtained from each standard solution, prepare a calibration curve by plotting absorbance on the y-axis and concentration on the x-axis. Use this calibration curve to determine the amount of protein in the test solution and calculate the content in the sample.

Assay (1) ***Test animals***—Use a healthy female white mice with a weight of about 45 g.

(2) ***Standard solution***—Dissolve chorionic gonadotropin RS in bovine serum albumin-Isotonic Sodium Chloride Injection to make solutions containing 7.5, 15, 30, and 60 units per 2.5 mL of this solution, respectively. Inject each of these solutions into four groups of test animals, each consisting of 5 animals according to the procedure (4), and measure the ovarian weight. Separately, inject bovine serum albumin-Isotonic Sodium Chloride Injection into one group, and use this as the control group. Based on the test results, the concentration of the standard substance, which is estimated to result in ovarian mass about 2.5 times that of the control group, is set as the concentration of the low-concentration standard solution. The concentration of the high-concentration standard solution is set at 1.5 to 2.0 times the concentration of the low-concentration standard solution. Dissolve the chorionic gonadotropin RS in bovine serum albumin-Isotonic Sodium Chloride Injection so that the concentration of this solution matches the predetermined concentration of the high-concentration standard solution and low-concentration standard solution, and use these solutions as the high-concentration standard solution S_H and the low-concentration standard solution S_L.

(3) ***Test solution***—Weigh accurately an appropriate amount of Chorionic Gonadotropin according to the labeling unit, dissolve in bovine serum albumin-Isotonic Sodium Chloride Injection to make solutions containing the same number of units in the same volume, and use these solutions as the high-concentration test solution T_H, and the low-concentration test solution T_L.

(4) ***Procedure***—Divide the test animals into four groups, A, B, C, and D, each with at least 10 individuals in a randomized manner. Inject subcutaneously 0.5 mL of S_H, S_L, T_H, and T_L to each group once a day for 5 days. On the 6th day, extract the ovaries, remove attached fat and other unnecessary tissues, absorb lightly with filter paper, and measure the ovarian mass immediately.

(5) ***Calculation***—The ovarian masses obtained from S_H, S_L, T_H, and T_L are denoted as y_1, y_2, y_3, and y_4, respectively. Sum the values of y_1, y_2, y_3, and y_4 for each group to obtain Y_1, Y_2, Y_3, and Y_4, respectively.

The number of units in each mg of Chorionic Gonadotropin = Anti log M × (the units per mL of the high-concentration standard solution) × $\frac{b}{a}$

$$M = \frac{IY_a}{Y_b}$$

$$I = \log\frac{S_H}{S_L} = \log\frac{T_H}{T_L}$$

$$Y_a = -Y_1 + Y_2 + Y_3 - Y_4$$

$$Y_b = Y_1 + Y_2 + Y_3 + Y_4$$

a: Sampling amount (mg)

b: Total volume (mL) of the high-concentration test solution with the sample dissolved in bovine serum albumin-Isotonic Sodium Chloride Injection

However, according to the following equation, F' is smaller than F_1 for n calculated based on S^2. Also, calculate L (P = 0.95) according to the following equation; L is NMT 0.3. If F' exceeds F_1 or L exceeds 0.3, increase the number of test animals or adjust the experimental conditions until these values are not exceeded, and repeat the test.

$$F = \frac{(Y_1 - Y_2 - Y_3 + Y_4)^2}{4fs^2}$$

$$s2 = \frac{\sum y^2 - \frac{Y}{f}}{n}$$

$$L = 2\sqrt{(C-1)(CM^2 + 0.09062)}$$

$$C = \frac{Y_b^2}{Y_b^2 - 4fs^2t^2}$$

$$Y = Y_1^2 + Y_2^2 + Y_3^2 + Y_4^2$$

$$n = 4(f\text{-}1)$$

f: The number of test animals in each group
$\sum y^2$: Sum of the squares of y_1, y_2, y_3, and y_4 for each group
t^2: The values in the table for s^2 calculated for different values of n.

n	$t^2 = F$	n	$t^2 = F$	n	$t^2 = F$
1	161.45	13	4.667	25	4.242
2	18.51	14	4.600	26	4.225
3	10.129	15	4.543	27	4.210
4	7.709	16	4.494	28	4.196
5	6.608	17	4.451	29	4.183
6	5.987	18	4.414	30	4.171
7	5.591	19	4.381	40	4.085
8	5.318	20	4.351	60	4.001
9	5.117	21	4.325	120	3.920
10	4.965	22	4.301	∞	3.841
11	4.844	23	4.279		
12	4.747	24	4.260		

Packaging and storage Preserve in light-resistant, tight containers in a cold place.

Chorionic Gonadotrophin for Injection
주사용 태반성성선자극호르몬

Chorionic Gonadotrophin for Injection is a preparation for injection, which is dissolved before use. It contains NLT 80.0% and NMT 125.0% of the labeled units of chorionic gonadotrophin.

Method of preparation Prepare as directed under Injections, with Chorionic Gonadotrophin.

Description Chorionic Gonadotrophin for Injection occurs as a white to pale yellowish brown powder or a mass. It is freely soluble in water.

Identification Perform the test as directed under the Identification of Chorionic Gonadotrophin.

Loss on drying NMT 5.0% (1.0 g, in vacuum, phosphorus pentoxide, 4 hours).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.03 EU per 1 unit of Chorionic Gonadotrophin for Injection.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay under Chorionic Gonadotrophin. The ratio of the quantified units to the labeled units is calculated by the following equation.

The ratio of the quantified units to the labeled units
= Antilog M

Packaging and storage Preserve in light-resistant, hermetic containers, and in a cold place.

Chromium in Dried Yeast
크롬함유건조효모

Chromium in Dried Yeast is prepared by culturing yeast in a culture medium containing chromium to make chromium to organically bind to the yeast.

Chromium in Dried Yeast contains NLT 500 μg of chromium (Cr : 52.00) per g.

Description Chromium in Dried Yeast occurs as a white or light gray powder and has taste and smell of yeast.

Identification Similar intensities of absorption are exhibited at the same wavelengths when measured as directed under the Assay.

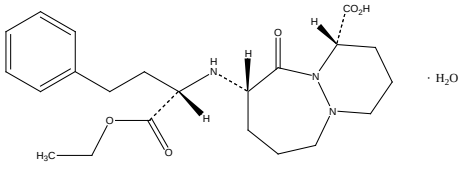
Loss on drying NMT 6.0% (1 g, 70 ℃, 3 hours).

Residue on ignition NMT 8.0% (1 g).

Assay Weigh accurately about 0.1 g of Chromium in Dried Yeast and perform the test as directed under the Analysis for Minerals.

Packaging and storage Preserve in light-resistant, tight containers.

Cilazapril Hydrate
실라자프릴수화물



Cilazapril $C_{22}H_{31}N_3O_5 \cdot H_2O$: 435.51
(1*S*,9*S*)-9-{[(2*S*)-1-Ethoxy-1-oxo-4-phenylbutan-2-yl]amino}-10-oxo-octahydro-1*H*-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid monohydrate [*92077-78-6*]

Cilazapril Hydrate contains NLT 98.5% and NMT 101.5% of cilazapril hydrate ($C_{22}H_{31}N_3O_5 \cdot H_2O$), calculated on the anhydrous basis.

Description Cilazapril Hydrate occurs as white to yellowish white crystals or a crystalline powder.
It is very soluble in methanol, freely soluble in ethanol(99.5) or acetic acid(100), and slightly soluble in water.
It is gradually changed to yellow by light.

Identification (1) To 4 mL of an aqueous solution of Cilazapril Hydrate (1 in 1000), add 2 mL of Dragendorff's TS; an orange precipitate is produced.

(2) Determine the infrared spectra of Cilazapril Hydrate and cilazapril hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy, respectively; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_{365\,nm}^{20}$: Between -383° and -399° [0.2 g calculated on the anhydrous basis, 0.067 mol/L phosphate buffer solution (pH 7.0), 50 mL, 100 mm)].

Purity (1) ***Chloride***—Perform the test using 1.0 g of Cilazapril Hydrate. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid TS (NMT 0.009%).

(2) ***Sulfate***—Dissolve 1.0 g of Cilazapril Hydrate in 40 mL of water and 1.5 mL of dilute hydrochloric acid, and add water to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution with 0.4 mL of 0.005 mol/L sulfuric acid TS (NMT 0.019%).

(3) ***Heavy metals***—Proceed with 1.0g of Cilazapril Hydrate according to Method 4, and perform the test. However, use 10 mL of a solution of magnesium nitrate in ethanol(95) (1 in 8). Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Related substance I***—Dissolve 0.20 g of Cilazapril Hydrate in methanol to make exactly 5 mL, and use this solution as the test solution. Separately, weigh accurately 2 mg of cilazapril related substance I {1,1-Dimethylethyl (1*S*,9*S*)-9-[[(*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-10-oxooctahydro-6*H*-pyridazino[1,2-α][1,2]diazepine-1-carboxylate} RS, dissolve in methanol to make exactly 50 mL, and use this solution as the standard solution (1). Dissolve 5 mg each of cilazapril related substance I RS and Cilazapril Hydrate in methanol to make exactly 10 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution, the standard solution (1) and the standard solution (2) on a plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetic acid, methanol, hexane, acetic acid and water (60 : 15 : 15: 5) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly a mixture of 12 w/v% ascetic acid and bismuth potassium iodide TS (10 : 1) on the plate, and then spray hydrogen peroxide TS; the spots of related substance I from the test solution are not more intense than those from the standard solution (1) (NMT 0.1%). However, the test is valid when the two spots obtained from the standard solution (2) are clearly separated.

(5) ***Other related substances***—Weigh accurately 25 mg of Cilazapril Hydrate, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the test solution. To 1.0 mL of the test solution, add the mobile phase to make exactly 50 mL, and to 5.0 mL of this solution, add the mobile phase to make exactly 20 mL, and use this solution as the standard solution (1). Separately, dissolve 10 mg of cilazapril related substance IV {(1S,9S)-9-[[(R)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-10-oxooctahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid} RS in the test solution to make exactly 20 mL, and use this solution as the standard solution (2). Perform the test with 20 μL each of the test solution and the standard solution (1) according to the following conditions, as directed under the Liquid Chromatography. The peak area corresponding to related substance IV from the test solution is not greater than 0.4 times the major peak area from the standard solution (1) (0.2%), the peak area corresponding to cilazapril related substance II {(1S,9S)-9-[[(S)-1-Carboxy-3-phenylpropyl]amino]-10-oxooctahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid} is not greater than the major peak area from the standard solution (1) (0.5%), the peak area corresponding to cilazapril related substance III {ethyl (1S,9S)-9-[[(S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-10-oxooctahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate} is not greater than 0.2 times the major peak area from the standard solution (1) (0.1%), the peak areas other than the major peak and peaks of related substances II, III, and IV of the test solution is not greater than 0.2 times the major peak area from the standard solution (1) (0.1%), and the total area of all peaks other than the major peak is not greater than 2 times the major peak area from the standard solution (1). However, the peaks with areas smaller than 0.1 times the major peak area obtained from the standard solution (1) and the peak area of related

substance I are excluded.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Add 10mL of triethylamine to 750 mL of water to mix, add phosphoric acid to adjust the pH to 2.3, add 200mL of tetrahydrofuran, and mix.

Flow rate: 1 mL/min

System suitability

Test for required detectability: Proceed with 20 μL each of the test solution and the standard solution (1) under the above conditions; the relative retention times of related substances II, IV and III to the peak retention time of cilazapril are about 0.6, 0.9 and 1.6, respectively.

System performance: Adjust the sensitivity of the system so that the height of the major peak obtained from the standard solution (1) by testing under the above conditions using 20 μL each of the standard solution (1) and standard solution (2) is NLT 50% of the full scale of the data collection device; the resolution of the cilazapril peak and related substance IV peak obtained from the standard solution (2) is NLT 2.5.

Time span of measurement: About 2 times the peak retention time of cilazapril. If related substance I with relative retention time between 4 and 5 is present, it is eluted.

Water Between 3.5% and 5.0% (0.3 g, volumetric titration, direct titration).

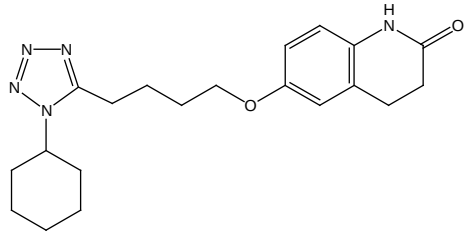
Residue on ignition 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Cilazapril Hydrate, dissolve in 10 mL of ethanol(95), add water to make 50 mL, and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 41.75 mg of $C_{22}H_{31}N_3O_5 \cdot H_2O$

Packaging and storage Preserve in well-closed containers.

Cilostazol
실로스타졸



$C_{20}H_{27}N_5O_2$: 369.46

6-[4-(1-Cyclohexyltetrazol-5-yl)butoxy]-3,4-dihydro-1*H*-quinolin-2-one [*73963-72-1*]

Cilostazol, when dried, contains NLT 98.5% and NMT 101.5% of cilostazol ($C_{20}H_{27}N_5O_2$).

Description Cilostazol occurs as white to pale yellowish white crystals or a crystalline powder.
It is slightly soluble in methanol, ethanol(99.5) and acetonitrile, and practically insoluble in water.

Identification (1) Determine the absorption spectra of solutions of Cilostazol and Cilostazol RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cilostazol and Cilostazol RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy, respectively; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 158 and 162 ℃.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Cilostazol according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Dissolve 25 mg of Cilostazol in 25 mL of acetonitrile, and use this solution as the test solution. Pipet 1 mL of the test solution, and add acetonitrile to make exactly 100 mL. Pipet 10 mL of this solution, add acetonitrile to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the each peak area other than cilostazol obtained from the test solution is not larger than 0.7 times the peak area of cilostazol from the standard solution. Also, the sum of peak areas other than the peak of cilostazol from the test solution is not larger than 1.2 times the peak area of cilostazol from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of hexane, ethyl acetate and methanol (10 : 9 : 1).

Flow rate: Adjust the flow rate so that the retention time of cilostazol is about 7 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution, and add acetonitrile to make exactly 10 mL. Confirm that the peak area of cilostazol obtained from 10 μL of this solution is equivalent to 7 to 13% of that of the standard solution.

System performance: Pipet 1 mL of the test solution, add 1 mL of a solution prepared by dissolving 5 mg of 3,4-dihydro-6-hydroxy-2(1H)-quinolinone in 10 mL of acetonitrile, and add acetonitrile to make exactly 100 mL. Proceed with 10 μL of this solution under the above conditions; 3,4-dihydro-6-hydroxy-2(1H)-quinolinone and cilostazol are eluted in this order with the resolution between these peaks being NLT 9.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above conditions; the relative standard deviation of the peak area of cilostazol is NMT 2.0%.

Time span of measurement: About 3 times the retention time of cilostazol beginning after the solvent peak.

Loss on drying NMT 0.1% (1 g, 105 °C, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg each of Cilostazol and Cilostazol RS, previously dried, dissolve each in methanol, add exactly 5 mL of the internal standard solution, and add methanol to make 50 mL. Take 1 mL each of these solutions, add methanol to make 10 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, of cilostazol to that of the internal standard.

$$\text{Amount (mg) of cilostazol } (C_{20}H_{27}N_5O_2) = \text{Amount (mg) of cilostazol RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of benzophenone in methanol (1 in 250).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of water, acetonitrile and methanol (10 : 7 : 3).

Flow rate: Adjust the flow rate so that the retention time of cilostazol is about 9 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution under the above conditions; cilostazol and the internal standard are eluted in this order with the resolution between these peaks being NLT 9.0.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solution under the above conditions; the relative standard deviation of the peak area ratio of cilostazol to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Cilostazol Tablets
실로스타졸 정

Cilostazol Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of cilostazol ($C_{20}H_{27}N_5O_2$: 369.46).

Method of preparation Prepare as directed under tablets, with Cilostazol.

Identification Weigh an amount of Cilostazol Tablets, previously powdered, equivalent to 50 mg of cilostazol according to the labeled amount, add 10 mL of acetone, mix well, and centrifuge. Take the clear supernatant and use the solution as the test solution. Separately, dissolve 25 mg of cilostazol RS in 5 mL of acetone and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 6 μL each of the test solution and the standard solution on a thin-layer chromatographic plate of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, acetonitrile, methanol and formic acid (75 : 25 : 5 : 1) as the developing solvent to a distance of about 12 cm and air-dry the plate. Spray evenly Dragendorff's TS on the plate; the principal spots from the test solution and the standard solution are orange and have the same R_f value.

Dissolution Perform the test with 1 tablet of Cilostazol Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of sodium lauryl sulfate solution (3 in 1000) as the dissolution medium.

Take NLT 20 mL of the dissolved solution 45 minutes for a 50 mg tablet and 60 minutes for a 100 mg tablet after starting the test and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 10 mL of the filtrate, take accurately *V* mL of the subsequent filtrate, add the solution of sodium lauryl sulfate (3 in 1000) to make exactly *V'* mL of a solution having known concentration of about 5.6 μg of cilostazol ($C_{20}H_{27}N_5O_2$) per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 28 mg of cilostazol RS, previously dried at 105 °C for 2 hours, and dissolve in methanol to make exactly 100 mL. Pipet 4 mL of this solution, add the solution of sodium lauryl sulfate (3 in 1000) to make exactly 200 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution at 257 nm as directed under the Ultraviolet-visible Spectroscopy using the solution of sodium lauryl sulfate (3 in 1000) as the control solution. It meets the requirements when the dissolution rates of 50 mg of Cilostazol Tablets and 100 mg of Cilostazol Tablets in 45 minutes are NLT 75% and NLT 70%, respectively.

Dissolution rate (%) with respect to the labeled amount of cilostazol ($C_{20}H_{27}N_5O_2$)

$$= \text{Amount (mg) of cilostazol RS} \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 18$$

C: Labeled amount of cilostazol ($C_{20}H_{27}N_5O_2$) in 1 table

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately and powder NLT 20 tablets of Cilostazol Tablets. Weigh accurately an amount, equivalent to about 50 mg of cilostazol ($C_{20}H_{27}N_5O_2$), add exactly 5 ml of the internal standard solution, and add methanol to make 50 mL. Shake well to mix for 10 minutes. Take 1 mL of this solution, add methanol to make 10 mL, filter through a membrane filter with a pore size not exceeding 0.5 μm, and use the filtrate as the test solution. Separately, weigh accurately about 50 mg of cilostazol RS, dissolve in methanol, add exactly 5 ml of the internal standard solution, and add methanol to make 50 mL. Take 1 mL of this solution, add methanol to make exactly 10 mL, and use the solution as the standard solution. Perform the test with each 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the ratios, Q_T and Q_S, of the peak area of cilostazol to that of the internal standard.

Amount (mg) of cilostazol ($C_{20}H_{27}N_5O_2$)

$$= \text{Amount (mg) of cilostazol RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of benzophenone in methanol (1 in 250).

Operating conditions

Proceed as directed under the operating conditions described in the Assay under Cilostazol.

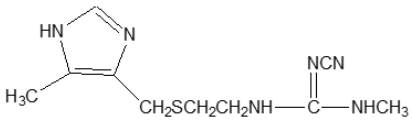
System suitability

System performance: Proceed as directed under the system suitability in the Assay under Cilostazol.

System repeatability: Repeat the test 6 times with each 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio of cilostazol to the internal standard is NMT 1.5%.

Packaging and storage Preserve in well-closed containers.

Cimetidine
시메티딘



$C_{10}H_{16}N_6S$: 252.34

2-Cyano-1-methyl-3-{2-[(5-methyl-1*H*-imidazol-4-yl)methylsulfanyl]ethyl}guanidine [*70059-30-2*]

Cimetidine, when dried, contains NLT 99.0% and NMT 101.0% of cimetidine ($C_{10}H_{16}N_6S$).

Description Cimetidine occurs as a white crystalline powder. It is odorless and has a bitter taste.
It is freely soluble in methanol or in acetic acid(100), sparingly soluble in ethanol(95), slightly soluble in water and practically insoluble in ether.
It dissolves in dilute hydrochloric acid.
It is gradually colored by light.

Identification (1) To 0.1 mL of a solution of Cimetidine in ethanol(95) (1 in 100), add 5 mL of citric acid-acetic anhydride TS and heat on a steam bath for 15 minutes; the resulting solution exhibits a purple color.

(2) Determine the infrared spectra of Cimetidine and cimetidine RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

pH Dissolve 0.5 g of Cimetidine in 50 mL of freshly boiled and cooled water, shake for 5 minutes to mix, and filter; the pH of this solution is between 9.0 and 10.5.

Melting point Between 140 and 144 °C.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Cimetidine in 10 mL of methanol; the resulting solution is colorless to pale yellow and clear.

(2) ***Heavy metals***—Proceed with 2.0 g of Cimetidine according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Dissolve 1.0 g of Cimetidine in 5 mL of dilute hydrochloric acid and perform the test using this solution as the test solution (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.5 g of Cimetidine in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution and add methanol to make exactly 100 mL. Pipet 1 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 4 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate using a mixture of ethyl acetate, methanol and ammonia water(28) (21 : 2 : 2) as the developing solvent to a distance of about 15 cm, air-dry the plate, and then dry further at 80 ℃ for 30 minutes. Allow the plate to stand in iodine vapor for 45 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.25%. (1 g).

Assay Weigh accurately about 0.24 g of Cimetidine, previously dried, dissolve in 75 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 25.234 mg of $C_{10}H_{16}N_6S$

Packaging and storage Preserve in light-resistant, well-closed containers.

Cimetidine Tablets
시메티딘 정

Cimetidine Tablets contains NLT 90.0% and NMT 110.0% of the labeled amount of cimetidine ($C_{10}H_{16}O_6$: 252.34).

Method of preparation Prepare as directed under Tablets, with Cimetidine.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Dissolution Perform the test with 1 tablet of Cimetidine Tablets at 100 revolutions per minute according to Method 1 under the Dissolution, using 900 mL of 0.01 mol/L hydrochloric acid TS as the dissolution medium. Take the dissolved solution 15 minutes after starting the Dissolution and, if necessary, dilute with 0.01 mol/L hydrochloric acid TS. Use this solution as the test solution. Separately, weigh accurately an appropriate amount of cimetidine RS, dissolve in 0.01 mol/L hydrochloric acid TS to make it the same concentration as the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using 0.01 mol/L hydrochloric acid TS as a control, and determine the absorbance at the absorbance maximum wavelength (λmax) of about 218 nm.

It meets the requirements if the dissolution rate of Cimetidine Tablets in 15 minutes is NLT 80%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Cimetidine Tablets and powder. Weigh accurately a portion of powder, equivalent to about 0.1 g of cimetidine ($C_{10}H_{16}N_6S$), add 50 mL of methanol, shake for 2 minutes to mix, add 40 mL of water, sonicate for 15 minutes, and add water to make exactly 250 mL. To 5.0 mL of this solution, add the mobile phase to it make exactly 200 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of cimetidine RS and dissolve in a mixture of water and methanol (4 : 1) to make exactly 50 mL. To 5.0 mL of this solution, add the mobile phase to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of cimetidine.

Amount (mg) of cimetidine ($C_{10}H_{16}N_6$)
$= \text{Amount (mg) of cimetidine RS} \times \frac{A_T}{A_S} \times 5$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: Add 0.3 mL of phosphoric acid and water to 200 mL of methanol to make 1000 mL.

Flow rate: 2 mL/min

System suitability

System repeatability: Repeat the test 6 times with 50 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area of cimetidine is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Cimetidine, Aldioxa and Magnesium Aluminosilicate Tablets
시메티딘·알디옥사·규산알루민산마그네슘 정

Cimetidine, Aldioxa and Magnesium Aluminosilicate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of cimetidine ($C_{10}H_{16}N_6S$: 252.34), aldioxa ($C_4H_7AlN_4O_5$: 218.10), magnesium oxide (MgO: 40.30) in magnesium aluminosilicate, and total aluminum oxide in magnesium aluminosilicate and aldioxa (Al_2O_3: 101.96).

Method of preparation Prepare as directed under Tablets, with Cimetidine, Aldioxa, and Magnesium Aluminosilicate.

Identification (1) ***Cimetidine***—The major peaks of the test solution and standard solution obtained under the Assay are the same in the retention time.

(2) ***Aldioxa***—The major peaks of the test solution and standard solution obtained under the Assay are the same in the retention time.

(3) ***Magnesium aluminometasilicate***—(i) To 0.5 g of Cimetidine, Aldioxa and Magnesium Aluminosilicate Tablets, add 5 mL of dilute sulfuric acid (1 in 3), heat until white fumes are evolved, cool, add 20 mL of water, then filter. Use the residue in Identification (3). Add ammonia TS to the filtrate to neutralize, and filter the obtained precipitate. Use the filtrate in Identification (2). The solution obtained by adding dilute hydrochloric acid to the residue responds to the Qualitative Analysis for aluminum salt.

(ii) The filtrate obtained in Identification (1) responds to the Qualitative Analysis for magnesium.

(iii) Wash the residue obtained in Identification (1) with 30 mL of water, add 2 mL of methylene blue solution (1 in 10,000), and wash with 30 mL of water again; a blue precipitate is produced.

Acid-neutralizing capacity Weigh accurately the mass of NLT 20 tablets of Cimetidine, Aldioxa and Magnesium Aluminosilicate Tablets, and powder. The volume of 0.1 mol/L hydrochloric acid consumed for daily dose (6 tablets) as directed under the Acid-neutralizing Capacity, is NLT 135 mL.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Cimetidine and aldioxa***—Weigh accurately the mass of NLT 20 tablets of Cimetidine, Aldioxa and Magnesium Aluminosilicate Tablets, and powder. Weigh accurately a portion of powder, equivalent to about 50 mg of cimetidine ($C_{10}H_{16}N_6S$) and about 50 mg of aldioxa ($C_4H_7AlN_4O_5$), and add 0.1 mol/L hydrochloric acid to make exactly 100 mL. Sonicate the resulting solution for about 20 minutes, filter the solution through a membrane filter with a pore size of 0.45 μm, discard the first 2 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately about 50 mg of cimetidine RS and about 50 mg of aldioxa RS, add 80 mL of 0.1 mol/L hydrochloric acid, sonicate for about 20 minutes, and add 0.1 mol/L hydrochloric acid to make exactly 100 mL. Use this solution as the standard solution. Take exactly 10 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas of cimetidine and aldioxa, A_{T1}, A_{S1}, A_{T2} and A_{S2}, for each solution.

$$\text{Amount (mg) of cimetidine } (C_{10}H_{16}N_6S) = \text{Amount (mg) of cimetidine RS} \times (A_{T1} / A_{S1})$$

$$\text{Amount (mg) of aldioxa } (C_4H_7AlN_4O_5) = \text{Amount (mg) of aldioxa RS} \times (A_{T2} / A_{S2})$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Use mobile phases A and B to control a stepwise or gradient elution-wise as follows.

Mobile phase A: A mixture of 0.01 mol/L potassium phosphate buffer solution (pH 8.0) and methanol (9 : 1).

Mobile phase B: A mixture of methanol and 0.01 mol/L potassium phosphate buffer solution (pH 8.0) (9 : 1).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0-3	100	0
3-10	100 → 0	0 → 100
10-15	0	100

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; aldioxa and cimetidine peaks are eluted in this order with the resolution being NLT 14.0.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of aldioxa and cimetidine is NMT 1.0%.

(2) ***Total aluminum oxide in magnesium aluminosilicate and aldioxa***—Weigh accurately the mass of NLT 20 tablets of Cimetidine, Aldioxa and Magnesium Aluminosilicate Tablets and powder. Weigh accurately a portion of powder equivalent to about 25 mg of aluminum oxide (Al_2O_3), dissolve in 3.5 mL of dilute hydrochloric acid by heating on a steam bath for 15 minutes, cool, and add water to make exactly 100 mL. Centrifuge this solution, and use the clear supernatant as the test solution. Pipet 25 mL of the test solution, add exactly 20 mL of 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS, add 8 mL of acetic acid-ammonium acetate buffer solution (pH 4.8) and 20 mL of water, boil for 5 minutes, and cool it. Add 50 mL of ethanol(95), and titrate with 0.02 mol/L zinc sulfate VS (indicator: 2 mL of dithizone TS). The endpoint of the titration is when the color of the solution changes from light dark green to light red. Perform a blank test in the same manner and make any necessary correction.

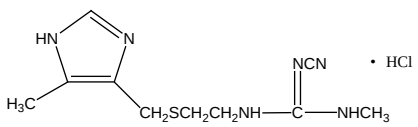
Each mL of 0.02 mol/L ethyldiaminetetraacetic acid disodium salt VS
= 1.020 mg of Al_2O_3

(3) ***Magnesium oxide in magnesium aluminosilicate***—Pipet 25 mL of the test solution obtained in Assay (2), add 50 mL of water and 10 mL of triethanolamine solution (1 in 2), and shake to mix well, and add 5 mL of ammonia-ammonium chloride buffer solution (pH 10.7). Titrate with 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 0.04 g of eriochrome black T-sodium chloride). The endpoint is when the reddish purple color of the solution appears with the blue color persisting for 30 seconds. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 0.8060 mg of MgO

Packaging and storage Preserve in well-closed containers.

Cimetidine Hydrochloride
시메티딘염산염



$C_{10}H_{16}N_6S \cdot HCl$: 288.80
2-Cyano-1-methyl-3-{2-[(5-methyl-1*H*-imidazol-4-yl)methylsulfanyl]ethyl}guanidine hydrochloride [*70059-30-2*]

Cimetidine Hydrochloride contains NLT 98.0% and NMT 102.0% of cimetidine hydrochloride ($C_{10}H_{16}N_6S \cdot HCl$), calculated on the dried basis.

Description Cimetidine Hydrochloride occurs as a white crystalline powder.
It is freely soluble in water and sparingly soluble in ethanol(95).

Identification (1) Weigh 15 mg of Cimetidine Hydrochloride and cimetidine hydrochloride RS, respectively, and dissolve in 0.05 mol/L sulfuric acid TS to make exactly 100 mL. Add 0.05 mol/L sulfuric acid TS to 5.0 mL each of these solutions to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cimetidine Hydrochloride and cimetidine hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Cimetidine Hydrochloride responds to the Qualitative Analysis (2) for chloride.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Cimetidine Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Weigh accurately 0.1 g of Cimetidine Hydrochloride, add the mobile phase to make exactly 250 mL, and use this solution as the test solution. Pipet 1.0 mL of the test solution, add the mobile phase to make exactly 500 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test and the standard solutions as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method and calculate the amount of each related substance; the amount of each related substance is NMT 0.2%, and the total amount of related substances is NMT 1.0%.

Content (%) of each related substance
$$= 0.2 \times \frac{A_i}{A_S}$$

A_i: Peak area of each related substance obtained from the test solution

A_S: Peak area of each related substance obtained from the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 0.94 g of sodium 1-hexanesulfonate in 240 mL of methanol, and add 0.3 mL of phosphoric acid and water to make 1000 mL.

Flow rate: 2 mL/minute

System suitability

System performance: Weigh 50 mg of Cimetidine Hydrochloride, dissolve in 100 mL of 1 mol/L hydrochloric acid TS, heat on a steam bath for 10 minutes, and cool. Pipet 1.0 mL of this solution and add the mobile phase to make 250 mL. Proceed with 50 μL of this solution under the above operating conditions; the resolution between the peaks of cimetidine and cimetidine amide analogue is NLT 4.0. Also, proceed with 50 μL of the standard solution under the above operating conditions; the mass distribution ratio is NLT 3.0 and the number of theoretical plates is NLT 2000.

System repeatability: Repeat the test 6 times with 50 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area of cimetidine is NMT 7.0%.

Loss on drying NMT 0.5% (1 g, 105 °C, 2 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.115 g of Cimetidine Hydrochloride, dissolve in 50 mL of water, and add 50 mL of methanol and water to make exactly 250 mL. Add the mobile phase to 5.0 mL of this solution to make exactly 200 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of cimetidine hydrochloride RS, add a mixture of water and methanol (80 : 20) to make exactly 100 mL. Add the mobile phase to 5.0 mL of this solution to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of cimetidine, A_T and A_S, respectively.

Amount (mg) of cimetidine hydrochloride ($C_{10}H_{16}N_6S \cdot HCl$)

$$= \text{Amount (mg) of cimetidine hydrochloride RS} \times \frac{A_T}{A_S} \times 2.5$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Add 0.3 mL of phosphoric acid and water to 200 mL of methanol to make 1000 mL.

Flow rate: About 2 mL/minute.

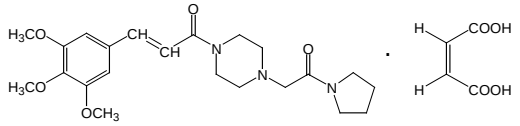
System suitability

System performance: Proceed with 50 μL of the standard solution under the above operating conditions; the mass distribution ratio is NLT 0.6 and the number of theoretical plates is NLT 1000.

System repeatability: Repeat the test 5 times with 50 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area of cimetidine is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Cinepazide Maleate
시네파지드말레산염



$C_{22}H_{31}N_3O_5 \cdot C_4H_4O_4$: 533.58

1-[4-[2-Oxo-2-(1-pyrrolidinyl)ethyl]-1-piperazinyl]-3-(3,4,5-trimethoxyphenyl)-2-propen-1-one (2*Z*)-2-butenedioate (1:1), [*26328-04-1*]

Cinepazide Maleate contains NLT 98.0% and NMT 101.0% of cinepazide maleate ($C_{22}H_{31}N_3O_5 \cdot C_4H_4O_4$).

Description Cinepazide Maleate occurs as a white to pale yellow powder. It is almost odorless and has a bitter taste.

It is very soluble in formic acid or in acetic acid(100), freely solution in water, soluble in chloroform, sparingly soluble in ethanol(95) and practically insoluble in ether. It dissolves in dilute hydrochloric acid.

Melting point—About 175 °C (with decomposition).

Identification (1) To 5 mL of the aqueous solution of Cinepazide Maleate (1 in 25), add 5 drops of Reinecke salt TS; a pale reddish brown precipitate is formed.

(2) Determine the infrared spectrum of Cinepazide Maleate, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; it exhibits absorption at the wavenumbers of about 1660 cm^{-1}, 1617 cm^{-1}, 1583 cm^{-1}, 1503 cm^{-1}, 1483 cm^{-1}, 1122 cm^{-1}, 998 cm^{-1} and 867 cm^{-1}.

pH Between 3.4 and 4.0 (1.0 g, water, 100 mL).

Absorption $E_{1cm}^{1\%}$ (304 nm): Between 384 and 420 (after drying, 20 mg, 0.1 mol/L hydrochloric acid TS, 2000 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Cinepazide Maleate in 10 mL of water; the resulting solution is colorless to pale yellow and clear.

(2) ***Chloride***—Proceed with 1.0 g of Cinepazide Maleate and perform the test as directed under the Chloride. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.014%).

(3) ***Heavy metals***—Proceed with 2.0 g of

Cinepazide Maleate according to Method 2 under the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Proceed with 1.0 g of Cinepazide Maleate according to Method 3 under the Arsenic and perform the test (NMT 2 ppm).

(5) ***Related substances***—Dissolve 0.10 g of Cinepazide Maleate in 10 mL of a mixture of chloroform, ethanol(95) and acetic acid(100) (8 : 2 : 1) and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of chloroform, ethanol(95) and acetic acid(100) (8 : 2 : 1) to make exactly 100 mL and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of chloroform, ethanol(95) and acetic acid(100) (8 : 2 : 1) to a distance of about 10 cm, and air-dry the plate. Allow the plate to stand in iodine vapor for 30 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.3% (1 g, in vacuum, phosphorus pentoxide, 80 ℃, 3 hours).

Residue on ignition NMT 0.10% (1 g).

Assay Weigh accurately about 0.45 g of Cinepazide Maleate, previously dried, dissolve in 2 mL of formic acid, add 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 53.36 mg of $C_{26}H_{35}N_3O_9$

Packaging and storage Preserve in tight containers.

Cinepazide Maleate Injection
시네파지드말레산염 주사액

Cinepazide Maleate Injection contains NLT 95.0% and NMT 105.0% of the labeled amount of cinepazide maleate ($C_{22}H_{31}N_3O_5 \cdot C_4H_4O_4$: 533.58).

Method of preparation Prepare as directed under Injections, with Cinepazide Maleate.

Identification Weigh an amount of Cinepazide Maleate Injection, equivalent to 0.1 g of cinepazide maleate according to the labeled amount, dissolve in water to make 10 mL, and use the solution as the test solution. Separately, weigh 0.1 g of cinepazide maleate RS, dissolve in water to make 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each 10 μL of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate using a mixture of isopropanol and 0.1 mol/L of boric acid (85 : 15) as the developing solvent to a distance of about 10 cm and air-dry the plate. Examine the plate under ultraviolet rays (main wavelength: 254 nm) or spray the plate with a solution of 0.5% potassium permanganate in 1 mol/L sodium hydroxide; the R_f values of the spots obtained from the test solution and the standard solution are the same.

pH Between 3.3 and 5.3.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Weigh accurately an amount of Cinepazide Maleate Injection, equivalent to about 85 mg of cinepazide maleate ($C_{22}H_{31}N_3O_5 \cdot C_4H_4O_4$) according to the labeled amount, transfer to a 250-mL Erlenmeyer flask with a stopper, add 25 mL of water, 75 mL of chloroform, 5 mL of acetate buffer (pH 2.8) and 5 mL of the indicator, and mix well. Titrate with 0.01 mol/L sodium docusate VS. Add 5 mL of 0.01 mol/L sodium docusate VS at first and continue to titrate very slowly. Add 0.01 mol/L sodium docusate VS until the color of the indicator changes from green to grayish pink. After each addition, stir vigorously and allow to stand for 30 seconds. Perform a blank test in the same manner and make any necessary correction.

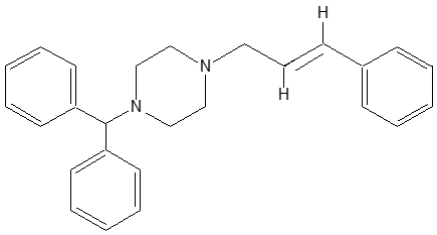
Each mL of 0.01 mol/L Sodium docusate VS
= 5.336 mg of $C_{22}H_{31}N_3O_5 \cdot C_4H_4O_4$

0.01 mol/L Sodium docusate—Weigh accurately about 4.446 g of anhydrous sodium docusate, dissolve in water to make exactly 1000 mL, and standardize as follows. Weigh accurately about 0.35 g of cinepazide maleate RS, previously dried, dissolve in water to make exactly 100 mL, and use the solution as the cinepazide maleate standard solution (prepare before use). Put exactly 10 mL of the standard solution to a 250-mL Erlenmeyer flask, add 15 mL of water, 75 mL of chloroform, 5 mL of acetate buffer (pH 2.8) and 5 mL of the indicator (prepare before use), prepared by mixing a solution of 15 mg of *p*-dimethylaminoazobenzen dissolved in 20 mL of chloroform and a solution of 15 mg of Oraset Blue B dissolved in 3 mL of acetic acid(100) and adding chloroform to

make 500 mL, mix well, and titrate with 0.01 mol/L sodium docusate VS. Add 5 mL of 0.01 mol/L sodium docusate VS at first and continue to titrate very slowly. Add 0.01 mol/L sodium docusate VS until the color of the indicator changes from green to grayish pink. After each addition, stir vigorously and allow to stand for 30 seconds. Perform a blank test in the same manner and make any necessary correction.

Packaging and storage Preserve in hermetic containers.

Cinnarizine
신나리진



$C_{26}H_{28}N_2$: 368.51

1-Benzhydryl-4-[(*E*)-3-phenylprop-2-enyl]piperazine [*298-57-7*]

Cinnarizine contains NLT 99.0% and NMT 101.0% of cinnarizine ($C_{26}H_{28}N_2$), calculated on the dried basis.

Description Cinnarizine occurs as a white powder.
It is freely soluble in dichloromethane, soluble in acetone, slightly soluble in methanol or ethanol(95), and practically insoluble in water.

Identification (1) Add 0.2 g of anhydrous citric acid to 20 mL of acetic anhydride, dissolve by heating on a steam bath at 80 °C for 10 minutes, and add about 20 mg of Cinnarizine; a purple color develops.

(2) Determine the infrared spectra of Cinnarizine and cinnarizine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy, respectively; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 10 mg of Cinnarizine in methanol to make 20 mL, and use this solution as the test solution. Separately, dissolve 10 mg of cinnarizine RS in methanol to make 20 mL, and use this solution as the standard solution (1). Dissolve 10 mg each of cinnarizine RS and flunarizine hydrochloride RS in methanol to make 20 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of acetone, methanol and 1 mol/L sodium chloride solution (50 : 30 : 20) to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength 254 nm); the R_f value of the principal spot from the test solution are the same with that from the standard solution (1). This test is valid when the two spots from the standard solution (2) are clearly separated.

Melting point Between 118 and 122 °C.

Purity (1) ***Clarity and color of solution*—**Dissolve 0.5 g of Cinnarizine in dichloromethane to make 20 mL. The solution is clear and not more intense than the following control solution.

Control solution—To a mixture of 24 mL of iron(III) chloride hexahydrate colorimetric stock solution, 10 mL of cobalt(II) chloride hexahydrate colorimetric stock solution and 4 mL of copper(II) sulfate pentahydrate colorimetric stock solution, add 62 mL of 1 w/v% hydrochloric acid to mix. To 2.5 mL of this solution, add 97.5 mL of 1 w/v% hydrochloric acid to mix.

(2) ***Acidity or alkalinity*—**Suspend 0.5 g of Cinnarizine in 15 mL of water, boil for 2 minutes, cool, and filter. Put water into the filtrate to make 20 mL, and use this solution as the test solution. To 10 mL of the test solution, add two drops of phenolphthalein TS and 0.25 mL of 0.01 mol/L sodium hydroxide solution; the solution exhibits a pink color. Add two drops of methyl red TS and 0.25 mL of 0.01 mol/L hydrochloric acid to 10 mL of the test solution; the solution exhibits a red color.

(3) ***Heavy metals*—**Dissolve 1.0 g of Cinnarizine in a mixture of acetone and water (85 : 15), add dilute hydrochloric acid to completely dissolve, and add a mixture of acetone and water (85 : 15) to make 20 mL. Use this solution as the test solution. Add a mixture of acetone and water (85 : 15) to 1.0 mL of lead standard stock solution to make exactly 100mL, and use this solution as the standard solution. To 12 mL of the test solution, add 2 mL of acetate buffer solution (pH 3.5) to mix, add 1.2 mL of thioacetamide TS to mix, and allow to stand for 2 minutes. The color of this solution is not more intense than the solution prepared by mixing 10 mL of the standard solution with 2 mL of the test solution and proceeding in the same manner (NMT 20 ppm).

(4) ***Related substances*—**Dissolve 25.0 mg of Cinnarizine in methanol to make exactly 100 mL, and use this solution as the test solution. Separately, dissolve 12.5 mg of cinnarizine RS and 15.0 mg of flunarizine hydrochloride RS in methanol to make exactly 100 mL. Add methanol to1.0 mL of this solution to make exactly 20 mL, and use the solution as the standard solution (1). Add methanol to 1.0 mL of the test solution to make 100 mL, put methanol into 5.0 mL of this solution to make 20 mL, and use this solution as the standard solution (2). Perform the test with 10 μL each of methanol (as the blank test solution), the test solution and the standard solutions as directed under the Liquid Chromatography according to the following conditions. The area of any peak other than the major peak obtained from the test solution is not

greater than the area of the major peak from the standard solution (2) (0.25%) and the sum of the peak areas other than the major peak obtained from the test solution is not more than twice the area of the major peak from the standard solution (2) (0.5%). However, exclude any peak with an area less than 0.2 times the area of the major peak from the standard solution (2).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 10 cm in length, packed with base-deactivated octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Mobile phase: Use mobile phases A and B to control stepwise or based on the gradient elution as follows.

Mobile phase A: 1 w/v% ammonium acetate solution.

Mobile phase B: 0.2 vol% solution of acetic acid(100) in acetonitrile.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 20	75 → 10	25 → 90
20 - 25	10	90
25 - 30	75	25
30 = 0	75	25

Flow rate: 1.5 mL/min

System suitability

System performance: Adjust the sensitivity of the system so that the height of the major peak obtained by testing under the above conditions using the standard solution (2) is at least 50% of the full scale of the data collection device. Proceed with the standard solution (1) under the above conditions; the retention times are about 11 minutes for cinnarizine and about 11.5 minutes for flunarizine with the resolution of the peaks of cinnarizine and flunarizine being NLT 5.0. If necessary, adjust the time program for the gradient elution control.

Loss on drying NMT 0.5% (1 g, in vacuum, 60 ℃, 4 hours).

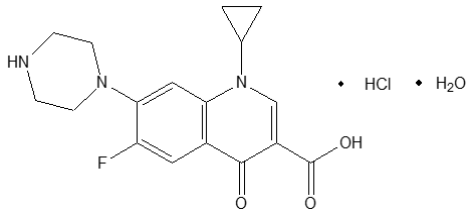
Residue on ignition NMT 0.1% (2 g).

Assay Weigh accurately 0.15 g of Cinnarizine, dissolve in 50 mL of a mixture of ethyl methyl ketone and acetic acid(100) (7 : 1), and titrate with 0.1 mol/L perchloric acid VS (indicator: 4 drops of 1-naphtholbenzein TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 18.426 mg of $C_{26}H_{28}N_2$

Packaging and storage Preserve in light-resistant, well-closed containers.

Ciprofloxacin Hydrochloride Hydrate
시프로플록사신염산염수화물



Ciprofloxacin Hydrochloride

$C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$: 385.82

1-Cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)quinoline-3-carboxylic acid hydrate hydrochloride [*86393-32-0*]

Ciprofloxacin Hydrochloride Hydrate contains NLT 98.0% and NMT 102.0% of ciprofloxacin hydrochloride ($C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$), calculated on the anhydrous basis.

Description Ciprofloxacin Hydrochloride Hydrate occurs as a pale yellow crystalline powder.

It is sparingly soluble in water, slightly soluble in acetic acid(31) or methanol, very slightly soluble in ethanol(99.5), and practically insoluble in acetone, acetonitrile, ethyl acetate, hexane or dichloromethane.

Identification (1) Determine the infrared spectra of Ciprofloxacin Hydrochloride Hydrate and ciprofloxacin hydrochloride hydrate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Weigh and dissolve 0.1 g of Ciprofloxacin Hydrochloride Hydrate in water to make 10 mL, and use this solution as the test solution. Separately, weigh and dissolve 0.1 g of ciprofloxacin hydrochloride hydrate RS to make 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin layer chromatographic plate made of silica gel for thin-layer chromatography. Allow it to stand for 15 minutes in ammonia gas. Next, develop the plate with a mixture of dichloromethane, methanol, ammonia water(28) and acetonitrile (4 : 4 : 2 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine under ultraviolet light (main wavelengths: 254 nm and 365 nm); the R_f value of the principal spots obtained from the test solution and the standard solution is the same.

(3) An aqueous solution of Ciprofloxacin Hydrochloride Hydrate (1 in 50) responds to the Qualitative Analysis for chloride.

pH Dissolve 1.0 g of Ciprofloxacin Hydrochloride Hydrate in 40 mL of freshly boiled and cooled water. The pH of this solution is between 3.0 and 4.5.

Purity (1) ***Heavy metals***—Weigh and proceed with 1.0 g of Ciprofloxacin Hydrochloride Hydrate according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Sulfate***—Perform the test with 0.375 g of Ciprofloxacin Hydrochloride Hydrate. Prepare the control solution with 0.30 mL of 0.005 mol/L sulfuric acid (NMT 0.04%).

(3) ***Fluoroquinolone acid***—Weigh an appropriate amount of ciprofloxacin hydrochloride hydrate RS, dissolve in water to make a solution containing 10 mg per mL, and use this solution as the test solution. Separately, weigh accurately 5.0 mg of fluoroquinolone acid RS, add 50 μL of ammonia TS, and add water to make 50 mL. Take 2.0 mL of this solution, add water to make 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin layer chromatographic plate made of silica gel for thin-layer chromatography. Allow the plate to stand for 15 minutes in the container containing 50 mL of ammonia TS, then develop the plate with a mixture of dichloromethane, methanol, ammonia water(28) and acetonitrile (4 : 4 : 2 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate for 15 minutes. Examine under ultraviolet light (main wavelength: 254 nm); any spot from the test solution, of which the R_f value is identical to that of the principal spot from the standard solution, is not larger and is not more intense than the principal spot from the standard solution (NMT 0.2%).

4) ***Related substances***—Perform the test according to the operating conditions as directed under the Assay. Determine each peak area A_i and the total area A_T for all peaks other than the major peak from the test solution, and calculate the content of each related substance in the test solution according to the following equation:

$$\text{Content (\%) of each related substance} = 100 \times \frac{A_i}{A_S}$$

Ciprofloxacin ethylenediamine analogue and each related substance are NMT 0.2% and the sum of all related substances is NMT 0.5%.

Water Between 4.7% and 6.7% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 25 mg of Ciprofloxacin Hydrochloride Hydrate, dissolve in mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of ciprofloxacin hydrochloride hydrate RS (previously determine the content of water), add the mobile phase to make a solution containing 0.5 mg per mL and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of ciprofloxacin hydrochloride hydrate, A_T and A_S, in each solution.

$$\text{Amount (mg) of ciprofloxacin hydrochloride hydrate } (C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O) = 50 \times C \times \frac{A_T}{A_S}$$

C: Concentration of ciprofloxacin hydrochloride hydrate in the standard solution (mg/mL), calculated on the anhydrous basis

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 278 nm).

Column: A stainless steel column, about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of 0.025 mol/L phosphoric acid, adjusted pH to 3.0 ± 0.1 with triethylamine, and acetonitrile (87:13).

Flow rate: 1.5 mL/min

System suitability

System performance: Dissolve ciprofloxacin ethylenediamine analogue RS in the ciprofloxacin standard solution to make a solution containing 0.5 mg per mL. Proceed with 10 μL of this solution according to the above conditions; ciprofloxacin ethylenediamine analogue and ciprofloxacin are eluted in this order with the resolution between these peaks being NLT 6.

System repeatability: Repeat the test 6 times according to the above conditions with 10 μL of the standard solution each time; the relative standard deviation of the peak areas of ciprofloxacin is NMT 1.5%.

Packaging and storage Preserve in light-resistant, tight containers.

Ciprofloxacin Hydrochloride Tablets
시프로플록사신염산염 정

Ciprofloxacin Hydrochloride Tablets

Ciprofloxacin Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of ciprofloxacin ($C_{17}H_{18}FN_3O_3$: 331.34).

Method of preparation Prepare as directed under Tablets, with Ciprofloxacin Hydrochloride Hydrate.

Identification (1) The retention times of the major peaks from the test solution and the standard solution prepared as directed under the Assay are the same.

(2) Place a number of tablets, equivalent to 1.5 g of Ciprofloxacin Hydrochloride Hydrate, in a suitable flask with 750 mL of water, sonicate for about 20 minutes, and add water to make 1000 mL. Centrifuge a portion of this suspension and use the clear supernatant obtained as the test solution. Separately, dissolve a suitable amount of ciprofloxacin hydrochloride hydrate RS in water to obtain a solution containing 1.5 mg per mL and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each 10 μL of the test solution and standard solution on a thin layer chromatographic plate made of silica gel for thin-layer chromatography. Allow the plate to stand in ammonia gas for about 15 minutes and develop the plate with a mixture of dichloromethane, methanol, ammonia TS and acetonitrile (4 : 4 : 2 : 1) as the developing solvent to a distance of about 15 cm in an unsaturated developing chamber. Remove the plate and air-dry for about 15 minutes. Examine under ultraviolet light (main wavelength: 254 nm and 366 nm); the R_f values of the principal spots from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 tablet of Ciprofloxacin Hydrochloride Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of 0.01 mol/L hydrochloric acid as the dissolution medium. Take the dissolved solution 30 minutes after starting the test and filter. If necessary, dilute with the dissolution medium and use the resulting solution as the test solution. Separately, weigh accurately an appropriate amount of ciprofloxacin hydrochloride hydrate RS, dissolve in the dissolution solution to the same concentration as the test solution, and use this solution as the standard solution. Determine the absorbances of the test solution and the standard solution at the absorbance maximum wavelength of about 276 nm as directed under the Ultraviolet-visible Spectroscopy, using the dissolution solution as a control solution.

It meets the requirements when the dissolution rate of Ciprofloxacin Hydrochloride Tablets in 30 minutes is NLT 80%.

Uniformity of dosage units Meets the requirements.

Assay Take 5 tablets of Ciprofloxacin Hydrochloride Tablets, add 400 mL of water, sonicate for about 20 minutes, and add water to make exactly 500 mL. Take accurately an appropriate amount of Ciprofloxacin Hydrochloride Tablets, add water to obtain a solution having known concentration of about 0.3 mg of ciprofloxacin per mL according to the labeled amount of ciprofloxacin ($C_{17}H_{18}FN_3O_3$), and use the solution as the test solution. Separately, weigh accurately an appropriate amount of ciprofloxacin hydrochloride hydrate RS (previously determine the water content), dissolve in water to obtain a solution having known concentration of about 0.3 mg of Ciprofloxacin Hydrochloride Tablets per mL, and use the solution as the standard solution. Perform the test with each 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the operating conditions described in the Assay under Ciprofloxacin Hydrochloride Hydrate and determine the peak areas, A_T and A_S, of ciprofloxacin for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of ciprofloxacin in 1 tablet} = C \times \frac{L}{D} \times \frac{A_T}{A_S} \times \frac{331.35}{367.81}$$

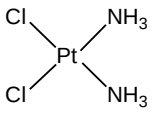
C: Concentration (mg/mL) of ciprofloxacin hydrochloride in the standard solution, calculated on the anhydrous basis

L: Amount (mg) of ciprofloxacin in 1 tablet

D: Concentration (mg/mL) of ciprofloxacin hydrochloride in the test solution

Packaging and storage Preserve in tight containers.

Cisplatin
시스플라틴



$Cl_2H_6N_2Pt$: 300.04

(*SP*-4-2)-Diamminedichloridoplatinum [*15663-27-1*]

Cisplatin, when dried, contains NLT 98.0% and NMT 102.0% of cisplatin ($Cl_2H_6N_2Pt$).

Description Cisplatin occurs as a yellow crystalline powder.

It is sparingly soluble in ammonium peroxydisulfate, slightly soluble in water and practically insoluble in ethanol(99.5).

Identification (1) Add 2 to 3 drops of tin(II) chloride dihydrate solution (1 in 100) to 5 mL of aqueous solution of Cisplatin (1 in 2000); a brown precipitate is produced.

(2) Determine the absorption spectra of the solutions of Cisplatin and cisplatin RS, respectively, in a solution of sodium chloride (1 in 2000) in 0.01 mol/L hydrochloric acid TS (9 in 1000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Cisplatin and cisplatin RS as directed in the potassium bromide disk

method under the Mid-infrared Spectroscopy, respectively; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) An aqueous solution of Cisplatin (1 in 2000) responds to the Qualitative Analysis (1) for chloride.

Crystallinity Meets the requirements.

Purity ***Trichloroammineplatinate***—Perform this procedure using light-resistant vessels. Dissolve 50 mg of Cisplatin in a sodium chloride solution (9 in 1000) to make exactly 100 mL and use this solution as the test solution. Separately, dissolve 10 mg of trichloroammineplatinate, previously dried at 80 ºC for 3 hours, in a sodium chloride solution (9 in 1000) to make exactly 200 mL. To 2.0 mL of this solution, add a sodium chloride solution (9 in 1000) to make exactly 20 mL and use this solution as the standard solution. Perform the test with 40 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine peak area of each solution of trichloroammineplatinate by the automatic integration method; the peak area from the test solution is not larger than the peak area from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 209 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with quartanaryammonium group introduced octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A solution of ammonium sulfate (1 in 800).

Flow rate: Adjust the flow rate so that the retention time of trichloroammineplatinate is about 8 minutes.

System suitability

System performance: Proceed with 40 μL of the standard solution under the above operating conditions; the number of theoretical plates and the symmetry factor of the peak of trichloroammineplatinate are NLT 1500 and NMT 2.0, respectively.

System repeatability: Repeat the test 6 times with 40 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak area of trichloroammineplatinate is NMT 3.0%.

Loss on drying NMT 0.1% (1 g, 105 °C, 4 hours).

Assay Perform this procedure using light-resistant vessels. Weigh accurately about 25 mg each of Cisplatin and cisplatin RS, previously dried, add ammonium peroxydisulfate to make exactly 25 mL and use the solutions as the test solution and the standard solution, respectively. Perform the test with exactly 40 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and determine peak area of cisplatin, A_T and A_S, by the automatic integration method, respectively.

$$\text{Amount (mg) of cisplatin } (Cl_2H_6N_2Pt) = \text{Amount (mg) of cisplatin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 310 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with aminopropylsilyl silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of ethyl acetate, methanol, water and ammonium peroxydisulfate (25 : 16 : 5 : 5).

Flow rate: Adjust the flow rate so that the retention time of cisplatin is about 4 minutes.

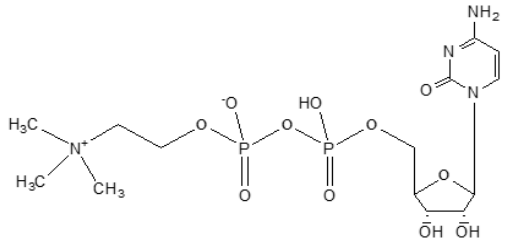
System suitability

System performance: Proceed with 40 μL of the standard solution under the above operating conditions; the number of theoretical plates and the symmetry factor of the peak of cisplatin are NLT 3000 and NMT 2.0, respectively.

System repeatability: Repeat the test 6 times with 40 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak area of cisplatin is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Citicoline
시티콜린



$C_{14}H_{26}N_4O_{11}P_2$: 488.32

Cytidine 5′-(trihydrogen diphosphate) *P′*-[2-(trimethylammonio)ethyl] ester inner salt, [*987-78-0*]

Citicoline, when dried, contains NLT 98.0% and NMT 102.0% of citicoline ($C_{14}H_{26}N_4O_{11}P_2$).

Description Citicoline occurs as a white, crystalline powder and is odorless.

It is very soluble in water, and practically insoluble in ethanol, acetone or chloroform.

It is very hygroscopic.

Identification (1) Put 0.2 g of Citicoline in a crucible, moisten with 4 drops of sodium hydroxide TS, and char carefully while heating gently. Add 10 mL of dilute nitric acid, heat on a steam bath for 30 minutes, add 10 mL of water, and filter. Neutralize the filtrate with sodium hydroxide TS; the resulting solution responds to the Qualitative Analysis for phosphates.

(2) To 1 mg of Citicoline, add 3 mL of dilute hydrochloric acid and heat on a steam bath for 30 minutes. Blow bromine away by air, and add 0.2 mL of orcin in ethanol (1 in 10). Next, add 3 mL of diluted ammonium iron(II) sulfate in hydrochloric acid (1 in 100), and heat on a steam bath; the resulting solution exhibits a green color.

(3) Dissolve 0.1 g of Citicoline in 5 mL of dilute hydrochloric acid, and heat on a steam bath for 60 minutes. Next, cool with water, and add 1mL of reinecke salt TS; a pale red precipitate is produced.

(4) With a solution dissolved 3 mg of Citicoline in 200 mL of hydrochloric acid TS, determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy; it exhibits maximum at the wavelength between 276 nm and 282nm.

pH Between 2.5 and 3.5 (1% aqueous solution).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Citicoline in 8 mL of water; the solution is colorless and clear.

(2) ***Ammonium***—Perform the test with 0.20 g of Citicoline. Prepare the control solution with 10.0 mL of ammonium RS (NMT 0.05%).

(3) ***Heavy metals***—Proceed with 2.0 g of Citicoline according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Proceed with 1.0 g of Citicoline according to Method 3 and perform the test (NMT 2 ppm).

(5) ***Free phosphoric acid***—Dissolve 0.1 g of Citicoline in 10 mL of water, add 1 mL of a solution of ammonium molybdate in 0.5 mol/L sulfuric acid (1 in 40) and 0.5 mL of 1-amino-2-naphthol-4-sulfonic acid TS, and allow to stand for 5 minutes; the color of the solution is not more intense than that of the following control solution.

Control solution—To 4.0 mL of phosphoric acid RS, add water to make 10 mL, and proceed with this solution in the same manner.

(6) ***5′-Cytidylic acid***—With the ion-exchange resin column used in the preparation of the test solution under the Assay elute with 0.01 mol/L hydrochloric acid using a 100-mL volumetric flask as a collecting vessel. Collect the running solution to make 100 mL, determine the absorbance A_T of this solution at the wavelength of 280 nm using the blank test solution prepared in the same manner as the test solution as the control solution, Calculate the amount of 5'-cytidylic acid using the A_T, weight (W_T mg) of the sample in the Assay, the amount of the reference standards (W_S mg), the absorbance (A_S) of the reference standards obtained from the Assay and the dry weight loss of the reference standards (L_S%) according to the following equation; the amount of 5′-cytidylic acid is NMT 1.0%.

$$\text{Amount (mg) of 5′-cytidylic acid } (C_{14}H_{25}N_4O_{11}P_2) = \frac{W_S}{W_T} \times \frac{1}{2} \times 0.6618 \times \frac{100 - L_S}{100 - L_T} \times \frac{A_T}{A_S} \times 100$$

L_T: dry weight loss of the sample

0.6618 = Molecular weight ratio of 5′-cytidylic acid ($C_9H_{14}N_3O_8P$) and citicoline ($C_{14}H_{26}N_4O_{11}P_2$)

Loss on drying NMT 5.0% (1 g, in vacuum, phosphorus pentoxide, 100 ℃, 4 hours)

Assay Weigh accurately about 0.1 g each of Citicoline and citicoline RS and dissolve in water to make exactly 100 mL. Take 3.0 mL each of these solutions and pass through the strongly basic ion exchange resin column. Next, elute with diluted 0.1 mol/L sodium chloride TS (1 in 10) using a 200-mL volumetric flask containing 20.0 mL of 0.1 mol/L hydrochloric acid TS as a collecting vessel, collect the running solutions to make 200 mL, and use these solutions as the test solution and the standard solution, respectively. With the test solution and the standard solution, perform the test as directed under the Ultraviolet-visible Spectroscopy using the blank test solution as the control solution, and determine the absorbances, A_T and A_S, at 280 nm.

$$\text{Amount (mg) of citicoline } (C_{14}H_{26}N_4O_{11}P_2) = \text{Amount (mg) of citicoline RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers in a cold place.

Citicoline Injection
시티콜린 주사액

Citicoline Injection contains NLT 90.0% and NMT 130.0% of the labeled amount of citicoline ($C_{14}H_{26}N_4O_{11}P_2$: 488.32).

Method of preparation Prepare as directed under Injections, with Citicoline.

Identification (1) Put about 4 mL of Citicoline Injection in a crucible, evaporate to dryness on a steam bath, add 4 drops of sodium hydroxide TS, and heat gently with care to carbonize slowly. Add 10 mL of dilute nitric acid and heat on a steam bath. Then, add 10 mL of water, filter,

and neutralize the filtrate with sodium hydroxide TS. This solution responds to the Qualitative Analysis for phosphate.

(2) To about 0.02 mL of Citicoline Injection, add 3 mL of dilute hydrochloric acid and 1 mL of bromine TS, heat on a steam bath for 30 minutes, and blow bromine away with air. To this solution, add 0.2 mL of orcin in ethanol solution (1 in 10) and 3 mL of ammonium ferric sulfate in hydrochloric acid solution (1 in 1000), and heat on a steam bath for 20 minutes; the solution exhibits a green color.

(3) To 2 mL of Citicoline Injection, add 2 mL of hydrochloric acid, heat on a steam bath for 60 minutes, cool, and add 1 mL of Reinecke salt; a pale precipitate is formed.

(4) To 0.1 mL of Citicoline Injection, add 0.1 mol/L hydrochloric acid to make 100 mL. Take 10 mL of this solution, and dilute with 0.01 mol/L hydrochloric acid to make 100 mL. Determine the absorption spectrum using 0.01 mol/L hydrochloric acid as a blank; the spectrum exhibits a maximum at 279 ± 3 nm.

pH Between 6.0 and 8.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.6 EU per mg of citicoline.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

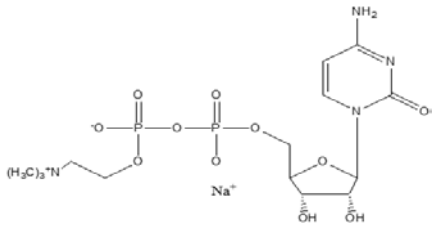
Extractable volume of injections Meets the requirements.

Assay Weigh exactly an amount of Citicoline Injection, equivalent to 0.1 g of citicoline ($C_{14}H_{26}N_4O_{11}P_2$) according to the labeled amount, add water to make exactly 100 mL, and shake well to mix. Pipet 3 mL of this solution and elute a column packed with strong base ion exchange resin column. Collect the eluate into a 200-mL volumetric flask, previously filled with 20 mL of 0.1 mol/L hydrochloric acid, and elute the column with 0.01 mol/L sodium chloride. Combine the eluates to make exactly 200 mL and use the solution as the test solution. Separately, weigh accurately about 0.1 g of citicoline RS and add water to make exactly 100 mL. Pipet 3 mL of this solution, proceed in the same manner as for the preparation of the test solution, and use the resulting solution as the standard solution. Determine the absorbance, A_T and A_S, of the test solution and the standard solution at 280 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of citicoline ($C_{14}H_{26}N_4O_{11}P_2$)
= Amount (mg) of citicoline RS × (A_T / A_S)

Packaging and storage Preserve in hermetic containers.

Citicoline Sodium
시티콜린나트륨



$C_{14}H_{25}O_{11}N_4P_2Na$: 510.31

P'-[2-(Trimethylammonio)ethyl] cytidine 5'-(trihydrogen diphosphate) ester sodium salt, [*33818-15-4*]

Citicoline Sodium, when dried, contains NLT 98.0% and NMT 101.0% of citicoline sodium ($C_{14}H_{25}O_{11}N_4P_2Na$).

Description Citicoline Sodium occurs as a white, crystalline powder and is odorless.
It is very soluble in water, and practically insoluble in ethanol, ether or chloroform.

Identification (1) Put 0.2 g of Citicoline Sodium in a porcelain crucible, moisten with 4 drops of sodium hydroxide TS, and char carefully while heating gently. Add 10 mL of dilute nitric acid, heat on a steam bath for 30 minutes, add 10 mL of water, and filter. Neutralize the filtrate with sodium hydroxide TS; the resulting solution responds to the Qualitative Analysis for phosphates.

(2) To 1 mg of Citicoline Sodium, add 3 mL of dilute hydrochloric acid and 1 mL of bromine TS, heat on a steam bath for 30 minutes, and blow bromine away by air. Add 0.2 mL of orcin in ethanol solution (1 in 10), add 3 mL of ammonium iron(III) sulfate 12-hydrate in hydrochloric acid solution (1 in 1000), and heat on a steam bath for 20 minutes; the resulting solution exhibits a green color.

(3) To 0.1 g of Citicoline Sodium, add 5 mL of dilute hydrochloric acid, and heat on a steam bath for 60 minutes, cool with water, and add 1 mL of reinecke salt TS; a pale red precipitate is produced.

(4) Dissolve 0.5 g each of Citicoline Sodium and citicoline sodium RS in water to make 50 mL, and perform the test under the same operating conditions for testing related substances; the R_f values of the spots obtained from the test solution and the standard solution are the same.

(5) Weigh about 0.15 g of Citicoline Sodium and dissolve in water to make 100.0 mL. Take 10.0 mL of this solution, transfer to a 1000-mL volumetric flask, and fill 0.1 mol/L potassium chloride-hydrochloric acid buffer solution, pH 2.0, to the gauge line. Next, determine the absorbance using 0.1 mL of

potassium chloride-hydrochloric acid buffer solution, pH 2.0, as the control solution; it exhibits a maximum at the wavelength around 282 nm.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Citicoline Sodium in 20 mL of water; the solution is colorless and clear.

(2) ***Chloride***—Perform the test with 0.5 g of Citicoline Sodium according to the Chloride and. Prepare the control solution with 0.14 mL of 0.01 mol/L hydrochloric acid (NMT 0.01%)

(3) ***Iron***—Prepare the test solution with 0.5 g of Citicoline Sodium as directed in Method 1 under the Iron and perform the test according to Method A. Prepare the control solution with 5.0 mL of iron standard solution (NMT 0.01%).

(4) ***Heavy metals***—Proceed with 1.0 g of Citicoline Sodium according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(5) ***Arsenic***—Proceed with 2.0 g of Citicoline Sodium according to Method 1 and perform the test (NMT 1 ppm).

(6) ***Related substances***—Weigh 0.5 g of Citicoline Sodium and citicoline sodium RS, dissolve in water to make 50 mL, and perform the test with these solutions as directed under the Paper Chromatography. Spot 5 mL of the test solution and the standard solution onto the filter paper, air-dry the filter paper, and develop with a mixture of ethanol, 1 mol/L ammonium acetate and 1 mol/L ammonia TS, pH 7.0 (5 : 4). After air-drying the filter paper, spray 2% ninhydrin-acetone solution, allow to stand at 90 °C for 10 minutes, and observe the colors and positions of the spots; no other spots appear on the filter paper.

Loss on drying NMT 5.0% (1 g, in vacuum, phosphorus pentoxide, 100 ℃, 4 hours).

Assay Weigh accurately about 0.15 g of Citicoline Sodium, previously dried, and dissolve in water to make exactly 100 mL. Pipet 10 mL of this solution, transfer to a 100-mL volumetric flask, add potassium chloride-hydrochloric acid buffer solution, pH 2.0 exactly up to the gauge line, and use the solution as the test solution. Separately, weigh accurately about 0.15 g citicoline sodium RS, previously dried, proceed in the same manner as the test solution, and use this solution as the standard solution. With the test solution and the standard solution, determine the absorbances A_T and A_S at the wavelength of 280 nm using the blank test solution as the control solution.

$$\text{Amount (mg) of citicoline sodium } (C_{14}H_{25}O_{11}N_4P_2Na) = \text{Amount (mg) of citicoline sodium RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers.

Citicoline Sodium Injection
시티콜린나트륨 주사액

Citicoline Sodium Injection contains NLT 90.0% and NMT 130.0% of the labeled amount of citicoline sodium ($C_{14}H_{25}O_{11}N_4P_2Na$: 510.31).

Method of preparation Prepare as directed under Injections, with Citicoline Sodium.

Identification (1) Weigh accurately an amount of Citicoline Sodium Injection, equivalent to about 0.2 g of citicoline according to the labeled amount, and add 4 drops of sodium hydroxide TS. Heat gently to carbonize, add 10 mL of dilute nitric acid, and filter. Neutralize the filtrate with sodium hydroxide TS; the resulting solution responds to the Qualitative Analysis for phosphate.

(2) Weigh accurately an amount of Citicoline Sodium Injection, equivalent to about 0.1 g of citicoline according to the labeled amount. Add 5 mL of dilute hydrochloric acid, heat on a steam bath for 60 minutes, cool, and add 1 mL of Reinecke salt TS; a pale red precipitate is formed.

(3) Weigh accurately an amount of Citicoline Sodium Injection, equivalent to about 0.15 g of citicoline according to the labeled amount. Add 0.1 mol/L of hydrochloric acid to make 100 mL, pipet 1 mL of this solution, and add 0.01 mol/L hydrochloric acid to make 100.0 mL. Determine the absorption spectrum using 0.01 mol/L hydrochloric acid as a control solution; the spectrum exhibits a maximum at about 280 nm.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

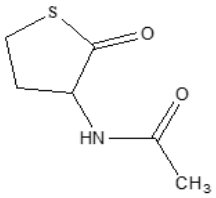
Assay Weigh accurately an amount of Citicoline Sodium Injection, equivalent to about 0.1 g of citicoline according to the labeled amount. Add water to make exactly 100 mL, pipet 3 mL of the solution, and pass through a strong base ion exchange resin column. Collect the running solution into a 200-mL flask, previously filled with 20 mL of 0.1 mol/L hydrochloric acid, and pass through 0.1 mol/L sodium chloride for complete elution. Combine the running solutions to make 200.0 mL and use the solution as the test solution. Separately, weigh accurately about 0.1 g of citicoline sodium RS, previously dried, and proceed in the same manner as for the preparation of the test solution. Use the resulting solution as the standard solution. Determine the absorbance, A_T and A_S, of the test

solution and the standard solution at 280 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of citicoline sodium ($C_{14}H_{25}O_{11}N_4P_2Na$)
= Amount (mg) of citicoline sodium RS × $\frac{A_T}{A_S}$

Packaging and storage Preserve in hermetic containers.

Citiolone
시티올론



$C_6H_9NO_2S$: 159.21
2-Acetamido-4-mercaptobutyric acid γ-thiolactone, [*1195-16-0*]

Citiolone, when dried, contains NLT 99.0% and NMT 101.0% of citiolone ($C_6H_9NO_2S$).

Description Citiolone occurs as a white crystalline powder and has a slight sulfur-like odor.
It is soluble in water, chloroform and ethanol(95).

Identification (1) Dissolve 10 mg of Citiolone in 5 mL of methanol, add 0.5 mL of ethanolic potassium hydroxide TS, shake to mix, and add 0.5 mL of saturated sodium nitroprusside methanol solution; the resulting solution exhibits a red color.

(2) Dissolve 20 mg of Citiolone in ethanol(99.5), and add ethanol(99.5) to make 100 mL. Take 10 mL of this solution, add ethanol(99.5) to make 100 mL, and use this solution as the test solution. Determine the absorption spectrum of the test solution using ethanol(99.5) as the control solution; it exhibits a maximum at the wavelength of around 235 nm.

Melting point Between 108 and 112 ℃.

Purity (1) ***Acyclic substances***—Dissolve 0.2 g of Citiolone in 20 mL of water, and add 0.2 mL of 0.05 mol/L Iodine solution; the solution exhibits a yellow color for several minutes.

(2) Perform the test under the Thin Layer Chromatography according to the conditions in (i) and (ii) below; no additional spots should appear, and also there should be no development of color on spraying 0.2% ninhydrin solution.

(i) Dissolve 10 mg of Citiolone in 10 mL of methanol, and use this solution as the test solution. Perform the test with the solution as directed under the Thin Layer Chromatography. Spot the test solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of n-butanol, water and acetic anhydride (4 : 1 : 1), and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f value of the spot obtained from the test solution is 0.53.

(ii) Dissolve 10 mg of Citiolone in 10 mL of methanol, and use this solution as the test solution. Perform the test with the solution as directed under the Thin Layer Chromatography. Spot the test solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, methanol and acetic anhydride (7 : 2 : 1) and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f value of the spot obtained from the test solution is 0.68.

Loss on drying NMT 0.2% (1.0 g, 80 ℃, in vacuum, 2 hours).

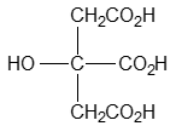
Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.3 g of Citiolone, previously dried, dissolve in 40 mL of water, add 20 mL of sodium hydroxide TS, and shake to mix well for 5 minutes. Next, adjust the pH to between 2 and 3 by adding slowly dilute hydrochloric acid, and titrate with 0.05 mol/L of iodine VS (indicator: starch TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L iodine VS
= 15.92 mg of $C_6H_9NO_2S$

Packaging and storage Preserve in tight containers.

Anhydrous Citric Acid
시트르산



$C_6H_8O_7$: 192.12
2-Hydroxypropane-1,2,3-tricarboxylic acid [77-92-9]

Anhydrous Citric Acid contains NLT 99.5% and NMT 100.5% of anhydrous citric acid (C6H8O7), calculated on the anhydrous basis.

Description Anhydrous Citric Acid is colorless crystals, white grains or a crystalline powder.
It is very soluble in water and freely soluble in ethanol(95).

Melting point—About 153 °C (with decomposition).

Identification Determine the infrared spectra of Anhydrous Citric Acid and citric acid monohydrate RS, previously dried at 105± 2°C for 2 hours, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity **(1)** ***Clarity and color of solution—Turbidity*** Dissolve about 2.0 g of Anhydrous Citric Acid in water to make 10 mL, and use this solution as the test solution. Take an appropriate amount each of the test solution, the control suspension (1), the control suspension (2) and water, transfer to colorless and transparent test tubes (15 - 25 mm × 40 mm), and observe the test tubes from the top for 5 minutes under a sufficient daylight against a black background that provides enough contrast to differentiate between the control suspension (1) and water, and between control suspension (1) and control suspension (2); the test solution is clear like water and is not more turbid than the control suspension (1).

◦ *Control suspension*—Pipet 25 mL of hydrazinium sulfate TS, previously allowed to stand for 4 to 6 hours, and add to a solution obtained by dissolving 2.5 g of hexamethylenetetramine in 25 mL of water, mix well, and allow the mixture to stand for 24 hours. Store the solution in a glass container and use it within 2 months. Pipet 15 mL of this suspension, and add water to make exactly 1000 mL before use.

◦ *Control suspension (1*)—Pipet 5 mL of the control suspension, and add water to make exactly 100 mL.

◦ *Control suspension (2)*—Pipet 10 mL of the control suspension, and add water to make exactly 100 mL.

Color Dissolve 2.0 g of Anhydrous Citric Acid in water to make 10 mL, and use this solution as the test solution. Take an appropriate amount each of the test solution and water, transfer to colorless and transparent test tubes (15 to 25 mm × 40 mm), and observe the test tubes from the side under a sufficient sunlight against a white background that provides enough contrast to differentiate the color; the color of the test solution is not more intense than that of water. If the color of the test solution is more intense than that of water, compare the color of the test solution with the colors of the control solutions (1), (2) and (3) in the same manner as above. In this case, the color of the test solution is not more intense than those of the control solutions (1), (2) and (3).

◦ *Control solution (1)*—To 1.5 mL of cobalt(II) chloride hexahydrate colorimetric stock solution and 6.0 mL of iron(III) chloride hexahydrate colorimetric stock solution, add diluted hydrochloric acid (1 in 10) to make 1000 mL.

◦ *Control solution (2)*—To 2.5 mL of cobalt(II) chloride hexahydrate colorimetric stock solution, 6.0 mL of iron(III) chloride hexahydrate colorimetric stock solution and 1.0 mL of copper sulfate colorimetric stock solution, add diluted hydrochloric acid (1 in 10) to make 1000 mL.

◦ *Control solution (3)*—To 0.15 mL of cobalt(II) chloride hexahydrate colorimetric stock solution, 7.2 mL of iron(III) chloride hexahydrate colorimetric stock solution and 0.15 mL of copper(II) sulfate pentahydrate colorimetric stock solution, add diluted hydrochloric acid (1 in 10) to make 1000 mL.

(2) ***Sulfate***—Dissolve 2.0 g of Anhydrous Citric Acid in water to make 30 mL, and use this solution as the test solution. Separately, dissolve 0.181 g of potassium sulfate in diluted ethanol(95) (3 in 10) to make exactly 500 mL. Pipet 5 mL of this solution, and add diluted ethanol(95) (3 in 10) to make exactly 100 mL. To 4.5 mL of this solution, add 3 mL of a solution of barium chloride dihydrate (1 in 4), shake to mix, and allow to stand for 1 minute. To 2.5 mL of this solution, add 15 mL of the test solution and 0.5 mL of acetic acid(31), and allow to stand for 5 minutes; the resulting solution is not more turbid than the following control solution (NMT 0.015%).

◦ *Control solution*—Dissolve 0.181g of potassium sulfate in water to make 500 mL. Pipet 5 mL of this solution, and add water to make exactly 100 mL. Instead of the test solution, proceed with 15 mL of this solution in the same manner as in the preparation of the test solution, and use this solution as the control solution.

(3) ***Oxalic acid***—To a solution of 0.80 g of Anhydrous Citric Acid dissolved in 4 mL of water, add 3 mL of hydrochloric acid and 1 g of zinc, and boil for 1 minute. Allow to stand for 2 minutes, take the clear supernatant, add 0.25 mL of a phenylhydrazinium hydrochloride solution (1 in 100), heat to boiling, and cool rapidly. To this solution, add an equal volume of hydrochloric acid and 0.25 mL of potassium hexacyanoferrate(III) solution (1 in 20), shake to mix, and allow to stand for 30 minutes; the color of the resulting solution is not more intense than the concurrently prepared control solution (NMT 0.036% as anhydrous oxalic acid).

◦ *Control solution*—Add 3 mL of hydrochloric acid and 1 g of zinc to 4 mL of oxalic acid dihydrate solution (1 in 10000).

(4) ***Aluminum***—Perform the test when used in the manufacturing of hemodialysis preparations. Dissolve 20.0 g of Anhydrous Citric Acid in 100 mL of water, add 10 mL of acetic acid-ammonium acetate buffer solution, pH 6.0, extract with 20 mL, 20 mL and 10 mL of 0.5% chloroform solutions of 8-hydroxyquinoline to collect in a 50-mL volumetric flask, and add chloroform to make 50 mL. Use this solution as the test solution. Separately, dissolve 0.352 g of aluminum potassium sulfate in a small amount of water, add 10 mL of dilute sulfuric acid, and then add water to make 100 mL. Pipet 1.0 mL of this solution and add water to make 100 mL before use. Take 2.0 mL of this solution, add 10 mL of acetic acid-ammonium acetate buffer solution, pH 6.0, and add 98 mL of water. Extract in the same procedure as the test solution, combine the extracts in a 50-mL volumetric flask, add chloroform to make 50 mL, and use this solution as the standard solution. To 10 mL of acetic acid-ammonium acetate buffer solution, pH 6.0, add 100 mL of water, extract with chloroform in the same manner as the test solution, and use this solution as the blank test solution. Perform the test with the test solution and the

standard solution as directed under the Fluorescence Spectroscopy using the blank test solution as the blank, and determine the fluorescence intensity at the excitation wavelength of 392 nm and the fluorescence wavelength of 518 nm; the fluorescence intensity obtained from the test solution is not greater than that of the standard solution (NMT 0.2 ppm).

(5) ***Readily carbonizable substances***—Rinse a Nessler tube with 10 mL of sulfuric acid, and decant for 10 minutes. Add 1.0 g of Anhydrous Citric Acid to the Nessler tube, add 10 mL of sulfuric acid, immediately heat at 90 °C on a water bath for 1 hour, and cool rapidly. Take 2.0 mL each of this solution and matching fluids for color K, transfer to test tubes with an outer diameter of 12 mm, and observe the test tubes from the side against a white background; the color of the solution is not more intense than that of matching fluids for color K.

Water NMT 1.0% (2 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

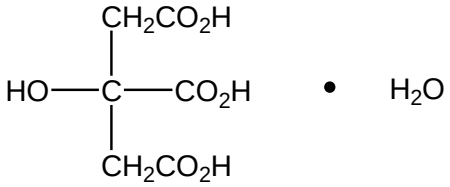
Bacterial endotoxins Less than 0.5 EU/mg per mL of citric acid, when used in the manufacturing of parenteral preparations without a procedure for the removal of bacterial endotoxins.

Assay Weigh accurately about 0.55 g of Anhydrous Citric Acid, dissolve in 50 mL of water, and titrate with 1 mol/ L sodium hydroxide VS (indicator: 2 drops of phenolphthalein TS).

Each mL of 1 mol/L sodium hydroxide VS
= 64.03 mg of $C_6H_8O_7$

Packaging and storage Preserve in tight containers.

Citric Acid Hydrate
시트르산수화물



Citric Acid $C_6H_8O_7 \cdot H_2O$: 210.14
2-Hydroxypropane-1,2,3-tricarboxylic acid hydrate [5949-29-1]

Citric Acid Hydrate contains NLT 99.5% and NMT 100.5% of citric acid ($C_6H_8O_7$: 192.12), calculated on the anhydrous basis.

When used in the manufacturing of hemodialysis preparations, it is labeled accordingly.

Description Citric Acid Hydrate is colorless crystals, white grains or a crystalline powder.
It is very soluble in water and freely soluble in ethanol(99.5).
It effloresces in dry air.

Identification Determine the infrared spectra of Citric Acid Hydrate and citric acid monohydrate RS, previously dried at 105 °C ± 2 for 2 hours, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Clarity and color of solution—Turbidity*** Dissolve about 2.0 g of Citric Acid Hydrate in water to make 10 mL, and use this solution as the test solution. Take an appropriate amount each of the test solution, the control suspension (1), the control suspension (2) and water, transfer to colorless and transparent test tubes (15 - 25 mm × 40 mm), and observe the test tubes from the top for 5 minutes under a sufficient daylight against a black background that provides enough contrast to differentiate between the control suspension (1) and water, and between control suspension (1) and control suspension (2); the test solution is clear like water and is not more turbid than the control suspension (1).

Control suspension—Pipet 25 mL of hydrazinium sulfate TS, previously allowed to stand for 4 to 6 hours, and add to a solution obtained by dissolving 2.5 g of hexamethylenetetramine in 25 mL of water, mix well, and allow the mixture to stand for 24 hours. Store the solution in a glass container and use it within 2 months. Pipet 15 mL of this suspension, and add water to make exactly 1000 mL before use.

Control suspension (1)— Pipet 5 mL of the control suspension, and add water to make exactly 100 mL.

Control suspension (2)— Pipet 10 mL of the control suspension, and add water to make exactly 100 mL.

Color Dissolve 2.0 g of Citric Acid Hydrate in water to make 10 mL, and use this solution as the test solution. Take an appropriate amount each of the test solution and water, transfer to colorless and transparent test tubes (15 to 25 mm × 40 mm), and observe the test tubes from the side under a sufficient sunlight against a white background that provides enough contrast to differentiate the color; the color of the test solution is not more intense than that of water. If the color of the test solution is more intense than that of water, compare the color of the test solution with the colors of the control solutions (1), (2) and (3) in the same manner as above. In this case, the color of the test solution is not more intense than those of the control solutions (1), (2) and (3).

Control solution (1)— To 1.5 mL of cobalt(II) chloride hexahydrate colorimetric stock solution and 6.0 mL

of iron(III) chloride hexahydrate colorimetric stock solution, add diluted hydrochloric acid (1 in 10) to make 1000 mL.

Control solution (2)— To 2.5 mL of cobalt(II) chloride hexahydrate colorimetric stock solution, 6.0 mL of iron(III) chloride hexahydrate colorimetric stock solution and 1.0 mL of copper sulfate colorimetric stock solution, add diluted hydrochloric acid (1 in 10) to make 1000 mL.

Control solution (3)— To 0.15 mL of cobalt(II) chloride hexahydrate colorimetric stock solution, 7.2 mL of iron(III) chloride hexahydrate colorimetric stock solution and 0.15 mL of copper(II) sulfate pentahydrate colorimetric stock solution, add diluted hydrochloric acid (1 in 10) to make 1000 mL.

(2) ***Sulfate***— Dissolve 2.0 g of Citric Acid Hydrate in water to make 30 mL, and use this solution as the test solution. Separately, dissolve 0.181 g of potassium sulfate in diluted ethanol(95) (3 in 10) to to make exactly 500 mL. Pipet 5 mL of this solution, and add diluted ethanol(95) (3 in 10) to make exactly 100 mL. To 4.5 mL of this solution, add 3 mL of a solution of barium chloride dihydrate (1 in 4), shake to mix, and allow to stand for 1 minute. To 2.5 mL of this solution, add 15 mL of the test solution and 0.5 mL of acetic acid(31), and allow to stand for 5 minutes; the resulting solution is not more turbid than the following control solution (NMT 0.015%).

Control solution—Dissolve 0.181g of potassium sulfate in water to make 500 mL. Pipet 5 mL of this solution, and add water to make exactly 100 mL. Instead of the test solution, proceed with 15 mL of this solution in the same manner as in the preparation of the test solution, and use this solution as the control solution.

(3) ***Oxalic acid***— To a solution of 0.80 g of Anhydrous Citric Acid dissolved in 4 mL of water, add 3 mL of hydrochloric acid and 1 g of zinc, and boil for 1 minute. Allow to stand for 2 minutes, take the clear supernatant, add 0.25 mL of a phenylhydrazinium hydrochloride solution (1 in 100), heat to boiling, and cool rapidly. To this solution, add an equal volume of hydrochloric acid and 0.25 mL of potassium hexacyanoferrate(III) solution (1 in 20), shake to mix, and allow to stand for 30 minutes; the color of the resulting solution is not more intense than the concurrently prepared control solution (NMT 0.036% as anhydrous oxalic acid).

Control solution— Add 3 mL of hydrochloric acid and 1 g of zinc to 4 mL of oxalic acid dihydrate solution (1 in 10000).

(4) ***Aluminum***— Perform the test when used in the manufacturing of hemodialysis preparations. Dissolve 20.0 g of Anhydrous Citric Acid in 100 mL of water, add 10 mL of acetic acid-ammonium acetate buffer solution, pH 6.0, extract with 20 mL, 20 mL and 10 mL of 0.5% chloroform solutions of 8-hydroxyquinoline to collect in a 50-mL volumetric flask, and add chloroform to make 50 mL. Use this solution as the test solution. Separately, dissolve 0.352 g of aluminum potassium sulfate in a small amount of water, add 10 mL of dilute sulfuric acid, and then add water to make 100 mL. Pipet 1.0 mL of this solution and add water to make 100 mL before use. Take 2.0 mL of this solution, add 10 mL of acetic acid-ammonium acetate buffer solution, pH 6.0, and add 98 mL of water. Extract in the same procedure as the test solution, combine the extracts in a 50-mL volumetric flask, add chloroform to make 50 mL, and use this solution as the standard solution. To 10 mL of acetic acid-ammonium acetate buffer solution, pH 6.0, add 100 mL of water, extract with chloroform in the same manner as the test solution, and use this solution as the blank test solution. Perform the test with the test solution and the standard solution as directed under the Fluorescence Spectroscopy using the blank test solution as the blank, and determine the fluorescence intensity at the excitation wavelength of 392 nm and the fluorescence wavelength of 518 nm; the fluorescence intensity obtained from the test solution is not greater than that of the standard solution (NMT 0.2 ppm).

(5) ***Readily carbonizable substances***—Rinse a Nessler tube with 10 mL of sulfuric acid for readily carbonizable substances, and decant for 10 minutes. Add 1.0 g of Citric Acid Hydrate to the Nessler tube, add 10 mL of sulfuric acid, immediately heat at 90 °C on a water bath for 1 hour, and cool rapidly. Take 2.0 mL each of this solution and matching fluids for color K, transfer to test tubes with an outer diameter of 12 mm, and observe the test tubes from the side against a white background; the color of the solution is not more intense than that of matching fluids for color K.

Water Between 7.5% and 9.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

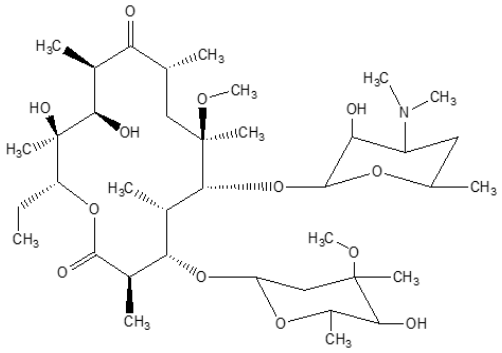
Bacterial endotoxins Less than 0.5 EU per mg of citric acid hydrate when used in the manufacturing of parenteral preparations without a procedure for the removal of bacterial endotoxins.

Assay Weigh accurately about 0.55 g of Citric Acid Hydrate, dissolve in 50 mL of water, and titrate with 1 mol/L sodium hydroxide VS (indicator: 2 drops of phenolphthalein TS).

Each mL of 1 mol/L sodium hydroxide VS
= 64.03 mg of $C_6H_8O_7$

Packaging and storage Preserve in tight containers.

Clarithromycin
클래리트로마이신



$C_{38}H_{69}NO_{13}$: 747.95
(3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-6-[(2*S*,3*R*,4*S*,6*R*)-4-(Dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy-14-ethyl-12,13-dihydroxy-4-[(2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-7-methoxy-3,5,7,9,11,13-hexamethyl-oxacyclotetradecane-2,10-dione [*81103-11-9*]

Clarithromycin is a derivative of erythromycin. Clarithromycin contains NLT 950 μg and NMT 1050 μg (potency) of clarithromycin ($C_{38}H_{69}NO_{13}$) per mg, calculated on the anhydrous basis.

Description Clarithromycin occurs as a white crystalline powder and has a bitter taste.
It is soluble in acetone or chloroform, slightly soluble in methanol or ethanol(95), and practically insoluble in water.

Identification (1) Take 5 mg of Clarithromycin, add 2 mL of sulfuric acid and shake to mix; the solution exhibits a reddish brown color.

(2) Add 2 mL of acetone to 3 mg of Clarithromycin, then add 2 mL of hydrochloric acid; the solution exhibits an orange color and immediately changes to red to dark violet.

(3) Determine the infrared spectra of Clarithromycin and clarithromycin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

(4) Dissolve 10 mg of Clarithromycin and clarithromycin RS in 4 mL of chloroform and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, methanol and ammonia solution(28) (100 : 5 : 1) to a distance of about 15 cm, and air-dry the plate. Spray evenly sulfuric acid on the plate, and heat it at 105 ℃ for 10 minutes; the R_f values of the spots obtained from the test and standard solutions are the same, and the spots have a dark purple color.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between -87° and -97° (0.25 g calculated on the anhydrous basis, chloroform, 25 mL, 100 mm).

Melting point Between 220 and 227 ℃.

pH Dissolve 50 mg of Clarithromycin in methanol to make 20 mL. Take 10 mL of this solution and add water to make 20 mL; the pH of this solution is between 8.0 and 10.0.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Clarithromycin as directed under Method 4 and perform the test. Prepare the control solution with 2.0 mL of standard lead solution (NMT 10 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Clarithromycin as directed under Method 3 and perform the test (NMT 2 ppm).

(3) ***Related substances***—Weigh accurately 0.1 g of Clarithromycin, dissolve in the mobile phase to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of clarithromycin RS, dissolve in the mobile phase to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid chromatography according to the following conditions and determine the peak area of each solution by automatic integration method; the amount of each related substance in the test solution is NMT 2.0% of clarithromycin, calculated on the anhydrous basis, and the total amount of related substances is NMT 5.0%. However, exclude any peaks smaller than 0.05%.

Content (%) of each related substance in Clarithromycin, calculated on the anhydrous basis

$$= \times \frac{W_S}{W_T} \times \frac{A_i}{A_S} \times 100$$

Total content (%) of related substances in Clarithromycin, calculated on the anhydrous basis

$$= \times \frac{W_S}{W_T} \times \frac{\sum A_i}{A_S} \times 100$$

W_S: Amount taken (mg) of clarithromycin RS

W_T: Amount of taken (mg) of Clarithromycin, calculated on the anhydrous basis

A_S: Peak area of each clarithromycin in the standard solution

A_i: Peak area of each related substance in the test solution

$\sum A_i$: Sum of peak areas other than clarithromycin in the test solution

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed under the operating conditions in the Assay.

System suitability

System performance: Proceed as directed under the system suitability under the Assay.

Test for required detectability: Pipet 2 mL of the standard solution, add the mobile phase to make exactly 10 mL, and use this solution as the system suitability solution. Confirm that the peak area of clarithromycin obtained from 10 μL of this solution is equivalent to 14% to 26% of the peak area of clarithromycin obtained from the standard solution.

System repeatability: Repeat the test 6 times with 10 μL of the system suitability solution under the above conditions; the relative standard deviation of the peak area of clarithromycin is NMT 3.0%.

Time span of measurement: About 5 times the retention time of the major peak from 2 minutes after introduction of the test solution.

Water NMT 2.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (2.0 g).

Assay Weigh accurately about 0.1 g (potency) of Clarithromycin and clarithromycin RS and dissolve each in the mobile phase to make exactly 20 mL. Pipet 2 mL of these solutions, add 2 mL of the internal standard solution, then add the mobile phase to make exactly 20 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of the peak area of clarithromycin to that of the internal standard.

$$\text{Potency (μg) of clarithromycin } (C_{38}H_{69}NO_{13}) = \text{Potency (μg) of clarithromycin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of propyl p-hydroxybenzoate in the mobile phase (1 in 20000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: A mixture of 0.05 mol/L potassium dihydrogen phosphate TS (pH 2.0) and methanol (2 : 3).

0.05 mol/L potassium dihydrogen phosphate TS (pH 2.0) —Add phosphoric acid to 0.05 mol/L potassium dihydrogen phosphate TS to adjust the pH to 2.0.

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the internal standard and clarithromycin are eluted in this order with the resolution being NLT 1.5.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above conditions; the relative standard deviation of the peak area ratio of clarithromycin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Clarithromycin for Injection
주사용 클래리트로마이신

Clarithromycin for Injection is a preparation for injection, which is dissolved before use. Clarithromycin for Injection contains NLT 90.0% and NMT 120.0% of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$: 747.96).

Method of preparation Prepare as directed under Injections, with Clarithromycin.

Description Clarithromycin for Injection occurs as a white or milky white powder.

Identification The retention time of the major peaks of the test solution correspond to those of the standard solution, as obtained in the Assay.

pH Dissolve Clarithromycin for Injection in water to make 50 mg (potency) per mL; the pH of the solution is 4.8 to 6.0.

Water NMT 5.0% (0.2 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.15 EU per mg (potency) of clarithromycin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately about 0.5 g (potency) of clarithromycin ($C_{38}H_{69}NO_{13}$), according to the labeled potency of Clarithromycin for Injection, add methanol and shake vigorously to prepare a solution containing about 5 mg (potency) of clarithromycin per mL. Pipet 2 mL of this solution, add 2 mL of the internal standard solution, add the mobile phase to make exactly 20 mL, filter, and use this solution as the test solution. Separately, weigh accurately about 50 mg (potency) of clarithromycin RS, dissolve in methanol and prepare a solution containing about 5 mg (potency) of clarithromycin RS per mL. Pipet 2 mL of this solution, add 2 mL of the internal standard solution, add the mobile phase to make exactly 20 mL and filter. Use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak area ratios for clarithromycin, Q_T and Q_S, to the peak area of the internal standard for each solution.

$$\text{Potency (μg) of clarithromycin } (C_{38}H_{69}NO_{13}) = \text{Potency of clarithromycin RS (μg)} \times \frac{Q_T}{Q_S} \times 10$$

Internal standard solution—A solution of propyl p-hydroxybenzoate in the mobile phase (1 in 20000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: A mixture of methanol and 0.05 mol/L potassium dihydrogen phosphate TS (pH 2.0) (3 : 2).

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the internal standard and clarithromycin are eluted in this order with the resolution being NLT 3.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions, the relative standard deviation of peak area ratios of clarithromycin to the peak area of the internal standard is NMT 1.0%.

0.05 mol/L potassium dihydrogen phosphate TS (pH 2.0)—Add phosphoric acid to 0.05 mol/L potassium dihydrogen phosphate TS to adjust the pH to 2.0.

Packaging and storage Preserve in hermetic containers.

Clarithromycin for Syrup
시럽용 클래리트로마이신

Clarithromycin for Syrup is a syrup which is suspended before use and contains NLT 90.0% and NMT 120.0% of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$: 747.96).

Method of preparation Prepare as directed under Syrups, with Clarithromycin.

Identification (1) Perform the test as directed in Identification (4) under Clarithromycin.

(2) The retention times of the major peaks obtained from the test solution and the standard solution in the Assay are the same.

pH Dissolve Clarithromycin for Syrup as labeled; the pH of this solution is 4.0 to 5.4.

Loss on drying NMT 2.0% (1.0 g, 0.7 kPa, 60 ℃, 3 hours).

Dissolution Perform the test with 10 mL of a solution of Clarithromycin for Syrup suspended as labeled at 50 revolutions per minute according to Method 2 at 37 ± 0.5 ℃, using 900 mL of 0.05 mol/L potassium dihydrogen phosphate buffer solution (pH 6.8) as the dissolution medium. Take NLT 20 mL of the dissolved solution 45 minutes after the start of the test, and filter through a membrane filter with a pore size of NMT 0.5 μm. Discard the first 10 mL of the filtrate, pipet the subsequent V mL, add the mobile phase to make exactly V□ mL so that each mL contains about 200 μg (potency) of clarithromycin ($C_{38}H_{69}NO_{13}$) according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 50 mg (potency) of clarithromycin RS and dissolve in methanol to make exactly 25 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, or clarithromycin. Meets the requirements if the dissolution rate of Clarithromycin for Syrup in 45 minutes is NLT 80% of the labeled potency.

$$\text{Dissolution rate (\%) with respect to the labeled amount of clarithromycin } (C_{38}H_{69}NO_{13}) = \frac{Potency\ (mg)\ of\ clarithromycin\ RS}{W_S} \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 360$$

W_S: Amount taken (g) of Clarithromycin for Syrup in 10 mL of suspension

C: Labeled amount [mg (potency)] of clarithromycin ($C_{38}H_{69}NO_{13}$) in 1 g

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Add phosphoric acid to a mixture of methanol and 0.067 mol/L potassium dihydrogen phosphate solution (65 : 35) to adjust pH to 4.0.

Flow rate: 1.0 mL/min

Uniformity of dosage units (distribution) Meets the requirements.

Assay Perform the test as directed in the Assay under Clarithromycin. Weigh accurately an amount of Clarithromycin for Syrup equivalent to about 0.5 g (potency) of clarithromycin ($C_{38}H_{69}NO_{13}$) according to the labeled potency, add 40 mL of water and shake to mix. Add methanol to make exactly 100 mL, then shake vigorously to mix for 30 minutes. Pipet 2 mL of this solution, add exactly 2 mL of the internal standard solution, add the mobile phase to make exactly 20 mL, and use this solution as the test solution. Separately, weigh about 50 mg (potency) of clarithromycin RS and dissolve in methanol to prepare a solution containing 5 mg (potency) per mL. Pipet 2 mL of this solution, add exactly 2 mL of the internal standard solution, add the mobile phase to make exactly 20 mL, and use this solution as the standard solution.

Packaging and storage Preserve in tight containers.

Clarithromycin Tablets
클래리트로마이신 정

Clarithromycin Tablets contain NLT 90.0% and NMT 107.0% of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$: 747.95).

Method of preparation Prepare as directed under Tablets, with Clarithromycin.

Identification Weigh an amount of Clarithromycin Tablets, previously powdered, equivalent to 60 mg (potency) of clarithromycin, add 40 mL of acetone, shake for 10 minutes, and centrifuge for 5 minutes at 4000 rotations per minute. Take 30 mL of the clear supernatant, and determine the infrared spectra of the residues as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; it exhibits absorption at the wavenumbers of about 2980 cm^{-1}, 2940 cm^{-1}, 1734 cm^{-1}, 1693 cm^{-1}, 1459 cm^{-1}, 1379 cm^{-1} and 1171 cm^{-1}.

Water NMT 7.0% (0.1 g, volumetric titration, direct titration).

Uniformity of dosage units Meets the requirements.

Dissolution Perform the test with 1 tablet of Clarithromycin Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of 0.05 mol/L dibasic sodium phosphate-citric acid buffer solution (pH 6.0) as the dissolution solution. Take NLT 20 mL of the dissolved solution after 30 minutes from the start of the Dissolution, and filter through a membrane filter with a pore size of NMT 0.45 μm. Discard 10 mL of the first filtrate, pipet V mL of the subsequent filtrate, and add the mobile phase to obtain exactly V′ mL of a solution containing about 28 μg (potency) of clarithromycin ($C_{38}H_{69}NO_{13}$) per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 28 mg (potency) of clarithromycin RS, and dissolve in acetonitrile for liquid chromatography to make exactly 100 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 100 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of clarithromycin, A_T and A_S, in each solution. Meets the requirements if the dissolution rate of Clarithromycin Tablets in 30 minutes is NLT 75%.

Dissolution rate (%) of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 90$$

W_S: Amount [mg (potency)] of clarithromycin RS

C: Labeled amount [mg (potency)] of clarithromycin ($C_{38}H_{69}NO_{13}$) in 1 tablet

Operating conditions

Proceed as directed under the operating conditions under the Assay.

System suitability

System performance: Proceed with 100 μL of the standard solution according to the above conditions; the symmetry factor of the clarithromycin peak is NMT 2.0.

System repeatability: Repeat the test 6 times with 100 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of clarithromycin is NMT 2.0%.

Assay Weigh accurately the mass of NLT 20 Clarithromycin Tablets, and powder. Weigh accurately the appropriate amount, add the mobile phase to obtain a solution

containing about 8 mg (potency) of clarithromycin ($C_{38}H_{69}NO_{13}$) per mL according to the labeled amount, and ultrasonicate. After dispersing the particles into small pieces, add accurately 1 mL of the internal standard solution (1) per 100 mg (potency) of clarithromycin ($C_{38}H_{69}NO_{13}$) according to the labeled amount. Then, add again the mobile phase to make a solution containing about 5 mg (potency) of clarithromycin ($C_{38}H_{69}NO_{13}$) per mL according to the labeled amount, sonicate for 10 minutes with occasional strong shaking, and centrifuge for 15 minutes at 4000 rotations per minute. The clear supernatant is filtered through a membrane filter with a pore size of NMT 0.45 μm. Discard the first 3 mL of the filtrate, take 2 mL of the subsequent filtrate, add the mobile phase to make 20 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg (potency) of clarithromycin RS, and dissolve in the mobile phase to make exactly 10 mL. Pipet 2 mL of this solution, add exactly 2 mL of the internal standard solution (2), add the mobile phase again to make 20 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, of clarithromycin to the peak area of the internal standard.

Potency (μg) of clarithromycin ($C_{38}H_{69}NO_{13}$)
= Potency (μg) of clarithromycin RS × Q_T / Q_S

Internal standard solution—(1) A solution of propyl p-hydroxybenzoate in the mobile phase (1 in 1000).

Internal standard solution—(2) Pipet 1 mL of the internal standard solution (1), and add the mobile phase to make exactly 20 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of 0.05 mol/L potassium dihydrogen phosphate TS (pH 2.0) and methanol (2 : 3).

0.05 mol/L potassium dihydrogen phosphate TS (pH 2.0)—Add phosphoric acid to 0.05 mol/L potassium dihydrogen phosphate TS, and adjust pH to 2.0.

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the internal standard and clarithromycin are eluted in this order with the resolution between their peaks being NLT 3.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above conditions; the relative standard deviation of the peak area ratios of clarithromycin to the peak area of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Clarithromycin Delayed-Release Tablets
클래리트로마이신 서방정

Clarithromycin Delayed-Release Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$: 747.96).

Method of preparation Prepare as directed under Tablets, with Clarithromycin.

Identification (1) Powder Clarithromycin Delayed-Release Tablets, extract with chloroform to obtain a concentration of 2.5 mg of clarithromycin per mL, and perform the test as directed under the Identification (4) of Clarithromycin.

(2) The retention times of the major peaks obtained from the test solution and the standard solution in the Assay are the same.

Dissolution Perform the test with 1 tablet of Clarithromycin Delayed-Release Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of 0.21 mol/L phosphate buffer solution (pH 4.0). Take the dissolved solution 2, 8, and 20 hours after the start of the Dissolution to filter, if necessary, add 0.21 mol/L phosphate buffer solution (pH 4.0) to contain about 560 μg (potency) of clarithromycin ($C_{38}H_{69}NO_{13}$) per mL according to the labeled amount. Dilute and use this solution as the test solution. Separately, weigh accurately about 28 mg (potency) of clarithromycin RS, dissolve in 7 mL of acetonitrile, add 0.21 mol/L phosphate buffer solution (pH 4.0) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Assay. Meets the requirements if the dissolution rate for 2 hours is NMT 15%, for 8 hours is 35% to 65%, and for 20 hours is NLT 60%.

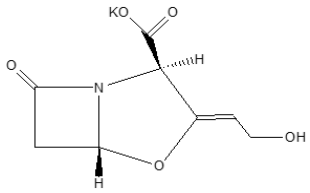
Uniformity of dosage units Meets the requirements.

Assay Perform the test according to the Assay under Clarithromycin. However, weigh accurately the mass of NLT 20 Clarithromycin Delayed-Release Tablets, and powder. Weigh accurately an amount equivalent to about 0.5 g (potency) according to the labeled potency, add it to methanol, and shake vigorously to mix and make a solution containing 5 mg (potency) per mL. Pipet 2 mL of this solution, add 2 mL of the internal standard solution,

then add the mobile phase to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg (potency) of clarithromycin RS, and dissolve it in methanol to make a solution containing 5 mg (potency) per mL. Pipet 2 mL of this solution, add 2 mL of the internal standard solution, then add the mobile phase to make exactly 20 mL, and use this solution as the standard solution.

Packaging and storage Preserve in tight containers.

Clavulanate Potassium
클라불란산칼륨



$C_8H_8KNO_5$: 237.25
Potassium(2*R*,3*Z*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate [*61177-45-5*]

Clavulanate Potassium contains between 810 μg and 860 μg (potency) of clavulanic acid ($C_8H_9NO_5$: 199.16) per mg, calculated on the anhydrous basis.

Description Clavulanate Potassium occurs as a white to pale yellowish white crystalline powder.
It is very soluble in water, soluble in methanol, and slightly soluble in ethanol(95).

Identification (1) Add 5 mL of imidazole TS to 1 mL of aqueous solutions (1 in 5000) of Clavulanate Potassium and clavulanic acid RS, heat for 12 minutes on a steam bath at 30 ℃, cool, and determine the absorption spectra according to the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Clavulanate Potassium and clavulanate potassium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Clavulanate Potassium responds to the Qualitative Analysis (1) for potassium salt.

Optical rotation $[\alpha]_D^{20}$: Between +53° and +63° (0.5 g calculated on the anhydrous basis, 50 mL of water, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Clavulanate Potassium according to Method 2 and perform the test. Prepare the control solution with 4.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Clavulanate Potassium according to Method 3 and perform the test (NMT 2 ppm).

(*3*) ***Related substances***—Weigh accurately about 0.1 g (potency) of Clavulanate Potassium, dissolve in mobile phase A water to make 10 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase A to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution according to the automatic integration method; each peak area other than the peak of clavulanic acid from the test solution is not greater than the peak area of clavulanic acid from the standard solution. The sum of the peak areas other than the peak area of clavulanic acid in the test solution is NMT 2 times the peak area of clavulanic acid in the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 100 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: 0.05 mol/L dibasic sodium phosphate solution adjusted to pH 4.0 with phosphoric acid.

Mobile phase B: A mixture of mobile phase A and methanol (1 : 1).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 4	100	0
4 - 15	100 → 0	0 → 100
15 - 25	0	100

Flow rate: 1.0 mL/min

System suitability

Test for required detectability: Pipet 1 mL of the standard solution and add the mobile phase A to make exactly 10 mL. Confirm that the peak area of clavulanic acid obtained from 20 μL of this solution is between 7% and 13% of the peak area of clavulanic acid obtained from 20 μL of the standard solution.

System performance: Weigh accurately about 10 mg each of clavulanic acid and amoxicillin, and add the mobile phase A to make exactly 100 mL. Proceed with 20 μL of this solution according to the above conditions; the resolution between clavulanic acid and amoxicillin is NLT 8, and the number of theoretical plates of clavulanic

acid is NLT 2500.

System repeatability: Repeat the test 3 times with 20 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area for clavulanic acid is NMT 2.0%.

Time span of measurement: About 6 times the retention time of clavulanic acid.

Water NMT 1.5% (5 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in a sterile preparation. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins It is less than 0.03 EU per mg (potency) of clavulanate potassium when used for the manufacturing of sterile preparations.

Assay Weigh accurately about 12.5 mg (potency) each of Clavulanate Potassium and clavulanic acid RS, dissolve in 30 mL water, add exactly 5 mL of internal standard solution, and then add water to make 50 mL. Use these solutions as the test solution and the standard solution, respectively. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S of clavulanic acid to the peak area of the internal standard for each solution, respectively.

$$\text{Potency (μg) of clavulanic acid } (C_8H_9NO_5) = \text{Potency (μg) of clavulanic acid RS} \times \frac{Q_T}{Q_S}$$

Separately, weigh accurately about 0.3 g of iron, sulfanilamide, dissolve in 30 mL of methanol, and add water to make 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 1.36 g of sodium acetate hydrate in 900 mL of water, adjust pH to 4.5 with acetic acid (2 in 5), add 30 mL of methanol, and add water to make 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of clavulanic acid is about 6 minutes.

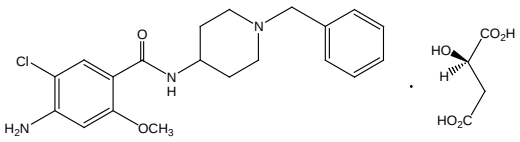
System suitability

System performance: Proceed with 5 μL of the standard solution under the above conditions; clavulanic acid and internal standard are eluted in this order with the resolution being NLT 4.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solutions as directed under the above conditions, the relative standard deviation of peak area ratios of clavulanic acid to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Clebopride Malate
클레보프리드말산염



and enantiomer

$C_{20}H_{24}ClN_3O_2 \cdot C_4H_6O_5$: 507.96

4-[(4-Amino-5-chloro-2-methoxybenzoyl)amino]-1-benzylpiperidinium 3-carboxy-2-hydroxypropanoate [*57645-91-7*]

Clebopride Malate, when dried, contains NLT 98.5% and NMT 101.0% of clebopride malate ($C_{20}H_{24}ClN_3O_2 \cdot C_4H_6O_5$).

Description Clebopride Malate occurs as a white crystalline powder.

It is sparingly soluble in methanol or water, slightly soluble in ethanol(95), and practically insoluble in dichloromethane.

Melting point—About 164 °C (with decomposition).

Identification (1) Dissolve 20 mg of Clebopride Malate in 1 mL of sulfuric acid, add 1 mL of 2-naphthol solution and expose to sunlight; the solution exhibits a yellow color with blue fluorescence.

(2) Dissolve 20.0 mg each of Clebopride Malate and clebopride malate RS in water to make 100 mL; add water to 10.0 mL of the resulting solution to make 100 mL, and use these solutions as the test solution and the standard solution. Determine the absorption spectra of both solutions as directed under the Ultraviolet-visible Spectroscopy: both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Clebopride Malate and clebopride malate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

(4) Dissolve 5 mg of Clebopride Malate in ethanol(95) to make 10 mL and use this solution as the test solution. Separately, dissolve 5 mg of clebopride malate RS in ethanol(95) to make 10 mL, and use this solution as the standard solution (1). Dissolve 5 mg of clebopride

malate RS and 5 mg of metoclopramide hydrochloride RS in ethanol(95) to make 10 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution, the standard solution (1) and the standard solution (2) in 10 mm bands on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of toluene, methanol, acetone and ammonia water (70 : 14 : 14 : 2) to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254nm); the R_f values of the principal spots obtained from the test solution and the standard solution (1) are the same.

This test is valid when performed in the same manner with the standard solution (2) and the two spots are clearly separated.

3-naphthol solution—Dissolve 5 g of 2-naphthol in 40 mL of 2 mol/L sodium hydroxide TS and add water to make 100 mL. Prepare before use.

pH Dissolve 1.0 g of Clebopride Malate in water to make 100 mL; pH of this solution is between 3.8 and 4.2.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Clebopride Malate in water to make 100 mL; the resulting solution is clear and colorless.

(2) ***Chloride***—Dissolve 1.0 g of Clebopride Malate in 20 mL of acetic acid(100), add 6 mL of dilute nitric acid and water to make 50 mL, and use this solution as the test solution. Prepare the control solution by mixing 20 mL of acetic acid(100), 6 mL of dilute nitric acid and 0.25 mL of 0.01 mol/L hydrochloric acid, then add water to make 50 mL (NMT 0.009%).

(3) ***Sulfate***—Dissolve 2.0 g of Clebopride Malate in 20 mL of acetic acid(100), add water to make 50 mL, and use this solution as the test solution. Prepare the control solution by mixing 20 mL of acetic acid(100) and 0.42 mL of 0.005 mol/L sulfuric acid, then add water to make 50 mL (NMT 0.01%).

(4) ***Heavy metals***—Proceed with 2.0 g of Clebopride Malate as directed under Method 2 under the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Related substances***—Weigh accurately about 0.10 g of Clebopride Malate and dissolve in 10 mL of the mobile phase, and use this solution as the test solution. Pipet 0.2 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area obtained from each solution according to the automatic integration method; the sum of peak areas other than clebopride for the test solution is not greater than the peak area of clebopride for the standard solution.

Operating conditions

Detector: An ultravioletphotometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanizedanized silica gel for liquid chromatography (7 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: Dissolve 3.85 g of ammonium acetate in water to make 500 mL, and filter through a membrane filter of pore size NMT 0.5 μm. Add 600 mL of methanol to 400 mL of the filtrate.

Flow rate: Adjust the flow rate so that the retention time of clebopride is about 15 minutes.

System suitability

Test for required detectability: Pipet 10 mL of the standard solution and add water to make exactly 100 mL. Confirm that the peak area of clebopride obtained from 10 mL of this solution is equivalent to between 7% and 13% of the peak area of clebopride obtained from the standard solution.

System performance: Dissolve 30 mg of Clebopride Malate and 5 mg of propyl p-hydroxybenzoate in the mobile phase to make 100 mL. Proceed with 10 mL of this solution according to the above conditions; propyl p-hydroxybenzoate and clebopride are eluted in this order with the resolution between these peaks being NLT 3.

System repeatability: Repeat the test 6 times according to the above conditions with 10 μL of the standard solution each time; the relative standard deviation of the peak areas of clebopride is NMT 2.5%.

Time span of measurement: About 2 times the retention time of clebopride.

Loss on drying NMT 0.5% (1 g, 105 ℃, constant mass).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Clebopride Malate, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 50.80 mg of $C_{20}H_{24}ClN_3O_2 \cdot C_4H_6O_5$

Packaging and storage Preserve in light-resistant, well-closed containers.

Clebopride Malate and Simethicone Capsules
클레보프리드말산염·시메티콘 캡슐

Clebopride Malate and Simethicone Capsules con-

tain NLT 90.0% and NMT 110.0% of the labeled amount of clebopride malate ($C_{20}H_{24}ClN_3O_2 \cdot C_4H_6O_5$: 507.96) and NLT 85.0% and NMT 115.0% of the labeled amount of polydimethylsiloxane ([-$(CH_3)_2$SiO-]n).

Method of preparation Prepare as directed under Capsules, with Clebopride Malate and Simethicone.

Identification (1) ***Clebopride malate***—Weigh an amount of Clebopride Malate and Simethicone Capsules equivalent to about 5 mg of clebopride malate, add 10 mL of dehydrated ethanol, dissolve by heating, filter the solution, and use the filtrate as the test solution. Separately, dissolve 5 mg of clebopride malate RS in 10 mL of anhydrous ethanol, and use this solution as the standard solution. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for silica gel with fluorescent indicator for thin-layer chromatography, develop the plate with a mixture of strong ammonia water, acetone, methanol and toluene (2 : 14 : 14 : 70) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the Rf values and the colors of the spots obtained from the standard solution and the test solution are the same.

(2) ***Simethicone***—Perform the test with Clebopride Malate and Simethicone Capsules as directed under the Assay; both exhibit absorption at the same wavenumber.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Clebopride malate***—Weigh accurately the contents of NLT 20 capsules of Clebopride Malate and Simethicone Capsules. Weigh accurately an amount equivalent to about 1 mg of clebopride malate ($C_{20}H_{24}ClN_3O_2 \cdot C_4H_6O_5$), add methanol to make 50 mL, separate the resulting solution by using a centrifuge, and use the clear supernatant as the test solution. Separately, weigh accurately about 50 mg of Clebopride malate RS and dissolve in the methanol to make 100 mL. Pipet 2.0 mL of this solution, add methanol to make 50 mL, and use it as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 310 nm as directed under the Ultraviolet-visible Spectroscopy.

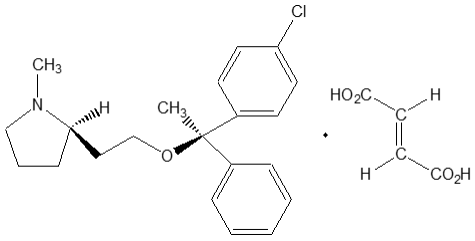
Amount (mg) of clebopride malate ($C_{20}H_{24}ClN_3O_2 \cdot C_4H_6O_5$)
= Amount (mg) of clebopride malate RS $\times \frac{A_T}{A_S} \times \frac{1}{50}$

(2) ***Simethicone***—Weigh accurately an amount of NLT 20 Clebopride Malate and Simethicone Capsules equivalent to about 50 mg of simethicone, put in a 120-mL flask, add 25 mL of toluene, and shake and disperse the resulting solution. Next, add 50 mL of diluted hydrochloric acid (2 in 5), close the flask by using a stopper with an inert surface, and use a vertical shaker to mix by shaking for exactly 5 minutes at an amplitude of 38 2 mm and about 200 reciprocations per minute. Transfer this mixture to a 125-mL separating funnel, put about 5 mL of the toluene layer in a 15-mL stoppered test tube containing 0.5 g of anhydrous sodium sulfate, close the test tube with the stopper with inert surface, and shake the tube vigorously. Centrifuge the solution, and use the clear supernatant as the test solution. Separately, proceed with about 50 mg of polydimethylsiloxane RS in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using the solution prepared in the same manner as the test solution with 25.0 mL of toluene as a control solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution by using a cell with 0.5 mm in thickness at the absorbance maximum wavelength (λ_{max}) around 1265 cm^{-1} as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of simethicone ([-$(CH_3)_2$SiO-]n)
= Amount (mg) of polydimethylsiloxane RS $\times \frac{A_T}{A_S}$

Packaging and storage Preserve in tight containers.

Clemastine Fumarate
클레마스틴푸마르산염



$C_{21}H_{26}ClNO \cdot C_4H_4O_4$: 459.96
(*E*)-but-2-Enedioic acid;(2*R*)-2-[2-[(1*R*)-1-(4-chlorophenyl)-1-phenylethoxy]ethyl]-1-methylpyrrolidine [*14976-57-9*]

Clemastine Fumarate, when dried, contains NLT 98.5% and NMT 101.0% of clemastine fumarate ($C_{21}H_{26}ClNO \cdot C_4H_4O_4$).

Description Clemastine Fumarate occurs as a white, crystalline, odorless powder.
It is sparingly soluble in methanol or acetic acid(100), slightly soluble in ethanol(95), very slightly soluble in ether, and practically insoluble in water.

Identification Determine the absorption spectra of Clemastine Fumarate and clemastine fumarate RS as directed

in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit the same intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +16° and +18° (0.1 g after drying, methanol, 10 mL, 100 mm).

Melting point Between 176 and 180 ℃ (with decomposition).

Purity (1) ***Clarity and color of solution*—**Dissolve 0.5 g of Clemastine Fumarate in 10 mL of methanol; the solution is clear and colorless.

(2) ***Heavy metals*—**Proceed with 1.0 g of Clemastine Fumarate as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic*—**Proceed with 1.0 g of Clemastine Fumarate as directed under Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances*—**Dissolve 0.10 g of Clemastine Fumarate in 5 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 250 mL, and use this solution as the standard solution (1). Pipet 5 mL of this solution, add methanol to make exactly 10 mL and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution, the standard solution (1), and the standard solution (2) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, methanol and ammonia water(28) (90 : 10 : 1) to a distance of about 15 cm, and air-dry the plate. Spray evenly Dragendorff TS for spraying and immediately spray evenly with hydrogen peroxide TS; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution (1) and the number of spots more intense than the spots from the standard solution (2) is NMT 2.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

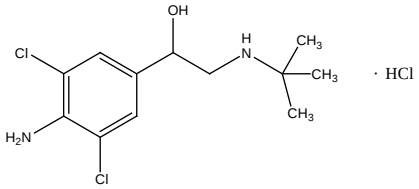
Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.4 g of Clemastine Fumarate, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 46.00 mg of $C_{21}H_{26}ClNO \cdot C_4H_4O_4$

Packaging and storage Preserve in tight containers.

Clenbuterol Hydrochloride
클렌부테롤염산염



$C_{12}H_{18}Cl_2N_2O \cdot HCl$: 313.65
1-(4-Amino-3,5-dichlorophenyl)-2-(*tert*-butyl-
Glutamic acid hydrochloride, [*21898-19-1*]

Clenbuterol Hydrochloride contains NLT 99.0% and NMT 101.0% of clenbuterol hydrochloride ($C_{12}H_{18}Cl_2N_2O \cdot HCl$), calculated on the anhydrous basis.

Description Clenbuterol Hydrochloride occurs as a white crystalline powder.
It is soluble in water or ethanol(95) and slightly soluble in acetone.

Melting point—About 173 ℃ (with decomposition).

Identification (1) Determine the infrared spectra of Clenbuterol Hydrochloride and clenbuterol hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve 10 mg of Clenbuterol Hydrochloride in 10 mL of methanol, and use this solution as the test solution. Separately, dissolve 10 mg of clenbuterol hydrochloride RS in 10 mL of methanol and use this solution as the standard solution. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of toluene, ethanol(95) and ammonia water(28) (15 : 10 : 0.15) as the developing solvent to a distance of about 10 cm and air-dry the plate. Spray evenly 1 mol/L hydrochloric acid solution of 1% sodium nitrite, and after 10 minutes, immerse in a methanol solution of 0.4% naphthylethylene diamine hydrochloride, take the plate out and air-dry. The spots from the test solution and the standard solution have the same color and R_f value.

(3) An aqueous solution of Clenbuterol Hydrochloride (1 in 100) responds to the Qualitative Analysis (2) for chloride.

Optical rotation $[\alpha]_D^{20}$: Between -0.10° and +0.10° (0.30 g, water, 10 mL, 100 mm).

pH Dissolve 0.5 g of Clenbuterol Hydrochloride in 10 mL of water; the pH of this solution is between 5.0 and 7.0.

Purity (1) ***Clarity and color of solution*—**Dissolve 0.5 g of Clenbuterol Hydrochloride in 10 mL of water. The

resulting solution is not more intense than the following control suspension.

Control suspension—Dissolve 1.0 g of hydrazinium sulfate in water to make exactly 100 mL, and allow to stand for 4 to 6 hours. Add 25.0 mL of this solution to a solution of 2.5 g of hexamethylenetetramine dissolved in 25.0 mL of water, mix well, and allow to stand for 24 hours. Store in a glass container and use within 2 months. Before use, add water to 15.0 mL of the suspension to make 1000 mL, then mix 10.0 mL of this suspension with 90.0 mL of water, and shake well to mix. Use this solution as the control suspension.

(2) ***Heavy metals***—Proceed with 1.0 g of Clenbuterol Hydrochloride as directed under Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Weigh 0.100 g of Clenbuterol Hydrochloride, dissolve in the mobile phase to make exactly 50 mL and use this solution as the test solution. Take 0.1 mL of the test solution, add water to make 100 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of each solution according to the automatic integration method. The peak areas other than the major peak from the test solution are not greater than the major peak area from the standard solution (0.1%), and the total area of peaks other than the major peak is not greater than 2 times the peak area from the standard solution. Exclude peaks smaller than 0.1 times the major peak area from the standard solution.

Operating conditions

Detector: An ultraviolet spectrophotometry (wavelength: 215 nm).

Column: A stainless steel column about 4 mm in internal diameter and 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: A mixture of phosphate buffer solution, methanol and acetonitrile (60 : 20 : 20).

Flow rate: 0.5 mL/min

System suitability

System performance: Dissolve 10 mg of clenbuterol related substance I RS {1-(4-amino-3,5-dichlorophenyl)-2-[(1,1-dimethylethyl)amino]ethanone(clenbuterol-ketone)} in 20 mL of the mobile phase, add 5 mL of the test solution, then add the mobile phase to make 50 mL. Proceed with 5 μL of this solution according to the above conditions; the resolution between the peaks of related substance I and clenbuterol is NLT 2.5.

Phosphate buffer solution—Dissolve 3.0 g of sodium decanesulfonate and 5.0 g of potassium dihydrogen phosphate in 900 mL of water, adjust pH to 3.0 with phosphoric acid, then add water to make 1000 mL.

Water NMT 1.0% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.25 g of Clenbuterol Hydrochloride, dissolve in 50 mL of ethanol(95), add 5.0 mL of 0.01 mol/L hydrochloric acid, and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Read the amount consumed between equivalence point 1 and equivalence point 2.

Each mL of 0.1 mol/L sodium hydroxide VS
= 31.365 mg of $C_{12}H_{18}Cl_2N_2 \cdot HCl$

Packaging and storage Preserve in well-closed containers.

Clenbuterol Hydrochloride Syrup
클렌부테롤염산염 시럽

Clenbuterol Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of clenbuterol hydrochloride ($C_{12}H_{18}Cl_2N_2O \cdot HCl$: 313.65).

Method of preparation Prepare as directed under Syrups, with Clenbuterol Hydrochloride.

Identification Take an amount of Clenbuterol Hydrochloride Syrup equivalent to about 0.1 mg of clenbuterol hydrochloride according to the labeled amount, transfer to a separatory funnel containing 50 mL of water, add 5 mL of 2 mol/L sodium hydroxide TS, then extract 3 times with 50 mL of ether each. Combine the ether extracts, wash with 50 mL of water, filter with a filter paper with anhydrous sodium sulfate, then evaporate the filtrate to dryness on a steam bath. Dissolve the residue in 0.1 mL of methanol and use this solution as the test solution. Separately, dissolve clenbuterol hydrochloride RS in methanol to obtain a solution containing 1.0 mg per mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of toluene, isopropanol, and ammonia (80 : 20 : 1) and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

pH Between 3.0 and 4.0.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Pipet an amount of Clenbuterol Hydrochloride Syrup equivalent to 0.1 mg of clenbuterol hydrochloride ($C_{12}H_{18}Cl_2N_2O \cdot HCl$) according to the labeled amount. Alkalify by adding 50 mL of water and 5 mL of 2 mol/L sodium hydroxide TS, extract 4 times by shaking with 40 mL of ether each, wash the extract with 30 mL of water, then extract the ether layer 2 times using 10 mL each of 1 mol/L hydrochloric acid TS. Transfer the water layer to a 25-mL volumetric flask, add 2.0 mL of the internal standard solution and add 1 mol/L hydrochloric acid TS to the gauge line. Use this solution as the test solution. Separately, weigh accurately about 25 mg of clenbuterol hydrochloride RS and add 1 mol/L hydrochloric acid TS to make 250 mL. Pipet 1.0 mL of this solution, add 2.0 mL of the internal standard solution and 1 mol/L hydrochloric acid TS to make 25 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios for clenbuterol hydrochloride, Q_T and Q_S, to the internal standard for each solution.

$$\text{Amount (mg) of clenbuterol hydrochloride } (C_{12}H_{18}Cl_2N_2O \cdot HCl) = \text{Amount (mg) of clenbuterol hydrochloride RS} \times \frac{Q_T}{Q_S} \times \frac{1}{250}$$

Internal standard solution—Weigh accurately about 50 mg of caffeine RS, and add water to make 100 mL. Pipet 10.0 mL of this solution, add water to make 100 mL, and use this solution as the internal standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with cyanosilyl silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Adjust the pH of a mixture of water, ethanol, isopropanol and 0.15% sodium 1-heptanesulfonate solution (80 : 18 : 2 : 0.15) with acetic acid(100) for non-aqueous titration to 3.0.

Flow rate: 1.5 mL/min

Packaging and storage Preserve in light-resistant, tight containers.

Clenbuterol Hydrochloride Tablets
클렌부테롤염산염 정

Clenbuterol Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of clenbuterol hydrochloride ($C_{12}H_{18}Cl_2N_2O \cdot HCl$: 313.65).

Method of preparation Prepare as directed under Tablets, with Clenbuterol Hydrochloride.

Identification Weigh the amount equivalent to 0.1 mg of clenbuterol hydrochloride according to the labeled amount of Clenbuterol Hydrochloride Tablets. Add 50 mL of water to make alkaline with dilute sodium hydroxide TS, and extract three times with 30 mL each of ether. Combine the ether extracts, wash with water, dehydrate with anhydrous sodium sulfate, and evaporate to dryness. Dissolve the residue in 0.1 mL of ethanol(95) and use this solution as the test solution. Separately, dissolve clenbuterol hydrochloride RS in ethanol(95) to contain 1.0 mg per mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of toluene, isopropanol, and ammonia (80 : 20 : 1) and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Clenbuterol Hydrochloride Tablets, and powder. Weigh accurately an amount equivalent to about 0.1 mg of clenbuterol hydrochloride ($C_{12}H_{18}Cl_2N_2O \cdot HCl$), and mix with 50 mL of water. Add 5 mL of 2 mol/L sodium hydroxide TS to make alkaline, extract by shaking 40 mL of ether 4 times, wash the extract with 30 mL of water, and extract the ether layer twice with 10 mL of 1 mol/L hydrochloric acid TS. Add exactly 2 mL of the standard solution and 1 mol/L hydrochloric acid TS to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg of clenbuterol hydrochloride RS, and add 1 mol/L hydrochloric acid TS to make 250 mL. Pipet 1.0 mL of this solution, and add 2 mL of internal standard solution and 1 mol/L hydrochloric acid TS to make exactly 250 mL. Pipet 1 mL of this solution, add exactly 2 mL of the internal standard solution and 1 mol/L hydrochloric acid TS to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution according to the following conditions as directed under the Liquid Chromatography, and determine the

ratio of peak areas, Q_T and Q_S, for clenbuterol hydrochloride to the peak area of the internal reference for each solution.

$$\text{Amount (mg) of clenbuterol hydrochloride } (C_{12}H_{18}Cl_2N_2O\cdot HCl) = \text{Amount (mg) of clenbuterol hydrochloride RS} \times (Q_T / Q_S) \times 0.004$$

Internal standard solution—Weigh accurately about 50 mg of caffeine RS, and add water to make 100 mL. Take exactly 10.0 mL of this solution, add water to make 100 mL, and use this solution as the test solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with cyanosilyl silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Adjust the pH of a mixture of water, methanol, isopropanol and 0.15% sodium 1-heptanesulfonate solution (80 : 18 : 2 : 0.15) to 3.0 with acetic acid(100) for non-aqueous titration.

Flow rate: 1.5 mL/min

Packaging and storage Preserve in light-resistant, tight containers.

Clidinium Bromide and Chlordiazepoxide Tablets
클리디늄브롬화물·클로르디아제폭시드 정

Clidinium Bromide and Chlordiazepoxide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of clidinium bromide ($C_{22}H_{26}BrNO_3$: 432.35) and chlordiazepoxide ($C_{16}H_{14}ClN_3O$: 299.76).

Method of preparation Prepare as directed under Tablets, with Clidinium Bromide and Chlordiazepoxide.

Identification (1) Weigh an amount of Clidinium Bromide and Chlordiazepoxide Tablets, equivalent to 5 mg of clidinium bromide, according to the labeled amount. Add 1 mL of water and 9 mL of methanol, shake for 10 minutes to mix, centrifuge, and use the clear supernatant as the test solution. Separately, add 10 mg of clidinium bromide RS and 20 mg of chlordiazepoxide RS to 10 mL of a mixture of methanol and water (45 : 5), and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, isopropanol and formic acid (45 : 40 : 15) as a developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet rays (major wavelength: 254 nm) or spray Dragendorff's TS evenly onto the plate; the color and R_f values of the spots obtained from the test solution and the standard solution are the same.

(2) The retention times of the major peaks obtained from the test solution and the standard solution under the Assay are the same.

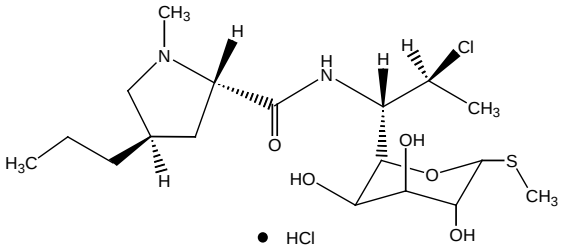
Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Clidinium bromide and chlordiazepoxide***—Weigh accurately the mass of NLT 20 Clidinium Bromide and Chlordiazepoxide Tablets, and powder. Weigh accurately an amount, equivalent to about 5 mg of chlordiazepoxide ($C_{16}H_{14}ClN_3O$) [about 2.5 mg of clidinium bromide ($C_{22}H_{26}BrNO_3$)], and perform the test as directed under the Assay of Clidinium Bromide and Chlordiazepoxide Tablets and Clidinium Bromide Capsules below in United States Pharmacopeia (USP). However, use clidinium bromide and chlordiazepoxide for the reference standard.

Packaging and storage Preserve in tight containers.

Clindamycin Hydrochloride
클린다마이신염산염



$C_{18}H_{33}ClN_2O_5S.HCl$: 461.44

(2*S*,4*R*)-N-{2-Chloro-1-[(2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-trihydroxy-6-(methylsulfanyl)oxan-2-yl]propyl}-1-methyl-4-propylpyrrolidine-2-carboxamide hydrochloride [*21462-39-5*]

Clindamycin Hydrochloride is the hydrochloride of a derivative of lincomycin. Clindamycin Hydrochloride contains NLT 838 μg and NMT 940 μg (potency) of clindamycin ($C_{18}H_{33}ClN_2O_5S$: 424.98) per mg, calculated on the anhydrous basis.

Description Clindamycin Hydrochloride occurs as white to grayish white crystals or a crystalline powder.
It is freely soluble in water or methanol, and slightly soluble in ethanol(95).

Identification (1) Determine the infrared spectra of

Clindamycin Hydrochloride and clindamycin hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Clindamycin Hydrochloride (1 in 100) responds to the Qualitative Analysis (2) for chloride.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{25}$: Between +135° and +150° (0.5 g calculated on the anhydrous basis, water, 25 mL, 100 mm).

pH Dissolve 1 g of Clindamycin Hydrochloride in 10 mL of water; the pH of this solution is between 3.0 and 5.5.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Clindamycin Hydrochloride according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Weigh accurately 0.125 g of Clindamycin Hydrochloride, add the mobile phase to make 25 mL, and use this solution as the test solution. Weigh accurately 50 mg each of lincomycin hydrochloride RS and clindamycin hydrochloride RS, and dissolve in the mobile phase to make 100 mL. Pipet 10 mL of the resulting solution, add the mobile phase to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, determine peak areas from each solution by the automatic integration method, and calculate the amount of the lincomycin according to the equation (1). Determine the amounts of 7-epi clindamycin, clindamycin B and other related substances according to the equation (2); the amounts of 7-epi clindamycin, clindamycin B and other related substances are NMT 4.0%, NMT 2.0 and NMT 1.0%, respectively, and the amount of total related substances containing lincomycin is NMT 6.0%.

$$\text{Content (\%) of lincomycin } (C_{18}H_{34}N_2O_6S) = 2.5 \times \frac{C_L \times P_L}{W} \times \frac{A_T}{A_S} (1)$$

C_L: Concentration (mg/mL) of lincomycin hydrochloride in the standard solution

P_L: Potency (μg/mg) of lincomycin ($C_{18}H_{34}N_2O_6S$) in lincomycin hydrochloride RS

W: Weight (mg) of sample taken

A_T: Peak area of lincomycin obtained from the test solution

A_S: Peak area of lincomycin obtained from the standard solution

$$\text{Content (\%) of related substances} = 2.5 \times \frac{C \times P}{W} \times \frac{A_i}{A_c} (2)$$

C: Concentration (mg/mL) of clindamycin B in the standard solution

P: Potency (μg/mg) of clindamycin ($C_{18}H_{33}ClN_2O_5S$) in clindamycin hydrochloride RS

W: Weight (mg) of sample taken

A_i: Peak area of each related substance obtained from the test solution

A_C: Peak area of clindamycin obtained from the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 5 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and a solution prepared by dissolving 6.8 g of potassium dihydrogen phosphate in 1000 mL of water and adjusting the pH to 7.5 with 8 mol/L potassium hydroxide solution (450 : 550).

Flow rate: 1.0 mL/min

System suitability

System performance: The relative retention times of lincomycin, clindamycin B and 7-epi clindamycin are 0.4, 0.65 and 0.9, respectively.

Time span of measurement: About 6 times the retention time of clindamycin.

Water NMT 6.0% (0.3 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in the manufacturing of a sterile preparation. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of sterile preparations.

Pyrogen It meets the requirements when used in a sterile preparation. However, weigh an appropriate amount of Clindamycin Hydrochloride, dissolve in 75 mL of Isotonic Sodium Chloride Injection to make a solution containing 5.0 mg per mL, and use this solution as the test solution. However, the test injection amount shall be 1.0 mL of the test solution per kg of the weight of a rabbit.

Assay Weigh accurately about 20 mg (potency) each of Clindamycin Hydrochloride and clindamycin hydrochloride RS, dissolve in the mobile phase to make exactly 20 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of clindamycin in each solution, A_T and A_S, respectively.

Potency (μg) of clindamycin ($C_{18}H_{33}ClN_2O_5S$)
= Potency (μg) of clindamycin hydrochloride RS × $\frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of the solution of 0.05 mol/L potassium dihydrogen phosphate and acetonitrile whose pH is adjusted to 7.5 with 8 mol/L potassium hydroxide solution (550: 450).

Flow rate: Adjust the flow rate so that the retention time of clindamycin is about 10 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution under the above operating conditions; the number of theoretical plates and the symmetry factor of the peak of clindamycin are NLT 6000 plates and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions; the relative standard deviation of the peak area of clindamycin is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Clindamycin Hydrochloride Capsules
클린다마이신염산염 캡슐

Clindamycin Hydrochloride Capsules contain NLT 93.0% and NMT 107.0% of the labeled amount of clindamycin hydrochloride ($C_{18}H_{33}ClN_2O_5S$: 424.98).

Method of preparation Prepare as directed under Capsules, with Clindamycin Hydrochloride.

Identification Weigh an amount equivalent to 10 mg (potency) of clindamycin hydrochloride according to the labeled amount of Clindamycin Hydrochloride Capsules, dissolve in 2 mL of methanol, shake well to mix, and separate with a centrifuge. Use the clear supernatant as the test solution. Separately, dissolve 10 mg of clindamycin hydrochloride RS in 2 mL of methanol, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of methanol, toluene, and ammonia water(28) (140 : 60 : 3) to a distance of about 12 cm, and air-dry the plate. Spray a solution prepared by adding 50 mL of bismuth subnitrate TS to 500 mL of L-tartaric acid (1 in 5); the R_f value of the principal spot obtained from the test solution is the same as that of the spot obtained from the standard solution.

Water NMT 7.0% (0.2 g, volumetric titration, direct titration).

Dissolution Take 1 Clindamycin Hydrochloride Capsule, proceed with 900 mL of water as the dissolution medium at 50 revolutions per minute according to Method 2, and perform the test. Take NLT 20 mL of the dissolved solution 30 minutes after starting the test and filter using a membrane filter with 0.45 μm in nominal pore size. Discard the first 10 mL of the filtrate, take exactly *V* mL of the subsequent filtrate, add water to make exactly *V'* mL so that each mL contains about 83 μg (potency) of clindamycin hydrochloride ($C_{18}H_{33}ClN_2O_5S$) according to the labeled amount, and then use this solution as the test solution. Separately, weigh accurately about 17 mg (potency) of clindamycin hydrochloride RS, dissolve in water make exactly 200 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of clindamycin, A_T and A_S, in each solution. It meets the requirements when the dissolution rate of Clindamycin Hydrochloride Capsules in 30 minutes is NLT 80%.

Dissolution rate (%) with respect to the labeled amount of clindamycin hydrochloride ($C_{18}H_{33}ClN_2O_5S$)
= Potency (μg) of clindamycin hydrochloride RS
$$\times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 450$$

C: Labeled amount [mg (potency)] of clindamycin hydrochloride ($C_{18}H_{33}ClN_2O_5S$) per capsule

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of acetonitrile and a solution prepared by adjusting 0.05 mol/L potassium dihydrogen phosphate TS to pH 7.5 with 8 mol/L potassium hydroxide TS (550 : 450).

Flow rate: Adjust the flow rate so that the retention time of clindamycin is about 7 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution under the above operating conditions; the number of theoretical plates and the symmetry factor of the peak of clindamycin are NLT 3000 plates and NMT 2.0, respectively.

System performance: Repeat the test six times with 20 μL each of the standard solutions under the above operating conditions; the relative standard deviation of the peak area of clindamycin hydrochloride is NMT 2.0%.

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following method. Take 1 Clindamycin Hydrochloride Capsule, add the mobile phase, shake to mix for 30 minutes, and then add the mobile phase to make exactly V mL so that the solution contains 0.75 mg (potency) of clindamycin. Separate this solution by using a centrifuge, and use the clear supernatant as the test solution. Separately, weigh accurately about 75 mg (potency) of clindamycin hydrochloride RS, add the mobile solution to make exactly 100 mL, and use this solution as the standard solution. Perform the test as directed under the Assay below.

Potency (μg) of clindamycin ($C_{18}H_{33}ClN_2O_5S$)
= Potency (μg) of clindamycin hydrochloride RS
$$\times \frac{A_T}{A_S} \times \frac{V}{100}$$

Assay Weigh accurately the mass of the contents of NLT 20 Clindamycin Hydrochloride Capsules. Weigh accurately an amount, equivalent to 75 mg (potency) of clindamycin, according to the labeled potency, add the mobile phase, shake to mix for 30 minutes to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 75 mg (potency) of clindamycin hydrochloride RS, add the mobile solution to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of clindamycin, A_T and A_S, in each solution.

Potency (μg) of clindamycin ($C_{18}H_{33}ClN_2O_5S$)
= Potency (μg) of clindamycin hydrochloride RS$\times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 150 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of 0.05 mol/L potassium dihydrogen phosphate adjusted the pH to 7.5 with 8 mol/L potassium hydroxide solution (550: 450) and acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of clindamycin is about 7 minutes.

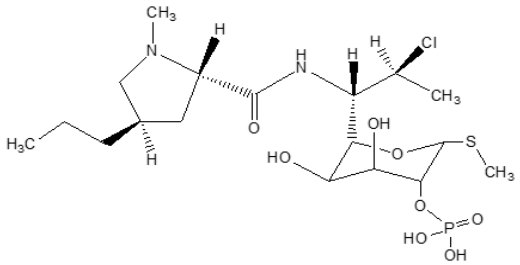
System suitability

System performance: Proceed with 20 μL of the standard solution under the above operating conditions; the number of theoretical plates and the symmetry factor of the peak of clindamycin are NLT 3000 plates and NMT 2.0, respectively.

System repeatability: Repeat the test six times with 20 μL each of the standard solutions under the above operating conditions; the relative standard deviation of the peak area of clindamycin is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Clindamycin Phosphate
클린다마이신포스페이트



$C_{18}H_{34}ClN_2O_8PS$: 504.97

Methyl 5-{2-chloro-1-[(1-methyl-4-propylprolyl)amino]propyl}-2-O-phosphono-1-thiopentopyranoside [*24729-96-2*]

Clindamycin Phosphate is the sulfate of a derivative of clindamycin.

Clindamycin Phosphate contains NLT 800 μg and NMT 846 μg (potency) of clindamycin ($C_{18}H_{33}ClN_2O_5S$: 424.98) per mg, calculated on the anhydrous basis.

Description Clindamycin Phosphate occurs as a white to pale yellowish white crystalline powder.
It is freely soluble in water, sparingly soluble in methanol, and practically insoluble in ethanol(95).

Identification Determine the infrared spectra of Clindamycin Phosphate and clindamycin phosphate RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Crystalline Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between° +115 and +130° (0.25 g calculated on the anhydrous basis, water, 25 mL, 100 mm).

pH Dissolve 0.10 g of Clindamycin Phosphate in 10 mL of water;, the pH of the solution is between 3.5 and 4.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g

of Clindamycin Phosphate in 10 mL of freshly boiled and cooled water; the resulting solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 2.0 g of Clindamycin Phosphate according to Method 4 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 5 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Clindamycin Phosphate according to the Method 4 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Weigh accurately 0.1 g of Clindamycin Phosphate, dissolve in 100 mL of the mobile phase, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to it make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine each peak area of each solution by the automatic integration method; the peak area of clindamycin, which has a relative retention time of about 1.8 to that of clindamycin phosphate from the test solution, is not larger than 1/2 times that of clindamycin phosphate from the standard solution. In addition, the sum of peak areas other than clindamycin phosphate from the test solution is not greater than 4 times that of clindamycin phosphate from the standard solution.

Internal standard solution—A solution of methyl *p*-hydroxybenzoate in the mobile phase (3 in 50000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 10.54 g of potassium dihydrogen phosphate in 775 mL of water, adjust the pH to 2.5 with phosphoric acid, and add 225 mL of acetonitrile to make exactly 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of clindamycin phosphate is about 8 minutes.

System suitability

Test for required detectability: Pipet 1.0 mL of the standard solution, and add the mobile phase to make exactly 10 mL. Confirm that the peak area of clindamycin phosphate obtained from 20 μL of this solution is within the range between 7% and 13% of that of clindamycin phosphate from the standard solution.

System performance: Weigh accurately the amount equivalent to 20 mg (potency) of clindamycin phosphate, dissolve in 25 mL of the internal standard solution, add the mobile phase to make 100 mL, and use this solution as the system suitability solution. Proceed with 20 μL of this solution under the above operating conditions; clindamycin phosphate and the internal standard solution are eluted in this order with the resolution being NLT 4.

System repeatability: Repeat the test 6 times with 20 μL each of the system suitability solutions according to the above conditions; the relative standard deviation of the peak area of clindamycin phosphate to that of the internal standard is NMT 2.5%.

Time span of measurement: About 2 times the retention time of clindamycin phosphate after the solvent peak.

Water NMT 6.0% (0.5 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in the manufacturing of a sterile preparation. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins It is less than 0.58 EU (potency) per mg of clindamycin phosphate when used in the manufacturing of sterile preparations.

Histamine It meets the requirements when used in the manufacturing of sterile preparations. Weigh an appropriate amount of Clindamycin Phosphate, dissolve in Isotonic Sodium Chloride Injection to prepare a solution containing 5 mg (potency) per mL, and use this solution as the test solution.

Assay Weigh accurately an amount of Clindamycin Phosphate and clindamycin phosphate RS, equivalent to about 20 mg (potency), dissolve each in exactly 25 mL of internal standard solution, add the mobile phase to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of peak area of clindamycin phosphate to those of the internal standards from each solution.

$$\text{Potency (μg) of clindamycin } (C_{18}H_{33}ClN_2O_5S) = \text{Potency (μg) of clindamycin hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal Standard solution—A solution of p-hydroxybenzoate in the mobile phase (3 in 50000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octylsilane silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 10.54 g of potassi-

um dihydrogen phosphate in 775 mL of water, and adjust pH to 2.5 with phosphoric acid. To this solution, add 225 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of clindamycin phosphate is about 8 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution under the above conditions; clindamycin phosphate and the internal standard are eluted in this order with the resolution between these peaks being NLT 4.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of clindamycin phosphate to that of the internal standard is NMT 2.5%.

Packaging and storage Preserve in tight containers.

Clindamycin Phosphate Vaginal Cream
클린다마이신포스페이트 질크림

Clindamycin Phosphate Gel contains NLT 90.0% and NMT 120.0% of the labeled amount of clindamycin phosphate ($C_{18}H_{33}ClN_2O_5S$: 424.99).

Method of preparation Prepare as directed under Creams, with Clindamycin Phosphate.

Identification The retention times of the major peaks obtained from the test solution and the standard solution in the Assay are the same.

pH Between 3.0 and 6.0.

Assay Weigh accurately an amount of Clindamycin Phosphate Gel equivalent to about 20 mg (potency), add exactly 20.0 mL of the internal standard solution, and completely dissolve it. Add the mobile phase to make exactly 100 mL to filter, and use this solution as the test solution. Separately, weigh accurately about 20 mg (potency) of clindamycin phosphate RS, add exactly 20.0 mL of the internal standard solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of the peak area of clindamycin phosphate to that of the internal standard.

$$\text{Potency (μg) of clindamycin } (C_{18}H_{33}ClN_2O_5S) = \text{Potency (μg) of clindamycin phosphate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh about 60 mg of methyl *p*-hydroxybenzoate and dissolve in the mobile phase to make exactly 1 L.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 250 mm in length, packed with octylsilane silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Dissolve 10.54 g of potassium dihydrogen phosphate in 775 mL of water, adjust pH to 2.5 with phosphoric acid, and add 225 mL of acetonitrile.

Flow rate: About 1.0 mL/min.

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of clindamycin is NMT 2.5%.

Packaging and storage Preserve in tight containers.

Clindamycin Phosphate Gel
클린다마이신포스페이트 겔

Clindamycin Phosphate Gel contains NLT 90.0% and NMT 120.0% of the labeled amount of clindamycin phosphate ($C_{18}H_{33}ClN_2O_5S$: 424.99).

Method of preparation Prepare as directed under Gels, with Clindamycin Phosphate.

Identification The retention times of the major peak obtained from the test solution in the Assay are the same.

pH Between 5.5 and 7.5.

Assay Weigh accurately an amount of Clindamycin Phosphate Gel equivalent to about 20 mg (potency), add exactly 20.0 mL of the internal standard solution, and completely dissolve it. Add the mobile phase to make exactly 100 mL to filter, and use this solution as the test solution. Separately, weigh accurately about 20 mg (potency) of clindamycin phosphate RS, add exactly 20.0 mL of the internal standard solution and then the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of the peak area of clindamycin phosphate to that of each solution internal standard.

$$\text{Potency (μg) of clindamycin } (C_{18}H_{33}ClN_2O_5S) = \text{Potency (μg) of clindamycin phosphate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh about 60 mg of methyl *p*-hydroxybenzoate and dissolve in the mobile phase to make exactly 1000 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Weigh 10.54 g of potassium dihydrogen phosphate, dissolve in 775 mL of water, adjust the pH to 2.5 with phosphoric acid, and add 225 mL of acetonitrile.

Flow rate: About 1.0 mL/min.

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions under the above operating conditions; the relative standard deviation of the peak area of clindamycin is NMT 2.5%.

Packaging and storage Preserve in tight containers.

Clindamycin Phosphate Injection
클린다마이신포스페이트 주사액

Clindamycin Phosphate Injection is an aqueous solution for injection and contains NLT 90.0% and NMT 110.0% of the labeled amount of clindamycin phosphate ($C_{18}H_{34}ClN_2O_8PS$: 504.96).

Method of preparation Prepare as directed under Injections, with Clindamycin Phosphate.

Description Clindamycin phosphate Injection occurs as a clear, colorless to pale yellow liquid.

Identification Weigh a volume of Clindamycin Phosphate Injection, equivalent to 0.15 g (potency) of clindamycin phosphate according to the labeled amount, add 4 mL of water, 2 mL of 8 mol/L sodium hydroxide TS and 0.1 mL of sodium pentacyanonitrosylferrate(III) TS, shake to mix, heat on a steam bath for 10 minutes, and add 2 mL of hydrochloric acid; the solution exhibits a bluish green color.

pH Between 6.0 and 7.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.1 EU per mg (potency) of clindamycin phosphate.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Perform the test as directed under the Assay under Clindamycin Phosphate. However, weigh accurately a volume of Clindamycin Phosphate Injection, equivalent to about 0.3 g (potency) according to the labeled potency, and add the mobile phase to make exactly 100 mL. Pipet 7 mL of this solution, add exactly 25 mL of the internal standard solution, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately 20 mg (potency) of clindamycin phosphate RS, dissolve in 25 mL of the internal standard solution, add the mobile phase to make 100 mL, and use this solution as the standard solution.

$$\text{Potency (μg) of clindamycin phosphate } (C_{18}H_{34}ClN_2O_8PS) = \text{Potency (μg) of clindamycin phosphate RS} \times \frac{Q_T}{Q_S} \times \frac{100}{7}$$

Internal standard solution—A solution of methyl *p*-hydroxybenzoate in the mobile phase (3 in 50000).

Packaging and storage Preserve in hermetic containers.

Clindamycin Phosphate Topical Solution
클린다마이신포스페이트 외용액

Clindamycin Phosphate Solution

Clindamycin Phosphate Topical Solution contains NLT 90.0% and NMT 120.0% of the labeled amount of clindamycin ($C_{18}H_{33}ClN_2O_5S$: 424.99), when quantified as a topical solution.

Method of preparation Prepare as directed under the Liquids, with Clindamycin Phosphate.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

pH Between 4.0 and 7.0.

Assay Weigh accurately an amount of Clindamycin Phosphate Topical Solution equivalent to 20 mg (potency), according to the labeled potency, add exactly 25.0 mL of the internal standard solution, add the mobile phase to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg (potency) of clindamycin phosphate RS, dissolve in 25.0 mL of the internal standard solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test

solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of clindamycin phosphate to that of the internal standard, for the test solution and the standard solution, respectively.

$$\text{Potency (μg) of clindamycin } (C_{18}H_{33}ClN_2O_5S) = \text{Potency (μg) of clindamycin phosphate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh about 40 mg of 4-hydroxyacetophenone, and add 10 mL of acetonitrile and the mobile phase, to make a concentration of 0.04 mg per mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Dissolve 10.54 g of potassium dihydrogen phosphate in 775 mL of water, adjust the pH to 2.5 with phosphoric acid, and add 225 mL of acetonitrile.

Flow rate: About 1.0 mL/min.

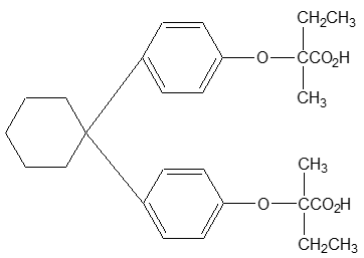
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the resolution between the two peaks of clindamycin and 4-hydroxyacetophenone is NLT 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of the ratio of the peak area of clindamycin to that of the internal standard is NMT 2.5%.

Packaging and storage Preserve in tight containers.

Clinofibrate
클리노피브레이트



$C_{28}H_{36}O_6$: 468.58

2-[4-[1-[4-(2-Carboxybutan-2-yloxy)phenyl]cyclohexyl]phenoxy]-2-methylbutanoic acid [*30299-08-2*]

Clinofibrate, when dried, contains NLT 98.5% and NMT 101.0% of clinofibrate ($C_{28}H_{36}O_6$).

Description Clinofibrate occurs as white to yellowish white crystals or a crystalline powder, and is odorless and tasteless.

It is freely soluble in methanol, ethanol(99.5), acetone or ether, and practically insoluble in water.

A solution of Clinofibrate in methanol (1 in 20) shows no optical rotation.

Melting point—About 146 °C (with decomposition).

Identification (1) Determine the absorption spectra of the solutions of Clinofibrate and clinofibrate RS in ethanol(99.5) (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Clinofibrate and clinofibrate RS as directed in the potassium bromide disk method under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Clinofibrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Prepare the test solution with 1.0 g of Clinofibrate according to Method 3 and perform the test (NMT 2 ppm).

(3) ***Related substances***—Dissolve about 0.10 g of Clinofibrate in 10 mL of acetone and use this solution as the test solution. Pipet 1 mL of this solution, and add acetone to make exactly 50 mL. Pipet 5 mL of this solution, add acetone to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 50 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, cyclohexane and acetic acid(100) (12 : 5 : 3) to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 1.0% (1 g, in vacuum, 60 ℃, 3 hours).

Residue on ignition NMT 0.2% (1 g).

Isomer rate To 50 mg of Clinofibrate, add 0.4 mL of thionyl chloride, close the stopper, warm on a steam bath at 60 ℃ for 5 minutes while shaking occasionally, and evaporate the excess thionyl chloride in vacuum at below 60 ℃. Dissolve the residue in 2 mL of toluene, dried with synthetic zeolite for drying, add 2 mL of a solution of

0.15 g of D-(+)-α-methylbenzylamine dissolved in 5 mL of toluene, dried with synthetic zeolite for drying, shake gently to mix, allow to stand for 10 minutes, and evaporate the toluene in vacuum at below 60 ℃. Dissolve the residue in 5 mL of chloroform and use this solution as the test solution. With 5 μL of the test solution, perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the areas, A_a, A_b and Ac, according to the order of elution, of three adjacent peaks eluted at the retention times of about 7 minutes; $A_b/(A_a+A_b+A_c) \times 100$ is between 40 and 70.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column : A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 20 °C.

Mobile phase: A mixture of hexane and 2-propanol (500 : 3).

Flow rate: Adjust the flow rate so that the retention time of the first eluted peak among three peaks of clinofibrate is about 35 minutes.

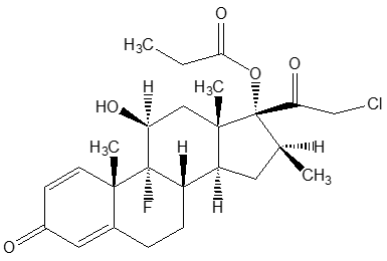
Selection of column: Proceed with 5 μL of the test solution under the above conditions; use the column where the three peaks are completely separated from each other.

Assay Weigh accurately 0.45 g of Clinofibrate, previously dried, dissolve in 40 mL of ethanol(99.5), add 30 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of phenol phthalein TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 23.43 mg of $C_{28}H_{36}O_6$

Packaging and storage Preserve in tight containers.

Clobetasol Propionate
클로베타솔프로피오네이트



$C_{25}H_{32}ClFO_5$: 466.97

[(8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*S*,17*R*)-17-(2-Chloro-acetyl)-9-fluoro-11-hydroxy-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16-octahydrocyclopenta[*a*]phenanthren-17-yl]propanoate [*25122-46-7*]

Clobetasol Propionate, when dried, contains NLT 97.0% and NMT 102.0% of clobetasol propionate ($C_{25}H_{32}$ CIFO $_5$).

Description Clobetasol Propionate occurs as a white to pale yellow crystalline powder.
It is soluble in methanol or ethanol(95), and practically insoluble in water.
It is gradually colored to yellow by light.

Melting point—About 196 ℃ (with decomposition).

Identification (1) Determine the infrared spectra of Clobetasol Propionate and clobetasol propionate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Optical rotation $[\alpha]_D^{20}$: Between +112 ° and + 118° (0.5 g after drying, acetone, 50 mL, 100 mm).

Purity (**1)** ***Heavy metals***—Proceed with 1.0 g of Clobetasol Propionate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) **Related substances—**Weigh accurately about 10 mg of Clobetasol Propionate, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution (1). Take 1 mL of this solution, add the mobile phase to make exactly 50 mL, and use this solution as the test solution (2). Weigh accurately about 10 mg of clobetasol propionate RS and 5mg of 9α-fluoro-11β-hydroxy-16β-methyl-3-oxo-androsta-1,4-diene-17(*R*)-spiro-2'-[4'-chloro-5'-ethylfuran-3-(2'*H*)-one] RS, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution (1), the test solution (2) and the standard solution as directed under the Liquid Chromatography according to the following conditions; the each peak area other than the major peak from the test solution (1) is NMT 0.5 times the major peak area from the test solution (2) (1.0%), and the total area of these peaks is NMT 1.25 times the major peak area from test solution (2) (2.5%). However, among the peaks from the test solution (2), disregard any peak whose area is NMT 0.025 times the major peak area (0.05%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in

internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile, 0.05 mol/L sodium dihydrogen phosphate (adjust the pH to 2.5 with phosphoric acid) and methanol (475 : 425 : 100).

Flow rate: 1 mL/min

System suitability

Selection of column: Proceed with 10 μL of the standard solution according to the above conditions; use a column with the resolution between clobetasol propionate and 9α-fluoro-11β-hydroxy-16β-methyl-3-oxo-androsta-1,4-diene-17(*R*)-spiro-2'-[4'-chloro-5'-ethylfuran-3-(2'*H*)-one] RS being NLT 3.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 10 mg each of Clobetasol Propionate and cobetasol propionate RS, previously dried, dissolve each in the mobile phase to make exactly 50 mL, add exactly 100 mL of the internal standard solution, add the mobile phase to make 250 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the conditions of the related substances, and determine the ratios, Q_T and Q_S, of the peak area of clobetasol propionate to that of the internal standard.

Amount (mg) of clobetasol propionate ($C_{25}H_{32}ClFO_5$)
= Amount (mg) of clobetasol propionate RS× $\frac{Q_T}{Q_S}$

Internal standard solution—A solution of beclomethasone dipropionate in the mobile phase (1 in 5000).

Packaging and storage Preserve in light-resistant, well-closed containers.

Clobetasol Propionate Cream
클로베타솔프로피오네이트 크림

Clobetasol Propionate Cream contains NLT 90.0% and NMT 115.0% of the labeled amount of clobetasol propionate ($C_{25}H_{32}ClFO_5$: 466.97).

Method of preparation Prepare as directed under Creams, with Clobetasol Propionate.

Identification (1) Weigh an amount of Clobetasol Propionate Cream equivalent to about 0.75 mg of clobetasol propionate ($C_{25}H_{32}ClFO_5$) according to the labeled amount, place in a 25-mL centrifuge tube, add 10 mL of methanol, and cover the tube with a stopper. Warm for 4 minutes on a steam bath at 60 ℃, remove from the bath, shake vigorously and extract. Repeat this procedure multiple times, cool to room temperature, add 3.5 mL of water, then centrifuge for about 10 minutes. Take 10 mL of the clear supernatant, place in a 100-mL separatory funnel, add 1 g of sodium chloride and 10 mL of water, and mix thoroughly. To this solution, add 5 mL of dichloromethane, extract after sonication for 1 minute, take the dichloromethane layer, evaporate to dryness under the current of nitrogen, dissolve the residue in 0.5 mL of dichloromethane and use this solution as the test solution. Perform the test as directed in Identification (1) under Clobetasol Propionate Ointment.

(2) The retention times of the major peaks obtained from the test solution and the standard solution in the Assay are the same.

Assay Weigh accurately an amount of Clobetasol Propionate Cream equivalent to about 1.0 mg of clobetasol propionate ($C_{25}H_{32}ClFO_5$) according to the labeled amount, add 10 mL of ethanol(99.5), warm on a steam bath while shaking occasionally until completely suspended, then cool for 30 minutes in iced water. Centrifuge, pipet 5 mL of the clear supernatant, add 5.0 mL of the internal standard solution and mix well. Use this solution as the test solution. With this test solution, perform the test as directed under the Assay under Clobetasol Propionate Ointment.

Amount (mg) of clobetasol propionate ($C_{25}H_{32}ClFO_5$)
= Amount (mg) of clobetasol propionate RS× $\frac{Q_T}{Q_S} \times \frac{1}{10}$

Internal standard solution—A solution of Beclometasone Dipropionate in 50% ethanol (1 in 5000).

Packaging and storage Preserve in tight containers and store NMT 30 ℃.

Clobetasol Propionate Ointment
클로베타솔프로피오네이트 연고

Clobetasol Propionate Ointment contains NLT 90.0% and NMT 115.0% of the labeled amount of clobetasol propionate ($C_{25}H_{32}ClFO_5$: 466.97).

Method of preparation Prepare as directed under Ointments, with Clobetasol Propionate.

Identification (1) Weigh accurately an amount of Clobetasol Propionate Ointment equivalent to about 0.5 mg of clobetasol propionate ($C_{25}H_{32}ClFO_5$) according to the labeled amount, place in a 25-mL centrifuge tube, add 10 mL of methanol, and stopper the tube. Warm on a 70 ℃ water bath for 4 minutes, take out, and shake vigorously to extract. Repeat this procedure several times, cool in iced water for 5 minutes, and centrifuge for about

10 minutes. Take 5 mL of the clear supernatant, evaporate to dryness in the nitrogen atmosphere, dissolve the residue in 0.5 mL of dichloromethane, and use this solution as the test solution. Separately, weigh accurately about 10 mg of clobetasol propionate RS, dissolve in dichloromethane to make 20 mL, and use this solution as the standard solution. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of dichloromethane, acetone and ethanol(99.5) (100 : 10 : 5) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 245 nm); the R_f values and colors of the principal spots obtained from the test solution and the standard solution are the same.

(2) The retention times of the major peaks from the test solution and the standard solution obtained in the Assay are the same.

Assay Weigh accurately an amount of Clobetasol Propionate Ointment equivalent to about 1.0 mg of clobetasol propionate ($C_{25}H_{32}ClFO_5$) according to the labeled amount, add 10 mL of ethanol(99.5), warm on a steam bath with occasional shaking to completely disperse, and cool in iced water for 30 minutes. Centrifuge, pipet 5 mL of the clear supernatant, add 5.0 mL of the internal standard solution, and shake well to mix. Use this solution as the test solution. Separately, weigh accurately about 10 mg of clobetasol propionate RS and dissolve in diluted ethanol (1 in 2) to make 100 mL. Pipet 5 mL of this solution, add 5.0 mL of the internal standard solution, mix well, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of clobetasol propionate to that of the internal standard in each solution.

Amount (mg) of clobetasol propionate ($C_{25}H_{32}ClFO_5$)
= Amount (mg) of clobetasol propionate RS$\times \frac{Q_T}{Q_S} \times \frac{1}{10}$

Internal standard solution—A solution of beclomethasone dipropionate in diluted ethanol (1 in 2) (1 in 5000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

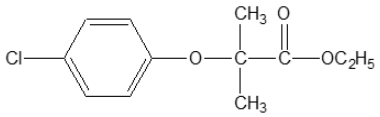
Mobile phase: A mixture of water and ethanol(99.5) (55 : 45).

Column temperature: 60 ℃

Flow rate: 2 mL/min

Packaging and storage Preserve in tight containers and store at below 30 ℃.

Clofibrate
클로피브레이트



$C_{12}H_{15}ClO_3$: 242.70

Ethyl 2-(4-chlorophenoxy)-2-methylpropanoate [*637-07-0*]

Clofibrate contains NLT 98.0% and NMT 101.0% of clofibrate ($C_{12}H_{15}ClO_3$) calculated on the anhydrous basis.

Description Clofibrate occurs as colorless or pale yellow, clear, oily liquid. It has a characteristic odor, and has a bitter taste at first followed by a sweet taste.
It is miscible with methanol, ethanol(95), ether or hexane, and practically insoluble in water.
It is gradually decomposed by light.

Identification (1) Determine the absorption spectra of the solutions of Clofibrate and clofibrate RS in ethanol(99.5) (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths. Determine the absorption spectra of solutions of Clofibrate and clofibrate RS in ethanol(99.5) (1 in 100000); both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Clofibrate and clofibrate RS as directed under the liquid film method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Refractive index n_D^{20}: Between 1.500 and 1.505.

Specific gravity d_{20}^{20}: Between 1.137 and 1.144.

Purity (1) ***Acid***—Dissolve 2.0 g of Clofibrate in 100 mL of neutralized ethanol, and add 1 drop of phenolphthalein TS and 0.20 mL of 0.1 mol/L sodium hydroxide TS; the resulting solution exhibits a red color.

(2) ***Heavy metals***—Weigh and proceed with 2.0 g of Clofibrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—To 5.0 g of Clofibrate, add 20 mL of nitric acid and 5 mL of sulfuric acid and heat until white fumes are evolved. After cooling, if necessary, add fur-

ther 5 mL of nitric acid, heat until white fumes are evolved, and repeat this procedure until the solution becomes colorless to pale yellow. After cooling, add 15 mL of saturated ammonium oxalate solution, and heat again until white fumes are evolved. Cool and add water to make 25 mL. Use 5 mL of this solution as the test solution and perform the test.

Standard color—Prepare a solution by proceeding in the same manner without using Clofibrate. Put 5 mL of the solution into a generator bottle, add 2.0 mL of arsenic standard solution, and then proceed as directed under the test solution (NMT 2 ppm).

(4) ***4-chlorophenol and other related substances***—Pipet 10.0 mL of Clofibrate, add 5.0 μL of tributyrin, and use this solution as the test solution. Separately, weigh accurately 50 mg of clofibrate RS and 15 mg of 4-chlorophenol, dissolve in chloroform to make 50 mL, pipet 1 mL of this solution, then add chloroform to make 10 mL as a solution containing 0.1 mg of clofibrate and 0.03 mg of 4-chlorophenol per mL. Pipet 10.0 mL of this solution, add 5.0 μL of tributyrin, and use this solution as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and determine the ratio, Q_i, of the peak area of each related substance other than 4-chlorophenol to that of tributyrin obtained from the test solution, and the ratio, Q_S, of the peak area of clofibrate to that of tributyrin obtained from the standard solution, by Equation (1); the amount of each related substance other than 4-chlorophenol is NMT 0.01%, and the amount of total related substances is NMT 0.12%. Furthermore, determine the ratio, Q_{Tc}, of the peak area of 4-chlorophenol to that of tributyrin obtained from the test solution, and ratio, Q_{Sc}, of the peak area of 4-chlorophenol to that of tributyrin obtained from the standard solution, by Equation (2); the amount of 4-chlorophenol is NMT 0.003%.

$$\text{Content (\%) of related substances} = 0.1\times C \times \frac{Q_i}{Q_S} \quad (1)$$

C: Concentration (mg/mL) of clofibrate in the standard solution

$$\text{Content (\%) of } p\text{-chlorophenol } (ClC_6H_4OH) = 0.1 \times C \times \frac{Q_{Tc}}{Q_{Sc}} \quad (2)$$

C: Concentration (mg/mL) of 4-chlorophenol in the standard solution

Operating conditions

Detector: A flame ionization detector

Column: A column about 0.53 mm in internal diameter and about 15 m in length, internally coated with dimethylpolysiloxane oil at 1.5 μm thick.

Column temperature: Maintain at 120 °C for the first minute, then increase up to 180 °C at a rate of 5 °C per minute for 12 minutes, and then keep this temperature for 9 minutes.

Carrier gas: Helium

Flow rate: 2 mL/min

Sample injection port temperature: 210 °C

Detector temperature: 220 °C

Split ratio: About 1 : 20.

System suitability

System performance: Proceed with 1 μL of the standard solution according to the above conditions, the relative retention times of 4-chlorophenol and clofibrate to tributyrin are about 0.2 and about 0.55, respectively.

Water NMT 0.2% (5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Clofibrate, add exactly 50 mL of 0.1 mol/L potassium hydroxide-ethanol solution, and heat on a steam bath under a reflux condenser with a carbon dioxide absorbing tube (soda-lime) for 2 hours with frequent shaking. Cool, and titrate immediately the excess potassium hydroxide with 0.1 mol/L hydrochloric acid VS (indicator: 3 drops of phenolphthalein TS). Perform a blank test in the same manner.

Each mL of 0.1 mol/L potassium hydroxide VS
= 24.270 mg of $C_{12}H_{15}ClO_3$

Packaging and storage Preserve in light-resistant, tight containers.

Clofibrate Capsules
클로피브레이트 캡슐

Clofibrate Capsules contain NLT 93.0% and NMT 107.0% of the labeled amount of clofibrate ($C_{12}H_{15}ClO_3$: 242.70).

Method of preparation Prepare as directed under Capsules, with Clofibrate.

Identification Open a capsule, take out the content and use it as a sample. Determine the absorption spectrum of a solution of the sample in ethanol(99.5) (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 278 nm and 282 nm. Determine the absorption spectrum of a solution of the sample in ethanol(99.5) (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 224 nm and 228 nm.

Purity ***4-chlorophenol***—Proceed with NLT 20 capsules of Clofibrate Capsules, open the capsules, take out and mix the contents, weigh 1.0 g of the mixed contents, and

perform the test as directed under the Purity (4) of Clofibrate.

Dissolution Perform the test with 1 capsule of Clofibrate Capsule at 100 revolutions per minute according to Method 2, using 1000 mL of sodium lauryl sulfate (5 in 100) as a control solution. After 45 minutes from the start the test, pipet 5.0 mL of the dissolved solution, add methanol to make 25.0 mL, and allow to stand for 5 minutes. Filter the resulting solution, and use the test solution. Separately, weigh accurately about 20 mg of clofibrate RS, dissolve mix in 20 mL of methanol, and add water to make exactly 50 mL. Take an appropriate amount of this solution, add methanol to obtain a solution having known concentration of about 80 μg per mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of clofibrate, A_T and A_S, in each solution. It meets the requirements when the dissolution rate for 180 minutes is NLT 80% (Q).

Dissolution rate (%) of the labeled amount of clofibrate ($C_{12}H_{15}ClO_3$)

$$= C_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 500000$$

C_S: Concentration (mg/mL) of the standard solution

C: Labeled amount (mg) of clofibrate ($C_{12}H_{15}ClO_3$) in 1 capsule

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 226 nm).

Column: A stainless steel column with about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (1.5 to 10 μm in particle diameter).

Mobile phase: A mixture of methanol and water (80 : 20).

Flow rate: 1 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution under the above operating conditions; the symmetry factor for clofibrate peak is NMT 1.5.

System repeatability: Repeat the test 5 times with 20 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area for clofibrate is NMT 2.0%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the contents of 20 capsules of Clofibrate Capsules equivalent to 0.1 g of clofibrate ($C_{12}H_{15}ClO_3$), dissolve in acetonitrile to make exactly 100 mL. Pipet 5.0 mL of this solution, add exactly 5 mL of the internal standard solution, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of clofibrate RS (previously determined the water), proceed in the same manner as the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of the clofibrate to that of the internal standard, respectively.

Amount (mg) of clofibrate ($C_{12}H_{15}ClO_3$)

= Amount (mg) of clofibrate RS, calculated on the anhydrous basis $\times \frac{Q_T}{Q_S}$

Internal standard solution—A solution of ibuprofen in the mobile phase (1 in 100).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 275 nm).

Column: A stainless steel column with about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

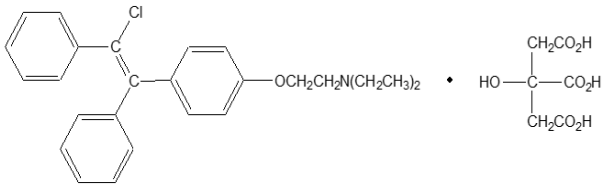
Mobile phase: A mixture of acetonitrile and diluted phosphoric acid (1 in 1000) (3: 2).

Flow rate: Adjust the flow rate so that the retention time of clofibrate is about 10 minutes.

Selection of column: Dissolve 50 mg of clofibrate and 0.3 g of Ibuprofen in 50 mL of acetonitrile. Proceed with 10 μL of this solution according to the above conditions; ibuprofen and clofibrate are eluted in this order with the resolution being NLT 6.

Packaging and storage Preserve in light-resistant, well-closed containers.

Clomifene Citrate
클로미펜시트르산염



$C_{26}H_{28}ClNO \cdot C_6H_8O_7$: 598.08

2-[4-[(*Z*)-2-Chloro-1,2-diphenylethenyl]phenoxy]-*N*,*N*-diethylethanamine;2-hydroxypropane-1,2,3-tricarboxylic acid [*50-41-9*]

Clomifene Citrate, when dried, contains NLT 98.0% and NMT 101.0% of clomifene citrate ($C_{26}H_{28}ClNO \cdot C_6H_8O_7$).

Description Clomifene Citrate occurs as a white to pale yellowish white powder and is odorless.
It is freely soluble in methanol or acetic acid(100), sparingly soluble in ethanol(95), slightly soluble in water, and practically insoluble in ether.
It is gradually colored by light.

Melting point—About 115 °C.

Identification (1) To 2 mL of a solution of Clomifene Citrate in methanol (1 in 200), add 2 mL of reinecke salt TS; a pale red precipitate is produced.

(2) Determine the absorption spectra of solutions of Clomifene Citrate and clomifene citrate RS in 0.1 mol/L hydrochloric acid TS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) A solution of Clomifene Citrate in methanol (1 in 200) responds to the Qualitative Analysis (1) and (2) for citrate.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Clomifene Citrate in 30 mL of methanol; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 2.0 g of Clomifene Citrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Weigh accurately 50 mg of Clomifene Citrate, add the mobile phase to make 100 mL. Pipet 10 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately 50 mg of clomifene citrate RS, and dissolve in the mobile phase to make 100 mL. Pipet 1 mL of this solution, add the mobile phase to make 50 mL, then pipet 1 mL of this solution, add the mobile phase to make a 10 mL solution containing about 1.0 μ*g* per mL, and use this solution as the standard solution. Perform the test with 50 μL of the test solution by the percentage peak area method under the Liquid Chromatography according to the following conditions; the amount of clomiphene related substance I {(*E*,*Z*)-2-[4-(1,2-diphenylethenyl)phenoxy]-*N*,*N*-diethyl ethanamine hydrochloride} obtained from the test solution is NMT 2.0%, the amount of individual related substances is NMT 0.5%, and the total amount of related substances is NMT 2.0%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 290 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with butylsilyl silica gel for liquid chromatography (3 μm -10 μm in particle diameter).

Mobile phase: A mixture of methanol, water and triethylamine (55 : 45 : 0.3) adjusted the pH to 2.5 with phosphoric acid.

Flow rate: 1 mL/min

System suitability

System performance: Weigh accurately an appropriate amount of chromiphene related substance I RS and chromiphene citrate RS, prepare a solution containing 0.002 mg of chromiphene related substance I per mL, and 0.05 mg of clomifene citrate per mL, and use this solution as the system suitability solution. Proceed with 50 μL of this solution according to the above conditions; the relative retention times of clomiphene related substances I, (*Z*)-isomer and (*E*)-isomer are about 0.9, 1.0 and 1.2, respectively, the resolution between clomiphene related substances I and (*Z*)-isomer is NLT 1.0, and the resolution between the (*Z*)-isomer and the (*E*)-isomer is NLT 1.5. Proceed with 50 μL of the standard solution according to the above conditions; the number of theoretical plates and the symmetry factor for (*E*)-isomers are NLT 2000 and NMT 3.0, respectively.

System repeatability: Repeat the test 5 times with 50 μL each of the standard solution according to the above conditions; the relative standard deviations of the peak areas of (*E*)-isomer and (*Z*)-isomer are NMT 2.0%.

Loss on drying NMT 1.0% (1 g, in vacuum, phosphorus penoxide, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Isomer ratio To 0.10 g of Clomifene Citrate, add 10 mL of water and 1 mL of sodium hydroxide TS, and extract 3 times with 15 mL each of ether. Combine all the ether layers and wash with 20 mL of water. To the ether layer, add 10 g of anhydrous sodium sulfate, shake to mix for 1 minute, filter, and evaporate the ether. Dissolve the residue in 10 mL of chloroform, and use this solution as the test solution. With 2 μL of the test solution, perform the test as directed under the Gas Chromatography according to the following conditions. Of the two peaks that appear at the retention time of about 20 minutes, measure the peak area, A_a, with the smaller retention time and the peak area, A_b, with the larger retention time; $A_b/(A_a+A_b)$ is between 0.3 and 0.5.

Operating conditions

Detector: A flame ionization detector

Column: A column about 3 mm in internal diameter and about 1 m in length, packed with diatomaceous earth for gas chromatography (125 μm to 150 μm in particle diameter) coated with 1% ratio of methyl silicone polymer for gas chromatography.

Column temperature: A constant temperature of about 195 °C.

Carrier gas: Nitrogen

Flow rate: Adjust the flow rate so that the retention time of the peak eluted first among the two peaks of clomifene citrate is about 20 minutes.

System suitability

Selection of column: Proceed with 2 μL of the test solution according to the above conditions; among the two peaks of clomiphene citrate, use the one with a resolution NLT 1.3.

Assay Weigh accurately about 1 g of Clomifene Citrate, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of methylrosanilinium chloride TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 59.81 mg of $C_{26}H_{28}ClNO \cdot C_6H_8O_7$

Packaging and storage Preserve in light-resistant, tight containers.

Clomifene Citrate Tablets
클로미펜시트르산염 정

Clomifene Citrate Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of clomifene citrate ($C_{26}H_{28}ClNO \cdot C_6H_8O_7$: 598.08).

Method of preparation Prepare as directed under Tablets, with Clomifene Citrate.

Identification (1) Weigh an amount, equivalent to 10 mg of clomifene citrate according to the labeled amount of Clomifene Citrate Tablets, previously powdered, add 100 mL of chloroform to shake vigorously, and filter. Concentrate the filtrate on a steam bath, allow to stand at room temperature, filter the educed crystals, and wash with a small amount of chloroform. With this crystal, and perform the test as directed under the Identification (1) and (3) under Clomifene Citrate.

(2) Determine the absorption spectrum of the crystals obtained in (1) as directed under the Ultraviolet-visible Spectroscopy with a solution of 0.1 mol/L hydrochloric acid TS (1 in 50000); it exhibits a maximum between 233 nm and 237 nm.

Dissolution Perform the test with 1 tablet of Clomifene Citrate Tablets at 100 revolutions per minute according to Method 1 under the Dissolution, using 900 mL of water as the dissolution medium. Take the dissolved solution after 30 minutes from starting the test, and filter. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add 0.1 mol/L hydrochloric acid TS to make exactly *V'* mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of clomifene citrate RS, dissolve in water to make it the same concentration as the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength of about 232 nm as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as the control solution. It meets the requirements when the dissolution rate in 30 minutes is NLT 75% (Q).

Dissolution rate (%) with respect to the labeled amount of clomifene citrate ($C_{26}H_{28}ClNO \cdot C_6H_8O_7$)

$$= C_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 90000$$

C_S: Concentration (mg/mL) of the standard solution
C: Labeled amount (mg) of clomifene citrate ($C_{26}H_{28}ClNO \cdot C_6H_8O_7$) in 1 tablet

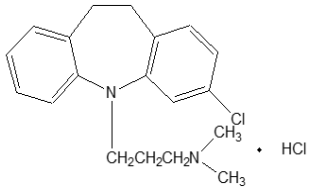
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Clomifene Citrate Tablets, and powder. Weigh accurately an amount, equivalent to 50 mg of clomifene citrate ($C_{26}H_{28}ClNO \cdot C_6H_8O_7$), add 50 mL of methanol, shake to mix for 10 minutes, and add methanol to make exactly 100 mL. Take a portion of this solution to centrifuge, pipet 4 mL of the clear supernatant, and add methanol to make exactly 100 mL. Separately, dry the clomifene citrate RS in a desiccator (in vacuum, phosphorus pentoxide) for 3 hours, weigh accurately about 50 mg of the dried matter, and dissolve in methanol to make exactly 100 mL. Pipet 4 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 295 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of clomifene citrate ($C_{26}H_{28}ClNO \cdot C_6H_8O_7$)
= Amount (mg) of clomifene citrate RS $\times \frac{A_T}{A_S}$

Packaging and storage Preserve in tight containers.

Clomipramine Hydrochloride
클로미프라민염산염



Clomipramine Hydrochloride $C_{19}H_{23}ClN_2 \cdot HCl$: 351.31
(3-{5-Chloro-2-azatricyclo[9.4.0.0^{3,8}]pentadeca-1(11),3(8),4,6,12,14-hexaen-2-yl}propyl)dimethyl-amine hydrochloride [*17321-77-6*]

Clomipramine Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$).

Description Clomipramine Hydrochloride occurs as a white to pale yellow crystalline powder and is odorless.
It is very soluble in acetic acid(100), freely soluble in

water, methanol or chloroform, soluble in ethanol(95), sparingly soluble in acetic anhydride, slightly soluble in acetone, and practically insoluble in ethyl acetate or ether.

Identification (1) Dissolve 3 mg of Clomipramine Hydrochloride in 1 mL of nitric acid; the resulting solution exhibits a dark blue color.

(2) Determine the absorption spectra of solutions of Clomipramine Hydrochloride and clomipramine hydrochloride RS in 0.1 mol/L hydrochloric acid TS (3 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Transfer 1 g of Clomipramine Hydrochloride to a separatory funnel, dissolve in 10 mL of water, add 5 mL of sodium hydroxide TS, and extract twice with 30 mL of ether each. [The water layer is used in the Identification (4)]. Combine the ether extracts, add 20 mL of water, shake to mix, then take the ether layer separately, dry it with a small amount of anhydrous sodium sulfate, and filter. Warm the filtrate on a steam bath to evaporate the ether. Perform the test with the residue as directed under the Flame Coloration (2); a green color is observed.

(4) Neutralize the water layer obtained in (3) with dilute nitric acid; the resulting solution responds to the Qualitative Analysis for chloride.

Melting point Between 192 and 196 ℃.

pH Dissolve 1.0 g of Clomipramine Hydrochloride in 10 mL of water; the pH of this solution is between 3.5 and 5.0.

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Clomipramine Hydrochloride in 10 mL of water; the solution is clear and colorless to pale yellow.

(2) ***Heavy metals*—**Proceed with 2.0 g of Clomipramine Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic*—**Proceed with 1.0 g of Clomipramine Hydrochloride according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.20 g of Clomipramine Hydrochloride in exactly 10 mL of methanol and use this solution as the test solution. Separately, dissolve 20 mg of imipramine hydrochloride RS in methanol to make exactly 100 mL and use this solution as the standard solution (1). Then, pipet 1mL of the test solution, and add methanol to make exactly 50 mL. Pipet 5 mL of this solution, add methanol to make 50 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution, the standard solution (1) and the standard solution (2) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Then, develop the plate with a mixture of ethyl acetate, acetone and ammonia water(28) (15 : 5 : 1) as a developing solvent to a distance of about 10 cm, air-dry the plate, and sprinkle potassium dichromate-sulfuric acid TS evenly on the plate; the spot obtained from the test solution, of which location corresponds to that of the spot from the standard solution (1), is not more intense than the spot obtained from the standard solution (1), and the spots other than the principal spot and the above spot obtained from the test solution are not more intense than the spots from the standard solution (2).

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

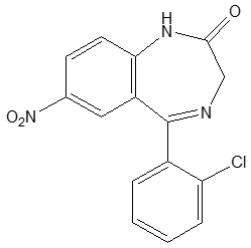
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately 0.5 g of Clomipramine Hydrochloride, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 35.131 mg of $C_{19}H_{23}ClN_2 \cdot HCl$

Packaging and storage Preserve in light-resistant, well-closed containers.

Clonazepam
클로나제팜



$C_{15}H_{10}ClN_3O_3$: 315.71

5-(2-Chlorophenyl)-7-nitro-1,3-dihydro-1,4-benzodiazepin-2-one [*1622-61-3*]

Clonazepam, when dried, contains NLT 99.0% and NMT 101.0% of clonazepam ($C_{15}H_{10}ClN_3O_3$).

Description Clonazepam occurs as white to pale yellow crystals or a crystalline powder.
It is sparingly soluble in acetic anhydride or acetone, slightly soluble in methanol or ethanol(95), very slightly soluble in ether, and practically insoluble in water.
It is gradually colored by light.

Melting point—About 240 ℃ (with decomposition).

Identification (1) Determine the absorption spectra of solutions of Clonazepam and clonazepam RS in methanol (1 in 100000) as directed under the Ultraviolet-visible

Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Determine the infrared spectra of Clonazepam and clonazepam RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Perform the Flame Coloration 2) with Clonazepam; it exhibits a green color.

Purity (1) ***Chloride***—Take 1.0 g of Clonazepam, add 50 mL of water, and allow to stand for 60 minutes with occasional shaking, and filter. Discard the first 20 mL of the filtrate, then add 6 mL of dilute nitric acid and water to the subsequent filtrate to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 6 mL of dilute nitric acid and water to 0.25 mL of 0.01 mol/L hydrochloric acid solution to make 50 mL (NMT 0.022%).

(2) ***Heavy metals*—**Proceed with 1.0 g of Clonazepam as directed under Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve 0.25 g of Clonazepam in 10 mL of acetone and use this solution as the test solution. Pipet 1 mL of this solution, and add acetone to make exactly 100 mL. Pipet 1 mL of this solution, add acetone to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of nitromethane and acetone (10 : 1) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.3% (1 g, 105 ℃, 4 hours).

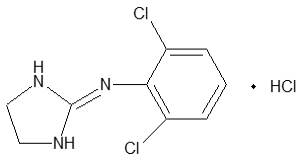
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Clonazepam, previously dried, dissolve in 70 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under Titrimetry). Perform a blank test in the same manner.

Each mL of 0.1 mol/L perchloric acid VS
= 31.57 mg of $C_{15}H_{10}ClN_3O_3$

Packaging and storage Preserve in light-resistant, well-closed containers.

Clonidine Hydrochloride
클로니딘염산염



$C_9H_9Cl_2N_3 \cdot HCl$: 266.56

N-(2,6-Dichlorophenyl)-4,5-dihydro-1*H*-imidazol-2-amine hydrochloride [*4205-91-8*]

Clonidine hydrochloride, when dried, contains NLT 99.0% and NMT 101.0% of clonidine hydrochloride ($C_9H_9N_2O_3 \cdot HCl$).

Description Clonidine Hydrochloride occurs as white crystals or a crystalline powder.
It is freely soluble in methanol, soluble in water or ethanol(95), slightly soluble in acetic acid(100), and practically insoluble in acetic anhydride or ether.

Identification (1) Take 5 mL of an aqueous solution of Clonidine Hydrochloride (1 in 1000) and add 6 drops of Dragendorff's TS; an orange precipitate is formed.

(2) Determine the absorption spectra of solutions of Clonidine Hydrochloride and clonidine hydrochloride RS in 0.01 mol/L hydrochloric acid VS (3 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Clonidine Hydrochloride and clonidine hydrochloride RS, previously dried, as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) An aqueous solution of Clonidine Hydrochloride (1 in 50) responds to the Qualitative Analysis for chloride.

pH Dissolve 1.0 g of Clonidine Hydrochloride in 20 mL of water; the pH of this solution is between 4.0 and 5.5.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Clonidine Hydrochloride in 20 mL of water; the solution is clear and colorless.

(2) ***Heavy metals*—**Proceed with 2.0 g of Clonidine Hydrochloride as directed under Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic*—**Proceed with 0.5 g of Clonidine Hydrochloride as directed under Method 3 and perform the test (NMT 4 ppm).

(4) ***Related substances***—Dissolve 0.20 g of Clonidine Hydrochloride in 2 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution and add methanol to make exactly 100 mL, pipet 1 mL and 2 mL of this solution, and add methanol to each to make exactly 20 mL. Use these solutions as the standard solution (1) and the standard solution (2), respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the test solution, the standard solution (1), and the standard solution (2) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of toluene, acetone, ethanol(99.5) and ammonia water(28) (10 : 8 : 2 : 1) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Dry the plate for 1 hour at 100 ℃, spray evenly sodium hypochlorite TS on the plate, then air-dry for 15 minutes. Spray evenly potassium iodide starch TS on the plate; the spots other than the principal spot and the spots of the starting point from the test solution are not more intense than the spots from the standard solution (2), and among the spots other than the principal spot and spots of the starting point, NMT 3 are more intense than the spots from the standard solution (1).

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

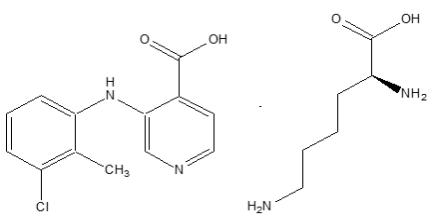
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Clonidine Hydrochloride, previously dried, add 30 mL of acetic acid(100) and dissolve by warming. After cooling, add 70 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 26.656 mg of $C_9H_9Cl_2N_3 \cdot HCl$

Packaging and storage Preserve in tight containers.

Clonixin Lysinate
클로닉신리시네이트



$C_{19}H_{25}ClN_4O_4$: 408.88
2-[(3-Chloro-2-methylphenyl)amino]-3-pyridinecarboxylic acid lysine salt, [*55837-30-4*]

Clonixin Lysinate contains NLT 98.0% and NMT 101.0% of clonixin lysinate ($C_{19}H_{25}ClN_4O_4$), calculated on the anhydrous basis.

Description Clonixin Lysinate occurs as an amorphous, pale yellow to pale white powder. It has a slightly characteristic odor.
It is freely soluble in water and soluble in methanol.

Melting point—Between 205 and 210 ℃ (with decomposition).

Identification (1) Dissolve 1 g of Clonixin Lysinate in 2 mL of water and add 5 mL of 1 mol/L hydrochloric acid. Filter the precipitate, wash with water several times, and dry at 105 ℃ to a constant mass; the measured melting point is between 233 and 236 ℃.

(2) Spray evenly 1% methanol solution on the filtration paper of (1), dry, and then, spray evenly 1% ninhydrin acetone solution; it exhibits purple spots.

Absorbance $E_{1cm}^{1\%}$ (252 nm): Between 350 and 370 (1 mol/L hydrochloric acid methanol solution).

Optical rotation $[\alpha]_D^{20}$: Between +5.0° and +5.4° (10% aqueous solution).

pH Between 7.3 and 7.6 (1% aqueous solution).

Purity (1) ***Heavy metals***—Proceed with 1 g of Clonixin Lysinate according to Method 3, and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Use 1% aqueous solution of Clonixin Lysinate as the test solution. Use a 1% aqueous solution of L-lysine hydrochloride RS and a 1% ethanol solution of clonixin lysinate RS as the standard solutions, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator) (105 ℃, activation for 30 minutes). Next, develop the plate with a mixture of 1-propanol and ammonia water(28) (67 : 33) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the principal spots from the test solution and clonixin lysinate RS are the same in R_f value. Spray evenly 1-butanol solution (add 3 mL of 3% acetic acid(100)-1-butanol solution) of 0.3% ninhydrin and heat at 105 ℃ for 10 minutes. The R_f value of the purple spots obtained from the test solution and L-lysine hydrochloride RS is the same and the spots obtained from the test solution is not more intense than that from the L-lysine hydrochloride RS.

Water NMT 1.0% (0.2 g, volumetric titration, direct titration).

Residue on ignition NMT 1.0% (1.0 g).

Assay Weigh accurately about 0.2 g of Clonixin Lysinate, put into a 100-mL beaker, dissolve in 60 mL of acetic acid(100), and titrate with 0.1 mol/L of perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 13.629 mg of $C_{19}H_{25}ClN_4O_4$

Packaging and storage Preserve in tight containers.

Clonixin Lysinate Tablets
클로닉신리시네이트 정

Clonixin Lysinate Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of clonixin lysinate ($C_{19}H_{25}ClN_4O_4$: 408.88)

Method of preparation Prepare as directed under Tablets, with Clonixin Lysinate.

Identification Weigh the amount equivalent to 10 mg of clonixin lysinate according to the labeled amount of Clonixin Lysinate Tablets, add a mixture of methanol and 1 mol/L hydrochloric acid (99 : 1) to make 10 mL, shake, and filter. Use the filtrate as the test solution. Weigh 10 mg of clonixin lysinate RS, add a mixture of methanol and 1 mol/L hydrochloric acid (99 : 1) to make 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop using a mixture of 1-propanol and 40% ammonia (7 : 3) as the developing solvent, and air-dry the thin-layer chromatographic plate. Examine the plate under ultraviolet light or spray 0.3% ninhydrin in 1-butanol solution evenly; the R_f values and colors of the spots obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 tablet of Clonixin Lysinate Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of the second solution as the dissolution solution. Take the dissolved solution 30 minutes after the start of the Dissolution and filter. Discard the first 10 mL of the filtrate, pipet V mL of the subsequent filtrate, and add the Solution 2 in the Dissolution to obtain exactly V′ mL of a solution containing about 100 μg of clonixin lysinate per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 10 mg of clonixin lysinate RS, dissolve in the Solution 2 in the Dissolution to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of clonixin lysinate in each solution. Meets the requirements if the dissolution rate of Clonixin Lysinate Tablets in 30 minutes is NLT 80%.

Dissolution rate (%) with respect to the labeled amount of clonixin lysinate ($C_{19}H_{25}ClN_4O_4$)

$$= W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 900$$

W_S: Amount (mg) of clonixin lysinate RS
C: Labeled amount (mg) of clonixin lysinate ($C_{19}H_{25}ClN_4O_4$) in 1 tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 252 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of methanol and 0.3% acetic acid (36: 36 : 28).

Flow rate: 1.5 mL/min

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Clonixin Lysinate Tablets, and powder. Weigh accurately an amount equivalent to about 12.5 mg of clonixin lysinate ($C_{19}H_{25}$ ClN_4O_4), add water to make 100 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 125 mg of clonixin lysinate RS, and add water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and calculate the peak areas, A_T and A_S, of clonixin lysinate, respectively, from each solution.

Amount (mg) of clonixin lysinate ($C_{19}H_{25}ClN_4O_4$)
= Amount (mg) of clonixin lysinate RS $\times \frac{A_T}{A_S} \times \frac{1}{10}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 252 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of methanol, 0.3% acetic acid and acetonitrile (36 : 36 : 28).

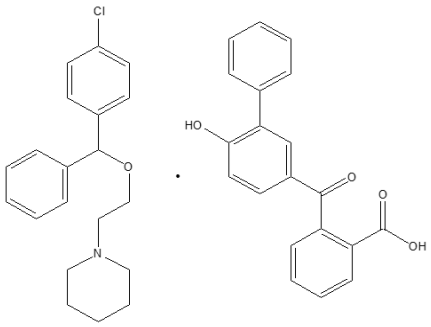
Flow rate: 1.5 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of clonixin lysinate is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Cloperastine Fendizoate
클로페라스틴펜디조산염



$C_{20}H_{24}ClNO \cdot C_{20}H_{14}O_4$: 648.19

2-[(6-Hydroxy[1,1'-biphenyl]-3-yl)carbonyl]-benzoic acid with 1-[2-[(4-chlorophenyl)phenylmethoxy]ethyl]piperidine (1:1), [*85187-37-7*]

Cloperastine Fendizoate, when dried, contains NLT 98.0% and NMT 101.0% of cloperastine fendizoate ($C_{20}H_{24}ClNO \cdot C_{20}H_{14}O_4$).

Description Cloperastine Fendizoate occurs as white or pale yellow crystals or a crystalline powder, which is odorless.

It is freely soluble in isopropylamine, slightly soluble in acetic acid(100), and practically insoluble in water, methanol, ethanol or ether.

Identification (1) To 0.1 mg of Cloperastine Fendizoate, add 1 mL of dilute hydrochloric acid and 10 mL of water, shake to mix on a steam bath, heat for 10 minutes, cool, and then filter. To 5 mL of the filtrate, add 5 drops of Reinecke salt TS; a pale red precipitate is produced.

(2) To 1 g of Cloperastine Fendizoate, add 20 mL of sodium hydroxide TS and 10 mL of ether, shake to mix, separate the water layer, wash the water layer with 10 mL of ether, and then add 25 mL of dilute hydrochloric acid; a white precipitate is produced. Filter the precipitate, wash with water, dry at 105 ºC for 3 hour; the melting point is between 260 and 263 ºC.

Melting point Between 185 and 189 ºC.

Purity (1) ***Chloride***—To 2.0 g of Cloperastine Fendizoate, add 50 mL of water, warm at 70 ºC for 5 minutes, cool, and then filter. To 25 mL of the filtrate, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid solution (NMT 0.014%).

(2) ***Heavy metals***—Weigh and proceed with 1.0 g of Cloperastine Fendizoate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***p-Chlorobenzophenone***—Weigh accurately about 0.2 g of Cloperastine Fendizoate, dissolve in a mixture of methanol and isopropylamine (19 : 1) to make 10 mL, and use this solution as the test solution. Separately, weigh and dissolve 10.0 mg of *p*-chlorobenzophenone in methanol to make 200 mL, and use this solution as the standard solution. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography as directed under the Thin Layer Chromatography, develop the plate with a mixture of ethyl acetate, methanol and strong ammonia water (90 : 10 : 1) as a developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots obtained from the test solution do not appear at the same positions as those of the spots obtained from the standard solution, or they are not more intense nor larger than the spots from the standard solution even if they appear.

Loss on drying NMT 0.5% (1 g, 105 °C, 3 hours).

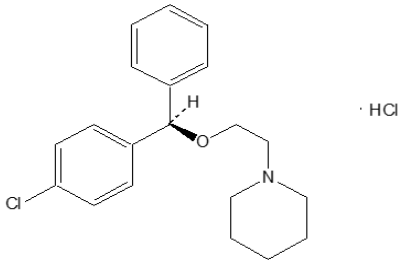
Residue on ignition NMT 0.10% (1 g).

Assay Weigh accurately about 1 g of Cloperastine Fendizoeate, previously dried, add 100 mL of acetic acid(100) for non-aqueous titration, warm to dissolve, and cool. Titrate with 0.1 mol/L perchloric acid VS (indicator: 3 drops of methylrosaniline chloride TS). However, the endpoint of the titration is when the bluish purple color of the solution changes to blue. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 64.82 mg of $C_{20}H_{24}ClNO \cdot C_{20}H_{14}O_4$

Packaging and storage Preserve in tight containers.

Cloperastine Hydrochloride
클로페라스틴염산염



and enantiomer

$C_{20}H_{24}ClNO \cdot HCl$: 366.33

1-[2-[(4-Chlorophenyl)-phenylmethoxy]ethyl] piperidine hydrochloride [*14984-68-0*]

Cloperastine Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of cloperastine hydrochloride ($C_{20}H_{24}ClNO \cdot HCl$).

Description Cloperastine Hydrochloride occurs as white crystals or a crystalline powder.
It is very soluble in water, methanol ethanol(95) or acetic acid(100) and sparingly soluble in acetic anhydride.
An aqueous solution of Cloperastine Hydrochloride (1 in 10) shows no optical rotation.

Identification (1) Determine the absorption spectra of solutions of Cloperastine Hydrochloride and cloperastine hydrochloride RS in 0.1 mol/L hydrochloric acid TS (1 in 2500) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectrum of Cloperastine Hydrochloride and cloperastine hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Add 2 mL of ammonia TS and 20 mL of ether to 10 mL of an aqueous solution of Cloperastine Hydrochloride (1 in 100), shake to mix, take the water layer separately, wash with 20 mL of ether, and filter. Acidify the filtrate with dilute nitric acid; the solution responds to the Qualitative Analysis for chloride.

Melting point Between 148 and 152 ℃.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Cloperastine Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 40 mg of Cloperastine Hydrochloride in 50 mL of the mobile phase and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area in each solution as directed in the automatic integration method; the peak areas, having the ratio of relative retention times of about 0.8 and about 3.0 to cloperastine from the test solution are not larger than the peak area of cloperastine from the standard solution, and the area of the peak having the ratio of the relative retention times of about 2.0 from the test solution is not larger than 5/3 times the peak area of cloperastine from the standard solution. The peak areas other than cloperastine and the peaks mentioned above from the test solution are not larger than 3/5 times the peak area of cloperastine from the standard solution. Also, the total area of these peaks is not larger than 2 times the peak area of cloperastine from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 222 nm).

Column: A stainless steel column about 5 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of methanol, 0.1 mol/L potassium dihydrogen phosphate TS and perchloric acid (500 : 250 : 1).

Flow rate: Adjust the flow rate so that the retention time of cloperastine is about 7 minutes.

System suitability

Selection of column: Dissolve 30 mg of Cloperastine Hydrochloride and 40 mg of benzophenone in 100 mL of the mobile phase. Pipet 2.0 mL of this solution and add the mobile phase to make 50 mL. Proceed with 20 μL of this solution under the above operating conditions; cloperastine and benzophenone are eluted in this order with the resolution being NLT 6.

Detection sensitivity: Adjust the sensitivity so that the peak height of cloperastine obtained from 20 μL of the standard solution is about 30% of the full scale.

Time span of measurement: About 4 times the retention time of cloperastine after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 °C, 3 hours).

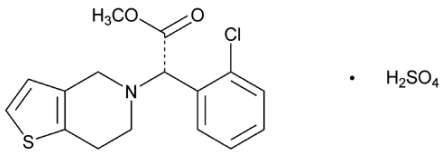
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Cloperastine Hydrochloride, previously dried, and dissolve it in 70 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 36.632 mg of $C_{20}H_{24}ClNO \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Clopidogrel Bisulfate
클로피도그렐황산수소염



Clopidogrel Hydrogen Sulfate

$C_{16}H_{16}ClNO_2S.H_2SO_4$: 419.90

Methyl(2S)-2-(2-chlorophenyl)-2-{4*H*,5*H*,6*H*,7*H*-thieno[3,2-c]pyridin-5-yl}acetate; sulfuric acid [*120202-66-6*]

Clopidogrel Bisulfate contains NLT 97.0% and NMT 101.5% of clopidogrel bisulfate ($C_{16}H_{16}ClNO_2S.H_2SO_4$: 419.90) calculated on the anhydrous basis.

Description Clopidogrel Bisulfate occurs as a white powder.
It is freely soluble in water and methanol, and practically insoluble in ether.

Identification (1) Determine the infrared spectra of Clopidogrel Bisulfate and clopidogrel bisulfate RS as directed in the potassium bromide disk method under the Mid-infrared Absorption Spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

(3) Clopidogrel Bisulfate responds to the Qualitative Analysis for sulfate.

Purity ***Related substances***—Weigh accurately about 0.1 g of Clopidogrel Bisulfate and dissolve in 5 mL of methanol, add the mobile phase to make exactly 200 mL, and use this solution as the test solution. Separately, weigh accurately appropriate amounts of clopidogrel bisulfate RS, clopidogrel related substance I {(+)-(*S*)-(*o*-chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridine-5(4*H*)-acetic acid} RS, clopidogrel related substance II {methyl(±)-(*o*-chlorophenyl)4,5-dihydrothieno[2,3-*c*]pyridine-6(7*H*)-acetate, hydrochloride} RS, and clopidogrel related substance III {methyl(-)-(*R*)-(*o*-chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridine-5(4*H*)-acetate, hydrogen sulfate}, dissolve in methanol, and dilute stepwise to make 20 μg, 40 μg, 120 μg and 200 μg per mL, respectively. To 5 mL of this solution, add the mobile phase to make exactly 200 mL to obtain solutions containing 0.5 μg, 1 μg, 3 μg and 5 μg per mL, respectively, and use these solution as the standard solutions. Perform the test with 10 μL each of the test solution and the standard solutions as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution as directed in the automatic integration method to calculate the amount of related substances in the test solution; the amount of clopidogrel related substance I having the relative retention time of about 0.5 to clopidogrel is NMT 0.2%, the amount of clopidogrel related substance III having the relative retention time of about 2.0 to clopidogrel is NMT 1.0%, the amount of a first enantiomer of clopidogrel related substance II having the relative retention time of about 0.8 to clopidogrel is NMT 0.3%, the amount of individual related substance is NMT 0.1%, and the amount of the total related substance is NMT 1.5%.

$$\text{Content (\%) of related substances I and III} = \frac{C_A}{C_T} \times \frac{A_U}{A_S} \times 100$$

C_A: Concentration (mg/mL) of each clopidogrel related substance in the standard solution

C_T: Concentration (mg/mL) of clopidogrel bisulfate in the test solution

A_U: Peak area of each related substance obtained from the test solution

A_S: Peak area of each clopidogrel related substance obtained from the standard solution

$$\text{Content (\%) of first enantiomer of related substance II} = \frac{C_B}{C_T} \times \frac{A_U}{A_S} \times 100 \times 0.5$$

C_B: Concentration (mg/mL) of clopidogrel related substance II in the standard solution

C_T: Concentration (mg/mL) of clopidogrel bisulfate in the test solution

A_U: Peak area of first enantiomer of clopidogrel related substance II obtained from the test solution

A_S: Peak area of first enantiomer of clopidogrel related substance II obtained from the standard solution

0.5: Correction factor of first enantiomer of clopidogrel related substance II

$$\text{Content (\%) of other related substances} = \frac{C}{C_T} \times \frac{A_U}{A_S} \times 100$$

C: Concentration (mg/mL) of clopidogrel bisulfate in the standard solution

C_T: Concentration (mg/mL) of clopidogrel bisulfate in the test solution

A_U: Peak area of clopidogrel related substances I, II and III, and the other individual related substances obtained from the test solution

A_S: Peak area of clopidogrel related substances obtained from the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column, 4.6 mm in inter-

nal diameter and 15 cm in length, packed with silica gel for liquid chromatography bound to ovomucoid, chiral-recognition protein for liquid chromatography (5 μm in particle diameter).

Flow rate: 1.0 mL/min

For mobile phase and system suitability solution, proceed as directed in the operating conditions under the Assay.

System suitability

System performance: Proceed with 10 μL of system suitability solution according to the above operation conditions; the relative retention times of the first and second enantiomers of the clopidogrel related substance II to clopidogrel are about 0.8 and about 1.2, respectively, with the resolution between the peaks of clopidogrel and the first enantiomer of the clopidogrel related substance II being NLT 2.5.

System repeatability: Repeat the test 6 times according to the above conditions with 10 μL each of the standard solution; the relative standard deviation of the each peak area is NMT 15%.

Loss on drying NMT 0.5% (1 g, 105 °C, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.1 g each of Clopidogrel Bisulfate and clopidogrel bisulfate RS, and add methanol to make exactly 100 mL. Pipet 5.0 mL each of this solution, add the mobile phase to make exactly 50 mL, and use each solution as the test solution and the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of clopidogrel bisulfate.

$$\text{Amount (mg) of clopidogrel bisulfate } (C_{16}H_{16}ClNO_2S\cdot H_2SO_4) = \text{Amount (mg) of clopidogrel bisulfate RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and about 15 cm in length, packed with silica gel for liquid chromatography bound to ovomucoid, chiral-recognition protein for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of phosphate buffer solution and acetonitrile (75 : 25).

Phosphate buffer solution—Dissolve 1.36 g of potassium dihydrogen phosphate in 500 mL of water and add water to make 1000 mL.

Flow rate: 1.0 mL/min

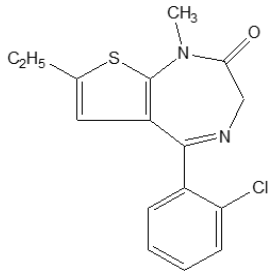
System suitability

System performance: Weigh accurately an appropriate amount of clopidogrel bisulfate RS and clopidogrel related substance II RS, and dissolve in methanol so that the solutions contain 100 μg and 200 μg per mL, respectively. Take 5 mL of this solution, add the mobile phase to make 200 mL, and use this solution as the system suitability solution. Proceed with 10 μL of this solution according to the above conditions; the relative retention times of the first and second enantiomers of the clopidogrel related substance II to clopidogrel are about 0.8 and about 1.2, respectively, with the resolution between the peaks of clopidogrel and the first enantiomer of the clopidogrel related substance II being NLT 2.5.

System repeatability: Repeat the test 6 times according to the above conditions with 10 μL each of the standard solution; the relative standard deviation of the peak areas of clopidogrel is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Clotiazepam
클로티아제팜



$C_{16}H_{15}ClN_2OS$: 318.82

5-(2-Chlorophenyl)-7-ethyl-1-methyl-1*H*,2*H*,3*H*-thieno[2,3-e][1,4]diazepin-2-one [*33671-46-4*]

Clotiazepam, when dried, contains NLT 98.5% and NMT 101.0% of clotiazepam ($C_{16}H_{15}ClN_2OS$).

Description Clotiazepam occurs as white to pale yellowish white crystals or a crystalline powder, which is odorless and has a slightly bitter taste.
It is very soluble in chloroform, freely soluble in methanol, acetic acid(100), ethanol(95), acetone and ethyl acetate, soluble in ether, and practically insoluble in water.
It dissolves in 0.1 mol/L hydrochloric acid TS.
It is gradually colored by light.

Identification (1) Dissolve 10 mg of Clotiazepam in 3 mL of sulfuric acid and examine the solution under ultraviolet light; the resulting solution exhibits a pale red fluorescence.

(2) Determine the absorption spectra of the solutions of Clotiazepam and clotiazepam RS in 0.1 mol/L hydrochloric acid TS (1 in 100000) as directed under Ultraviolet-visible Spectrophotometry: both spectra exhibit simi-

lar intensities of absorption at the same wavelengths.

(3) Weigh and proceed with 10 mg of Clotiazepam as directed under the Oxygen Flask Combustion, using 10 mL of diluted hydrogen peroxide(30) (1 in 5) as the absorbent to prepare the test solution. Add a small amount of water to the upper part of the apparatus A, carefully open C, wash C, B and the inner wall of A with 15 mL of methanol, and use the resulting solution as the test solution. Add 0.5 mL of dilute nitric acid to 15 mL of the test solution; this solution responds to the Qualitative Analysis (2) for chloride. Also, the remaining test solution responds to the Qualitative Analysis (1) for sulfate.

Melting point Between 106 and 109 ºC.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Clotiazepam in 10 mL of ethanol(95); the solution is clear and the color is not more intense than the following control solution.

Control solution—Take 5 mL of the Matching Fluid for Color C and add 0.01 mol/L hydrochloric acid TS to make 10 mL.

(2) ***Chloride***—To 1.0 g of Clotiazepam, add 50 mL of water, shake for 30 minutes, and filter. To 30 mL of the filtrate, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid (NMT 0.015%).

(3) ***Heavy metals***—Weigh and proceed with 2.0 g of Clotiazepam according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Weigh and proceed with 1.0 g of Clotiazepam according to Method 3 and perform the test (NMT 2 ppm).

(5) ***Related substances***—Dissolve 0.25 g of Clotiazepam in 10 mL of acetone and use this solution as the test solution. Pipet 1 mL of this solution, and add acetone to make exactly 20 mL. Pipet 2 mL of the resulting solution, add acetone to make exactly 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform and acetone (5 : 1) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); any spot other than the principal spot obtained from the test solution is not intense than the spot from the standard solutions.

Loss on drying NMT 0.5% (1 g, 80 °C, 3 hours).

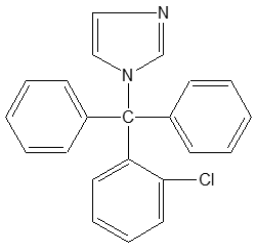
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Clotiazepam, previously dried, dissolve in 80 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid
= 31.882 mg of $C_{16}H_{15}ClN_2OS$

Packaging and storage Preserve in light-resistant, tight containers.

Clotrimazole
클로트리마졸



$C_{22}H_{17}ClN_2$: 344.84

1-[(2-Chlorophenyl)diphenylmethyl]-1*H*-imidazole [*23593-75-1*]

Clotrimazole, when dried, contains NLT 98.0% and NMT 101.0% of clotrimazole ($C_{22}H_{17}ClN_2$).

Description Clotrimazole occurs as a white crystalline powder, is odorless and tasteless.
It is freely soluble in acetic acid(100) or dichloromethane, soluble in methanol, ethanol(95) or *N*,*N*-dimethylformamide, slightly soluble in ether, and practically insoluble in water.

Identification (1) To 0.1 g of Clotrimazole, add 10 mL of 5 mol/L hydrochloric acid TS, and warm to dissolve. After cooling, add 3 drops of reinecke salt TS; pale red precipitates are formed.

(2) Determine the absorption spectra of solutions of Clotrimazole and clotrimazole RS in methanol (1 in 5000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Clotrimazole and clotrimazole RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) Perform the test with Clotrimazole as directed under the Flame Coloration (2); a green color is observed.

Melting point Between 142 and 145 ºC.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g

of Clotrimazole in 10 mL of dichloromethane; the resulting solution is clear and colorless.

(2) ***Chloride***—Dissolve 1.0 g of Clotrimazole in 40 mL of *N*,*N*-dimethylformamide, and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 0.60 mL of 0.01 mol/L hydrochloric acid, 40 mL of *N*,*N*-dimethylformamide, 6 mL of dilute nitric acid and water to make 50 mL (NMT 0.021%).

(3) ***Sulfate***—Dissolve 0.5 g of Clotrimazole in 10 mL of methanol, and add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid, adding 10 mL of methanol, 1 mL of dilute hydrochloric acid and water to make 50 mL (NMT 0.048%).

(4) ***Heavy metals***—Proceed with 2.0g of Clotrimazole according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Arsenic***—Proceed with 1.0 g of Clotrimazole according to Method 3 and perform the test (NMT 2 ppm).

(6) ***Imidazol***—Dissolve 0.1 g of Clotrimazole in exactly 10 mL of dichloromethane, and use this solution as the test solution. Separately, weigh accurately 25 mg of imidazol RS, dissolve in the dichloromethane to make exactly 50 mL. Pipet 5 mL of this solution, add dichloromethane to make exactly 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of methanol and chloroform (3 : 2) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Sprinkle sodium hypochlorite TS evenly on the plate, air-dry for 15 minutes, and then sprinkle potassium iodide starch TS evenly; the spot obtained from the test solution, of which location corresponds to that of the spot from the standard solution, is not more intense than the spot obtained from the standard solution.

(7) ***(2-Chlorophenyl)-diphenylmethanol***—Dissolve 0.2 g of Clotrimazole in exactly 10 mL of dichloromethane, and use this solution as the test solution. Separately, weigh 10 mg of (2-chlorophenyl)-diphenylethanol RS, dissolve in dichloromethane to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate and ammonia water(28) (50 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the spot obtained from the test solution, of which location corresponds to that of the spot from the standard solution, is not more intense than the spot obtained from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

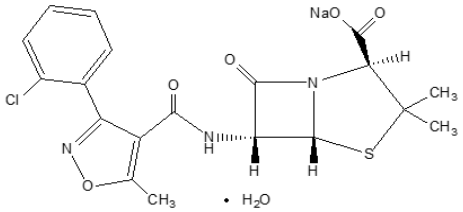
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.35 g of Clotrimazole, previously dried, dissolve in 80 mL of acetic acid(100), and titrate with 0.1 mol/L hydrochloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 34.484 mg of $C_{22}H_{17}ClN_2$

Packaging and storage Preserve in light-resistant, well-closed containers.

Cloxacillin Sodium Hydrate
클록사실린나트륨수화물



$C_{19}H_{17}ClN_3NaO_5S.H_2O$: 475.88

Sodium (2*S*,5*R*,6*R*)-6-[[3-(2-chlorophenyl)-5-methyl-2-oxazole-4-carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylatehydrate [*7081-44-9*]

Cloxacillin Sodium Hydrate contains NLT 900 μg and NMT 960 μg (potency) of cloxacillin ($C_{19}H_{18}ClN_3O_5S$: 435.88) per mg, calculated on the anhydrous basis.

Description Cloxacillin Sodium Hydrate occurs as white to light yellowish white crystals or a crystalline powder.
It is freely soluble in water, *N*,*N*-dimethylformamide or methanol, and sparingly soluble in ethanol(95).

Identification (1) Determine the absorption spectra of the solutions of Cloxacillin Sodium Hydrate and cloxacillin sodium hydrate RS in methanol (1 in 2500) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cloxacillin Sodium Hydrate and cloxacillin sodium hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Cloxacillin Sodium Hydrate responds to the Qualitative Analysis (1) for sodium salt.

Crystalline Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between +163° and +171° (1 g calculated on the anhydrous basis, water, 100 mL, 100 mm).

pH Dissolve 1.0 g of Cloxacillin Sodium Hydrate in 10 mL of water; the pH of this solution is between 5.0 and 7.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Cloxacillin Sodium Hydrate in 10 mL of water; the solution is clear and colorless to pale yellow.

(2) ***Heavy metals***—Proceed with 1.0 g of Cloxacillin Sodium Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Cloxacillin Sodium Hydrate according to Method 5 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Weigh accurately 50 mg of Cloxacillin Sodium Hydrate, dissolve in the mobile phase to make 50 mL, and use this solution as the test solution. Pipet 1.0 mL of this solution, add the mobile phase to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of each solution by the automatic integration method; each peak area other than the cloxacillin peak detected from the test solution is not larger than the peak area of the cloxacillin detected from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 4.953 g of dibasic ammonium phosphate in 700 mL of water, and add 250 mL of acetonitrile. Adjust the pH to 4.0 with phosphoric acid, and add water to make exactly 100 mL.

Flow rate: Adjust the flow rate so that the retention time of cloxacillin is about 24 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution, and add the mobile phase to make exactly 10 mL. Proceed with 10 μL of this solution according to the above conditions, and confirm that the peak area of cloxacillin is equivalent to 7% - 13% of the peak area of cloxacillin from the standard solution.

System performance: Weigh exactly about of 50 mg of cloxacillin sodium RS, dissolve in an appropriate amount of the mobile phase, add 5 mL of a solution of guaifenesin in the mobile phase (1 in 200), add the mobile phase again to make exactly 50 mL, and use the resulting solution as the system suitability solution. Proceed with 10 μL of this solution according to the above conditions; guaifenesin and cloxacillin are eluted in this order with the resolution between these peaks being NLT 25.

System repeatability: Repeat the test 6 times with 10 μL each of the system suitability solutions according to the above operating conditions; the relative standard deviation of the ratios of the peak area of cloxacillin to that of guaifenesin is NMT 1.0%.

Time span of measurement: About 3 times the retention time of cloxacillin.

(5) ***Dimethylaniline***—Weigh accurately about 1.0 g of Cloxacillin Sodium Hydrate, add 5 mL of 1 mol/L sodium hydroxide TS and 1 mL of the internal standard solution, centrifuge, if necessary, and use the supernatant as the test solution. Separately, weigh accurately about 50 mg of dimethylaniline, add 2.0 mL of hydrochloric acid, and add water to make 50 mL. Pipet 5.0 mL of this solution and add water to make exactly 250 mL. Pipet 1.0 mL of this solution, add 5.0 mL of 1 mol/L sodium hydroxide TS, add 1.0 mL of the internal standard solution, centrifuge, if necessary, and use the supernatant as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of dimethylaniline to that of the internal standard from the test solution and the standard solution, respectively (NMT 20 ppm).

$$\text{Content (ppm) of dimethylaniline} = \text{Amount (mg) of dimethylaniline taken} \times \frac{Q_T}{Q_S} \times \frac{Purity\ (\%)\ of\ dimethylaniline}{Amount\ (mg)\ of\ \text{Cloxacillin Sodium Hydrate taken}} \times 4$$

Internal standard solution—Dissolve 50.0 mg of naphthalene in cyclohexane to make 50 mL. Take 5.0 mL of this solution, add cyclohexane to make 100 mL, and use this solution as the internal standard solution.

Operating conditions

Detector: A flame ionization detector

Column: A column about 2 mm in internal diameter and about 2 m in length, packed with diatomaceous earth for gas chromatography, which is coated with 50% phenyl-50% methylpolysiloxane for gas chromatography equivalent to 3% of the mass of the diatomaceous earth for gas chromatography.

Column temperature: 120 °C

Temperatures of the sample injection port and the detector : 150 °C

Carrier gas: Nitrogen
Flow rate: 30 mL/min

Water NLT 3.0% and NMT 4.5% (0.2 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, it is exempt from the requirements there is a terminal sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins It is less than 0.20 EU per mg of cloxacillin when used in the manufacturing of sterile preparations.

Assay Weigh accurately about 50 mg (potency) each of Cloxacillin Sodium Hydrate and cloxacillin sodium RS, dissolve each in water to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of cloxacillin sodium from the test solution and the standard solution, respectively.

Potency (μg) of cloxacillin ($C_{19}H_{17}ClN_3NaO_5S$)
= Potency (μg) of cloxacillin sodium RS × $\frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

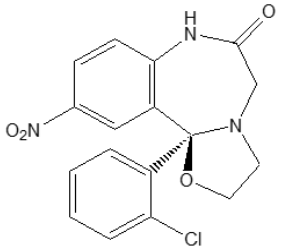
Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of 500 mL of acetonitrile and 1000 mL of a solution prepared by dissolving 2.72 g of potassium dihydrogen phosphate in water to make 1000 mL, and adjusting the pH to 5.0 with 8 mol/L potassium hydroxide.

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Cloxazolam
클록사졸람



and enantiomer

$C_{17}H_{14}Cl_2N_2O_2$: 349.21

10-Chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydrobenzo[f]oxazolo[3,2-d][1,4]diazepin-6(5*H*)-one [*24166-13-0*]

Cloxazolam, when dried, contains NLT 99% and NMT 101.0% of cloxazolam ($C_{17}H_{14}Cl_2N_2O_2$).

Description Cloxazolam occurs as white crystals or a crystalline powder, and is odorless and tasteless.
It is freely soluble in acetic acid(100), sparingly soluble in dichloromethane, slightly soluble in anhydrous ethanol or ether, very slightly soluble in ethanol, and practically insoluble in water.
It dissolves in dilute hydrochloric acid.
It is gradually colored by light.

Melting point—About 200 °C (with decomposition).

Identification (1) To 10 mg of Cloxazolam, add 10 mL of anhydrous ethanol, dissolve by heating, and add one drop of hydrochloric acid; the resulting solution exhibits a pale yellow color. Expose to ultraviolet light (wavelength of 365 nm); the solution exhibits a yellowish green fluorescence. To this solution, add 1 mL of sodium hydroxide TS; the color and fluorescence of the solution disappear immediately.

(2) To 10 mg of Cloxazolam, add 5 mL of dilute hydrochloric acid, dissolve by heating on a steam bath for 10 minutes, and then cool the solution. 1 ml of the resulting solution responds to the Qualitative Analysis for primary aromatic amines.

(3) Place 2 g of Cloxazolam into a 200-mL flask, add 50 mL of ethanol and 25 mL of hydrochloric acid TS, connect the flask to a reflux condenser, and reflux for 4 hours. After cooling, neutralize the solution with dilute hydrochloric acid, and extract with 30 mL of dichloromethane. Dehydrate the extract with 3 g of anhydrous sodium sulfate, filter, and evaporate the dichloromethane. Add 5 mL of methanol to the residue, dissolve by heat on a steam bath, and cool in iced water rapidly. Filter the precipitated crystals, and dry the residue in vacuum at 60 ℃ for 1 hour; the melting point is between 87 and 91 ℃.

(4) Determine the absorption spectra of solutions of Cloxazolam and cloxazolam RS in anhydrous ethanol (1 in 100000) as directed under the Ultraviolet-visible Spec-

troscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(5) Perform the test with Cloxazolam as directed under the Flame Coloration (2); a green color is observed.

Absorbance $E_{1cm}^{1\%}$ (244 nm): Between 390 and 410 (1 mg after drying, anhydrous ethanol, 100 mL).

Purity (1) ***Chloride***—To 1.0 g of Cloxazolam, add 50 mL of water, and allow to stand for 1 hour with shaking occasionally, and filter the resulting solution. Pipet 25 mL of the filtrate, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.20 mL of 0.01 mol/L hydrochloric acid solution (NMT 0.014%).

(2) ***Heavy metals*—**Proceed with 1.0 g of Cloxazolam according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Weigh 1.0 g of Cloxazolam**,** put into a Kjeldahl flask, add 5 mL of sulfuric acid and 5 mL of nitric acid, and heat over low heat. While adding 2 mL - 3 mL portions of nitric acid from time to time, continue heating until the solution becomes colorless to pale yellow. After cooling, add 15 mL of saturated ammonium oxalate, heat to concentrate until thick white fumes are produced to make 2 mL - 3 mL. After cooling, add water to make 10 mL, and perform the test with this solution as the test solution (NMT 2 ppm).

(4) ***Related substances***—Dissolve 50 mg of Cloxazolam in 10 mL of dichloromethane and use this solution as the test solution. Pipet 1 mL of this solution, add dichloromethane to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of toluene and acetone (5:1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Observe the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution is not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 °C, 3 hours).

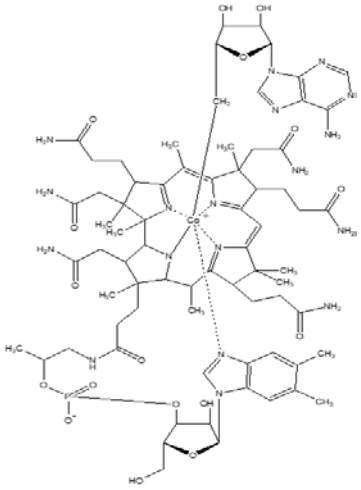
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Cloxazolam, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of methylosaniline chloride TS). The endpoint of the titration is when the color of the solution changes from violet through blue to bluish green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 34.921 mg of $C_{17}H_{14}Cl_2N_2O_2$

Packaging and storage Preserve in light-resistant, tight containers.

Cobamamide
코바마이드



Coenzyme B_{12} $C_{72}H_{100}CoN_{18}O_{17}P$: 1579.58
Co-(5′-deoxyadenosine-5′) derivative of 3′-ester of cobinamidedihydrogenphosphate(ester) with 5,6-dimethyl-1-alpha-*D*-ribofuranosyl-1*H*benzimidazole, inner salt, [*13870-90-1*]

Cobamamide contains NLT 95.0% and not more 101.0% of cobamamide ($C_{72}H_{100}CoN_{18}O_{17}P$), calculated on the dried basis.

Description Cobamamide occurs as a dark red crystal, or crystalline or amorphous powder.
It is sparingly soluble in water, very slightly soluble in ethanol, and practically insoluble in acetone, ether or chloroform.
It is extremely hygroscopic and is decomposed by light.

Identification (1) Determine the absorption spectra of the test solution and the standard solution from the Assay as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Add 50 mg of potassium hydrogen sulfate to 1 mg of Cobamamide to mix, and ignite to dissolve. After cooling, break up the molten product with a glass rod, add 3 mL of water, boil, add 1 drop of phenolphthalein TS, and drop sodium hydroxide TS until the solution exhibits a light red. Add 0.5 g of sodium acetate, 0.5 mL of dilute acetic acid and 0.5 mL of 1-nitroso-2-naphthol-3.6-disulfonic acid disodium solution (1 in 500); the solution immediately exhibits a red to orange red color. Add 0.5

mL more of hydrochloric acid, and boil for 1 minute; the red color of the solution does not disappear.

(3) Put 5 mg of Cobamamide in a 50-mL distillation flask, dissolve in 5 mL of water, add 2.5 mL of hypophosphoric acid, attach a short chiller, and immerse the tip of the chiller in 1 mL of sodium hydroxide solution (1 in 50) in a test tube. Next, boil at a low heat for 10 minutes, and distill until 1 mL of distillate is obtained. To the solution in the test tube, add 4 drops of saturated solution of ammonium ferrous sulfate, and shake gently to mix. Add 30 mg of sodium fluoride, heat to a boil, and immediately add diluted sulfuric acid (1 in 7) dropwise until the solution becomes clear. Add 3 to 5 drops of diluted sulfuric acid (1 in 7) again; the solution exhibits a blue to bluish green color.

Purity (1) ***Hydroxocobalamin***—Weigh 2.5 mg of Cobamamide, and dissolve in potassium chloride-hydrochloric acid buffer solution, pH 2.0, to make 50.0 mL. With this solution, determine the absorbance A_1 and A_2 at 352 nm and 460 nm as directed under Ultraviolet-visible Spectroscopy; A_2/A_1 is NLT 0.800. Perform all of the above in the dark.

(2) ***Colored impurities*—**Weigh accurately 10 mg each of Cobamamide and cyanocobalamin RS, dissolve in 0.50 mL of water, and use these solutions as the test solution and standard solution. Mark a horizontal line at 100 mm from the edge of a sheet of filter paper for chromatography (500 mm x 220 mm) using a pencil, and adsorb 0.25 mL of the test solution about 100 mm to the target, leaving 50 mm on one end. Then, spot 5 μL of the standard solution on the remaining portion of the same line, leaving 20 mm of space in between. After air-drying, test as directed under the descent method under the Paper Chromatography using a mixture of 2-butanol, water and acetic acid(100) (100 : 50 : 3) as the developing solvent. Cut and discard the cobamamide part with an R_f value of about 0.8, and the developed part of the standard solution. Cut the colored part of the remaining filter paper, and join the two ends to create a cylinder. Insert this cylindrical filter paper into a petri dish of diameter 120 mm and with a sheet of filter paper wet with water placed on the bottom. Allow to stand until the colored part rises and collects at the top portion of the filter paper. Next, cut the colored part and extract 3 times by shaking using 7 mL of water each time; combine the extracts, then add water to make 20 mL, and filter using a glass filter (G_3). Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using the blank test solution as the control, and determine the absorbance at the absorbance maximum wavelength at about 525 nm. At the time, the absorbance is NMT 0.070. Perform all of the above in the dark.

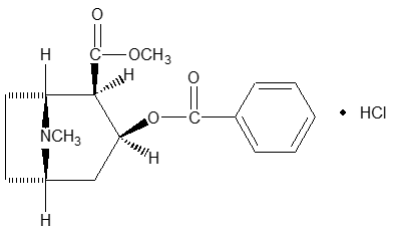
Loss on drying NMT 12.0% (0.1 g, in vacuum, NMT 0.67 kPa, phosphorus pentoxide, 60 ℃, 15 hours).

Assay Weigh accurately about 20 mg each of Cobamamide and cobamamide RS (Measure the loss on drying in the same manner as Cobamamide.), and add water to make exactly 50 mL. Pipet 5 mL of these solutions, add water to make exactly 25 mL, and use these solutions as the test solution and the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at 525 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of cobamamide } (C_{72}H_{100}CoN_{18}O_{17}P) = \text{Amount (mg) of cobamamide RS, as calculated on the dried basis} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in light-resistant, tight containers.

Cocaine Hydrochloride
코카인염산염



$C_{17}H_{21}NO_4 \cdot HCl$: 339.81

Methyl (1*R*,3*R*,4*S*,5*S*)-3-Benzoyloxy-8-methyl-8-azabicyclo[3.2.1]octane-4-carboxylate hydrochloride [*53-21-4*]

Cocaine Hydrochloride, when dried, contains NLT 98.0% and NMT 101.0% of cocaine hydrochloride ($C_{17}H_{21}NO_4 \cdot HCl$).

Description Cocaine Hydrochloride occurs as colorless crystals or a white crystalline powder.
It is very soluble in water, freely soluble in ethanol(95) or acetic acid(100), slightly soluble in acetic anhydride, and practically insoluble in ether.

Identification (1) Determine the absorption spectra of solutions of Cocaine Hydrochloride and cocaine hydrochloride RS in 0.01 mol/L hydrochloric acid TS (1 in 10000) as directed under the Ultraviolet-visible spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavelengths. In addition, determine the absorption spectra of the solutions of Cocaine Hydrochloride and cocaine hydrochloride RS in 0.01 mol/L hydrochloric acid (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cocaine Hydrochloride and cocaine hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit

similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Cocaine Hydrochloride (1 in 50) responds to the Qualitative Analysis (2) for chloride.

Optical rotation $[\alpha]_D^{20}$: -70° to -73° (0.5 g, after drying, water, 20 mL, 100 mm).

Purity (1) ***Acid***—Dissolve 0.5 g of Cocaine Hydrochloride in 10 mL of water, add 1 drop of methyl red TS and neutralize with 0.01 mol/L sodium hydroxide solution; the amount consumed is NMT 1.0 mL.

(2) ***Cinnamyl cocaine*—**Dissolve 0.10 g of Cocaine Hydrochloride in 5 mL of water, then add 0.3 mL of diluted sulfuric acid (1 in 20) and 0.10 mL of 0.02 mol/L potassium permanganate solution; the red color of the resulting solution does not disappear within 30 minutes.

(3) ***Isoatropyl cocaine*—**Weigh 0.10 g of Cocaine Hydrochloridee in a beaker, dissolve in 30 mL of water, and separately collect 5 mL of the resulting solution in a test tube. Add 30 mL of water again to the previous beaker, add 1 drop of ammonia TS to the test tube, and shake to mix. When precipitates are formed, add 10 mL of water, place in the previous beaker and wash the test tube with 10 mL of water by adding the washings to the beaker. Add 3 drops of ammonia TS and gently shake to mix; crystalline precipitates are formed. When allowed to stand for 1 hour, the supernatant is clear.

(4) ***Readily carbonizable substances*—**Weigh 0.5 g of Cocaine Hydrochloride and perform the test. The color of this solution is not more intense than that of the control solution F.

Loss on drying NMT 1.0% (1 g, 105℃, 4 hours).

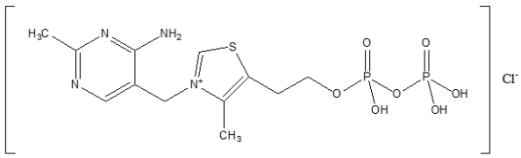
Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh exactly about 0.5 g of Cocaine Hydrochloride, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 33.982 mg of $C_{17}H_{21}NO_4 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Cocarboxylase
코카르복실라제



Coenzyme B_1 $C_{12}H_{19}ClN_4O_7P_2S$: 460.77
3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-4-methyl-5-(4,6,6-trihydroxy-3,5-dioxa-4,6-diphosphahex-1-yl)thiazolium chloride *P*,*P*′-dioxide, [*154-87-0*]

Cocarboxylase contains NLT 95.0% and NMT 101.0% of cocarboxylase ($C_{12}H_{19}ClN_4O_7P_2S$), calculated on the dried basis.

Description Cocarboxylase occurs as a white crystalline powder. It is odorless or has a slight characteristic odor and sour taste.
It is freely soluble in water, and practically insoluble in acetonitrile, anhydrous ethanol or ether.

Melting point—About 230 °C (with decomposition).

Identification (1) To 1 mL of aqueous solution of Cocarboxylase (1 in 500), add 1 mL of lead acetate TS and 1 mL of sodium hydroxide solution (1 in 10), and heat; the resulting solution turns yellow to brown, and blackish brown precipitates are formed when left to stand.

(2) To 10 mL of the aqueous solution of Cocarboxylase (1 in 300), add sodium acetate to adjust pH to between 4.5 and 5.0. Then, add 4 mL of enzyme TS and warm on a steam bath at 50 ℃ for 1 hour, and use this solution as the test solution. Take 5 mL of the test solution, add 2.5 mL of sodium hydroxide TS and 0.5 mL of tpotassium hexacyanoferrate(III) TS, add 5 mL of isubutanol and shake vigorously for 2 minutes to mix, and centrifuge. Take the isobutanol layer and examine under ultraviolet light (main wavelength: 365 nm); a bluish-purple fluorescence is exhibited. This fluorescence disappears when the solution is acidified and reappears when the solution is alkalized.

(3) To 7 mL of the test solution from (2), add 2 mL of strong ammonia water, shake to mix, and centrifuge; the clear supernatant responds to the Qualitative Analysis for phosphate.

(4) An aqueous solution of Cocarboxylase (1 in 50) responds to the Qualitative Analysis for chloride.

pH Between 1.0 and 1.4 (10% aqueous solution).

Purity (1) ***Clarity and color of solution*—**Dissolve 0.2 g of Cocarboxylase in 10 mL of water; the solution is clear and colorless.

(2) ***Sulfate***—Perform the test with 1.5 g of Cocarboxylase. Use 0.35 mL of 0.005 mol/L sulfuric acid as the control solution (NMT 0.011%).

(3) ***Heavy metals*—**Dissolve about 1.0 g of Cocar-

boxylase in 30 mL of water, and add ammonia TS to adjust pH to 3.5. Then, add 5 mL of hydrochloric acid-ammonium acetate buffer solution, pH 3.5, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding hydrochloric acid-ammonium acetate buffer solution, pH 3.5, and water to 2.0 mL of lead standard solution to make 50 mL (NMT 20 ppm).

(4) ***Free phosphoric acid***—Weigh accurately about 50 mg of Cocarboxylase, add water to make 100 mL, and use this solution as the test solution. Pipet 5.0 mL each of the test solution, diluted standard phosphoric acid solution (1 in 5) and water, transfer to a 25 mL volumetric flask, add 2.5 mL of ammonium molybdate-sulfuric acid TS and 1 mL of 1-amino-2-naphthol-4-sulfonic acid TS, shake to mix, and add water to make 25 mL. Allow the solutions to stand for 10 minutes at 20 ± 1 ℃, and determine the absorbances A_1, A_2, and A_3 of each solution at 740 nm, using water as the control, as directed under the Ultraviolet-visible Spectroscopy within 30 minutes; the amount of free phosphoric acid is NMT 1.5%.

$$\text{Content (\%) of free phosphoric acid } (H_3PO_4) = \frac{A_1 - A_3}{A_2 - A_3} \times \frac{1}{W} \times 51.56$$

W: Amount (mg) of sample, calculated on the dry basis

(5) ***Thiamine hydrochloride, thiamine monophosphate chloride and other related substances***—Dissolve 60 mg of Cocarboxylase in 100 mL of the mobile phase, and use this solution as the test solution. With 10 μL of the test solution, perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution according to the automatic integration method and determine the amounts of related substances; the amount of each related substance is NMT 0.5% for thiamine hydrochloride, NMT 4.0% for thiamine monophosphate chloride, and 1.5% for other related substances. The peak areas for retention time about 2 minutes (thiamine hydrochloride), about 3 minutes (thiamine monophosphate chloride), about 5 minutes (cocarboxylase) and related substances eluted later than cocarboxylase are A_1, A_2, A_3 and A_4, respectively.

$$\text{Amount (mg) of thiamine hydrochloride } (C_{12}H_{17}ClN_4OS\cdot HCl) = \frac{A_T}{A_S} \times 73$$

$$\text{Content (\%) of thiamine monophosphate chloride } (C_{12}H_{18}ClN_4O_4PS) = \frac{A_2}{A} \times 82$$

$$\text{Content (\%) of other related substances (\%)} = \frac{A_1}{A} \times 100$$

Operating conditions

Time span of measurement: About 5 times the retention time of cocarboxylase.

Other: Follow the operating conditions of Assay.

(6) ***Arsenic***—Weigh 0.65 g of Cocarboxylase and perform the test according to Method 3. However, use ethanol solution (1 in 5) of magnesium nitrate, and dissolve the residue after incineration using 10 mL of dilute hydrochloric acid (NMT 3.1 ppm).

Loss on drying NMT 2.0% (1 g, 130 ℃, 4 hours).

Assay Weigh accurately about 60 mg each of Cocarboxylase and cocarboxylase RS (measure loss on drying in advance), add the mobile phase to make 50 mL, add 10.0 mL of the internal standard solution to each, add the mobile phase to make 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and calculate the ratios, Q_T and Q_S, of the peak area of cocarboxylase to that of the internal standard.

$$\text{Amount (mg) of cocarboxylase } (C_{12}H_{19}ClN_4O_7P_2S) = \text{Amount (mg) of cocarboxylase (mg), calculated on the dry basis} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of caffeine in the mobile phase (3 in 2000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Take 2.3 g of ammonium phosphate dibasic and 12 mL of tetrabutylammonium hydroxide TS for liquid chromatography, and add water to make 1000 mL. Add 100 mL of acetonitrile to 900 mL of this solution and mix.

Flow rate: Adjust the flow rate so that the retention time of cocarboxylase is about 5 minutes.

Selection of column: Proceed with 10 μL of the standard solution under the above operating conditions. Use a column giving elution of cocarboxylase and caffeine in this order with the resolution between these peaks being NLT 3.

Packaging and storage Preserve in light-resistant, tight containers.

Cod Liver Oil
간유

Cod Liver Oil is the fatty oils obtained from fresh livers and pyloric appendages of *Gadus macrocephalus* Tilesius or *Theragra chalcogramma* Pallas (Gadidae).
Cod Liver Oil contains NLT 2000 vitamin A units and NMT 5000 vitamin A units per g.

Description Cod Liver Oil occurs as a yellow to orange oily liquid, and has a characteristic, slightly fishy odor and a mild taste.
It is miscible with chloroform.
It is slightly soluble in ethanol(95) and practically insoluble in water.
Decomposition of Cod Liver Oil is accelerated by air or light.

Identification Dissolve 0.1 g of Cod Liver Oil in 10 mL of chloroform, take 1 mL of this solution, and add 3 mL of antimony(III) chloride TS; the solution immediately turn to blue, but the color disappears rapidly.

Specific gravity d_{20}^{20}: Between 0.918 and 0.928.

Acid value NMT 1.7.

Saponification value Between 180 and 192.

Unsaponifiable matter NMT 3.0%.

Iodine value Between 130 and 170.

Anisidine value Weigh accurately 0.5 g of Cod Liver Oil, add isooctane, dissolve to make exactly 25 mL, and use this solution as the test stock solution. Pipet 0.5 g of this solution, add 1 mL of a solution of *p*-anisidine in acetic acid(100) (2.5 in 1000), shake to mix, and use this solution as the test solution. Separately, pipet 0.5 mL of isooctane, add 1 mL of a solution of *p*-anisidine in acetic acid(100) (2.5 in 1000), shake to mix, and use this solution as the standard solution. Preserve the test and standard solutions, protected from light. With isooctane as the blank test solution, determine the absorbance A_{S1} of the test stock solution at 350 nm of wavelength. With the standard solution using as a control solution, 10 minutes exactly after preparing the test solution, determine the absorbance A_{S2} of the test solution at 350 nm of wavelength and calculate anisidine value according to the following equation; the anisidine value is NMT 30.

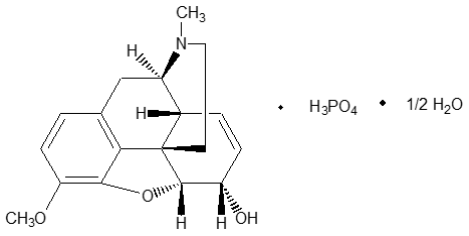
$$\text{Anisidine value} = 25 \times \frac{(1.2 \times A_{S2}) - A_{S1}}{\text{Amount of Cod Liver Oil taken (g)}}$$

Purity ***Rancidity***—No unpleasant odor of rancid oil is perceptible when warming Cod Liver Oil.

Assay Weigh accurately about 0.5 g of Cod Liver Oil and perform the test according to Method 2 under the Vitamin A Assay.

Packaging and storage Preserve in light-resistant, tight containers, as almost well-filled or under the nitrogen atmosphere.

Codeine Phosphate Hydrate
코데인인산염수화물



Codeine phosphate $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$: 406.37
(5*R*,6*S*)-4,5-Epoxy-3-methoxy-17-methyl-7,8-didehydromorphinan-6-ol monophosphate hemihydrate [*41444-62-6*]

Codeine Phosphate Hydrate contains NLT 98.0% and NMT 101.0% of codeine phosphate $C_{18}H_{21}NO_3 \cdot H_3PO_4$: 397.36), calculated on the anhydrous basis.

Description Codeine Phosphate Hydrate occurs as white to yellow crystals or a crystalline powder.
It is freely soluble in water or acetic acid(100), slightly soluble in methanol or ethanol(95), and practically insoluble in ether.
Dissolve 1.0 g of Codeine Phosphate Hydrate in 10 mL of water; the pH of this solution is between 3.0 and 5.0.
It is affected by light.

Identification (1) Determine the absorption spectra of aqueous solutions of Codeine Phosphate Hydrate and Codeine Phosphate Hydrate RS (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelength.

(2) Determine the infrared spectrum of Codeine Phosphate Hydrate and Codeine Phosphate Hydrate RS, previously dried for 4 hours at 105 ℃, as directed in the potassium bromide disk method under the Ultraviolet-visible spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) A solution of Codeine Phosphate Hydrate (1 in 20) responds to the Qualitative Analysis (1) for phosphate.

Optical rotation $[\alpha]_D^{20}$: Between -98° and -102° (0.4 g, calculated on the anhydrous basis, 20 mL of water, 100

mm).

Purity (1) ***Chloride***—Perform the test with 0.5 g of Codeine Phosphate Hydrate. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.021%).

(2) ***Sulfate***—Perform the test with 0.20 g of Codeine Phosphate Hydrate. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.240%).

(3**) *Related substances*—**Dissolve 0.20 g of Codeine Phosphate Hydrate in 10 mL of a mixture of hydrochloric acid TS and ethanol(99.5) (4 : 1), and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of 0.01 mol/L hydrochloric acid TS and ethanol(99.5) (4 : 1) to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of ethanol(99.5), toluene, acetone, and ammonia water(28) (14 : 14 : 7 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Water Between 1.5% and 3.0% (0.5 g, volumetric titration, direct titration).

Assay Weigh accurately about 0.5 g of Codeine Phosphate Hydrate, dissolve in 70 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 3 drops of methylrosaniline chloride TS). The endpoint of the titration is when the solution changes from violet to blue, then finally to greenish blue. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 39.736 mg of $C_{18}H_{21}NO_3 \cdot H_3PO_4$

Packaging and storage Preserve in light-resistant, tight containers.

1% Codeine Phosphate Powder
코데인인산염 100 배산

Codeine Phosphate 1%

1% Codeine Phosphate Powder contains NLT 0.90% and not more the 1.10% of Codeine Phosphate Hydrate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$: 406.37).

Method of preparation

Codeine Phosphate Hydrate	10 g
Lactose hydrate	An appropriate amount
Total amount	1000 g

Prepare as directed under Powders, with the above.

Identification Determine the absorption spectrum of an aqueous solution of 1% Codeine Phosphate Powder as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at 283 nm to 287 nm.

Particle size distribution estimation by analytical sieving Meets the requirements.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Weigh accurately about 5 g of 1% Codeine Phosphate Powder, dissolve in water to make exactly 100 mL, Pipet 10 mL of this solution, add exactly 10 mL of the internal standard solution, and use this solution as the test solution. Separately, weigh accurately about 50 mg of Codeine Phosphate Hydrate RS, previously determined the water content in the same manner as Codeine Phosphate Hydrate, dissolve in water to make exactly 100 mL, Pipet 10 mL of this solution, add exactly 10 mL of the internal standard solution, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of codeine to the peak area of the internal standard.

Amount (mg) of Codeine Phosphate Hydrate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$)
= Amount (mg) of Codeine Phosphate RS, calculated on the anhydrous basis× $1.0227 \times \frac{Q_T}{Q_S}$

Internal standard solution—An aqueous solution of etilefrine hydrochloride (3 in 10000).

Operating conditions

Proceed as directed under the operating conditions in the Assay under 10% Codeine Phosphate Powder.

Packaging and storage Preserve in tight containers.

10% Codeine Phosphate Powder
코데인인산염 10 배산

Codeine Phosphate 10%

10% Codeine Phosphate Powder contains NLT 9.3% and NMT 10.7% of Codeine Phosphate Hydrate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$: 406.37).

Method of preparation

Codeine Phosphate Hydrate	100 g

Lactose hydrate	An appropriate amount
Total amount	1000 g

Prepare as directed under Powders, with the above.

Identification Determine the absorption spectrum of an aqueous solution of 10% Codeine Phosphate Powder (1 in 1000) as directed under the Ultraviolet-visible spectrophotometry; it exhibits a maximum at 283 nm to 287 nm.

Particle size distribution estimation by analytical sieving Meets the requirements.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Weigh accurately about 2.5 g of 1% Codeine Phosphate Powder, dissolve in water to make exactly 100 mL, Pipet 2 mL of this solution, add exactly 10 mL of the internal standard solution, add water to make 20 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of Codeine Phosphate Hydrate RS (previously determine the water in the same manner as Codeine Phosphate Hydrate), dissolve in water to make exactly 100 mL, Pipet 10 mL of this solution, add exactly 10 mL of the internal standard solution, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of codeine to the peak area of the internal standard.

Amount (mg) of Codeine Phosphate Hydrate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$) = Amount (mg) of Codeine Phosphate RS, calculated on the anhydrous basis $\times 1.0227 \times \frac{Q_T}{Q_S} \times 5$

Internal standard solution—An aqueous solution of etilefrine hydrochloride (3 in 10000).

Operating conditions

Detector: An ultraviolet photometer (wavelength: 280 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm to 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: Dissolve 1.0 g of sodium lauryl sulfate in 500 mL of diluted phosphoric acid (1 in 1000), then add sodium hydroxide TS to adjust the pH to 3.0. To 240 mL of this solution, add 70 mL of tetrahydrofuran, and mix.

Flow rate: Adjust the flow rate so that the retention time of codeine is about 10 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above operating conditions; codein and the internal standard are eluted in this order with the resolution being NLT 4.

System repeatability: Repeat the test 5 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio of codeine to the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Codeine Phosphate Tablets
코데인인산염 정

Codeine Phosphate Tablets contains NLT 93.0% and NMT 107.0% of the labeled amount of Codeine Phosphate Hydrate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$: 406.37).

Method of preparation Prepare as directed under Tablets, with Codeine Phosphate Hydrate.

Identification Powder Codeine Phosphate Tablets, weigh an amount of the powder, equivalent to 0.1 g of Codeine Phosphate Hydrate according to the labeled amount, add 20 mL of water, shake to mix, and filter. To 2 mL of this filtrate, add water to make 100 mL, and determine the absorption spectrum of the resulting solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 283 nm and 287 nm.

Dissolution Perform the test with 1 tablet of Codeine Phosphate Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take NLT 20 mL of the dissolved solution 30 minutes after starting the dissolution test and filter through a membrane filter with a pore diameter of NMT 0.45 μm. Discard the first 10 mL of the filtrate, take exactly V mL of the subsequent filtrate, and add water to make exactly V' mL of a solution containing about 5.6 μg of Codeine Phosphate Hydrate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1/2H_2O$) per mL according to the labeled amount, and se this solution as the test solution. Separately, weigh accurately about 28 mg of the Codeine Phosphate RS (previously determined the water content in the same manner as for Codeine Phosphate Hydrate), dissolve in water to make exactly 100 mL. Pipet 2 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 100 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_s, of codeine in each solution. Meets the requirements if the dissolution rate of Codeine Phosphate Tablets in 30 minutes is NLT 80%.

Dissolution rate (%) with respect to the labeled amount of Codeine Phosphate Hydrate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1/2H_2O$)

$$= WS \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 18 \times 1.0227$$

Ws: Amount (mg) of Codeine Phosphate RS, calculated on the anhydrous basis.

C: Labeled amount (mg) of Codeine Phosphate Hydrate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1/2H_2O$) in 1 tablet

Operating conditions

Proceed as directed under the operating conditions under the Assay.

System suitability

System performance: Proceed with 100 μL of the standard solution under the above operating conditions; the number of theoretical plates and the symmetry factor are NLT 5000 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 100 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of codeine is NMT 2.0%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Codeine Phosphate Tablets, and powder. Weigh accurately an amount of this powder, equivalent to about 0.1 g of Codeine Phosphate Hydrate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$), add 30 mL of water, sonicate for 10 minutes, and add water to make exactly 100 mL. Filter, pipet 2 mL of the filtrate, add exactly 10 mL of the internal standard solution, add water to make exactly 20 mL, and use this solution as the standard solution. Separately, weigh accurately about 50 mg of Codeine Phosphate RS (previously determine the water content in the same manner as for Codeine Phosphate Hydrate) and dissolve in water to make exactly 100 mL. Pipet 10 mL of this solution, add exactly 10 mL of the internal standard solution, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of codeine to the peak area of the internal standard.

Amount (mg) of codeine phosphate hydrate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$)
= Amount (mg) of codeine phosphate RS, calculated on the anhydrous basis $\times 1.0227 \times \frac{Q_T}{Q_S} \times 2$

Internal standard solution—An aqueous solution of etilefrine hydrochloride (3 in 10000).

Operating conditions

Detector: An ultraviolet photometer (wavelength: 280 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm to 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 1.0 g of sodium lauryl sulfate in 500 mL of diluted phosphoric acid (1 in 1000), then add sodium hydroxide TS to adjust the pH to 3.0. To 240 mL of this solution, add 70 mL of tetrahydrofuran, and mix.

Flow rate: Adjust the flow rate so that the retention time of codeine is about 10 minutes.

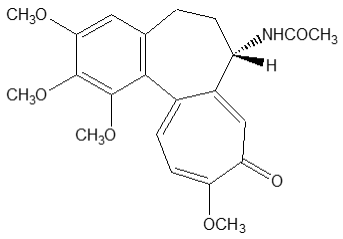
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above operating conditions; codein and the internal standard are eluted in this order with the resolution being NLT 4.

System repeatability: Repeat the test 5 times with 20 μL each of the standard solution under the above operating conditions; the relative standard deviation of the ratios of the peak area of codein to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Colchicine
콜키신



$C_{22}H_{25}NO_6$: 399.44

N-{3,4,5,14-Tetramethoxy-13-oxotricyclo[9.5.0.0^{2,7}]hexadeca-1(16),2(7),3,5,11,14-hexaen-10-yl}acetamide [*64-86-8*]

Colchicine contains NLT 97.0% and NMT 102.0% of colchicine ($C_{22}H_{25}NO_6$), calculated on the anhydrous and ethyl acetic acid-free basis.

Description Colchicine occurs as a yellowish white powder.
It is very soluble in methanol, freely soluble in ethanol(95), acetic anhydride or *N*,*N*-dimethylformamide and sparingly soluble in water.
It is colored by light.

Identification (1) Determine the absorption spectra of Colchicine and ethanol(95) solution of colchicine RS as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the

same wavelengths.

(2) Add 0.5 mL of Colchicine and methanol solution (1 in 50) of colchicine RS to 1 g of potassium bromide for the Mid-infrared Spectroscopy, mix well, and dry under vacuum for 1 hour at 80 ℃; measure as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -235° and -250° (0.1 g, calculated on the anhydrous and ethyl acetic acid-free basis, ethanol(95), 10 mL, 100 mm).

Purity (1) ***Colchicine*—**Dissolve 0.10 g of Colchicine in 10 mL of water and add 2 drops of iron(III) chloride TS to 5 mL of this solution; the resulting solution does not exhibit a clear green color.

(2) ***Ethyl acetate and chloroform*—**Weigh accurately 0.6 g of Colchicine, dissolve in exactly 2 mL of internal standard solution, add *N*,*N*-dimethylformamide to make 10 mL, and use this solution as the test solution. Separately, add 0.30 g of chloroform to a 100-mL volumetric flask containing about 20 mL of *N*,*N*-dimethylformamide, and add *N*,*N*-dimethylformamide to make exactly 100 mL. Pipet 2 mL of this solution, add *N*,*N*-dimethylformamid to make exactly 200 mL and use this solution as the standard solution (1). Separately, add exactly about 1.8 g of ethyl acetate to a 100-mL volumetric flask containing about 20 mL of *N*,*N*-dimethylformamide, and add *N*,*N*-dimethylformamide to make exactly 100 mL. Take exactly 2 mL of this solution, add exactly 2 mL of the internal standard solution, add *N*,*N*-dimethylformamide to make 10 mL, and use this solution as the standard solution (2). Perform the test with 2 μL each of the standard solution (1) and the standard solution (2) as directed under the Gas Chromatography according to the following conditions. The peak area of chloroform from the test solution is not greater than the peak area of chloroform from the standard solution (1). Find the peak area ratios, Q_T and Q_S, of ethyl acetate to the peak area of the internal standard, for the test solution and standard solution (2). Determine the amount of ethyl acetate using the following formula; the amount is NMT 6.0%.

$$\text{Content (\%) of ethyl acetate } (C_4H_8O_2) = \frac{W_S}{W_T} \times \frac{Q_T}{Q_S} \times 2$$

W_S: Amount (g) of ethyl acetate
W_T: Amount (g) of colchicine

Internal standard solution—*N*,*N*-dimethylformamide solution (3 in 200) of 1-propanol.

Operating conditions

Detector: A flame ionization detector

Column: Coat the inside of a quartz glass column of 0.53 mm in internal diameter and 30 m in length with polyethylene glycol 20 M for gas chromatography to a thickness of 1.0 μm.

Column temperature: Maintain at 60 °C for 7 minutes, heat at a rate of 40 to 100 °C per minute, if necessary and keep at 100 °C for 10 minutes.

Sample injection port temperature: A constant temperature of about 130 ℃.

Detector temperature: A constant temperature of about 200 ℃.

Carrier gas: Helium

Flow rate: Adjust the flow rate so that the retention time of ethyl acetate is about 3 minutes.

Split ratio: About 1 : 20.

System suitability

Test for required detectability: Pipet 2 mL of the standard solution (2) and add *N*,*N*-dimethylformamide to make exactly 25 mL. Pipet 1 mL of this solution and add *N*,*N*-dimethylformamide to make exactly 50 mL. Confirm that the peak area of ethyl acetate obtained from 2 μL of this solution is equivalent to 0.11% to 0.21%.

System performance: Weigh 1 mL of chloroform and add *N*,*N*-dimethylformamide to make 10 mL. Take 1 mL of this solution and 2 mL of ethyl acetate, and add *N*,*N*-dimethylformamide to make 100 mL. Pipet 2 mL of this solution, add 2 mL of the internal standard solution, and add *N*,*N*-dimethyl formamide to make 10 mL. Proceed with 2 μL of this solution according to the above conditions; ethyl acetate, chloroform and the internal standard are eluted in this order, with the resolution between chloroform and the internal standard being NLT 2.0.

System reproducibility: Repeat the test 3 times with 2 μL each of the standard solution (2) according to the above conditions; the relative standard deviation of the peak area ratio of ethyl acetate to that of the internal standard is NMT 3.0%.

(3) ***Related substances*—**Dissolve 60 mg of Colchicine in 100 mL of diluted methanol (1 in 2). Pipet 1 mL of this solution, add diluted methanol (1 in 2) to make exactly 100 mL, and use this solution as the test solution. Take 20 μL of the test solution and perform the test as directed under the Liquid Chromatography according to the following conditions. Measure each peak area by the automatic integration method, and calculate the sum of peak areas other than colchicine by the percentage peak area method; the sum is NMT 5.0%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: To 450 mL of 0.05 mol/L potassium dihydrogen phosphate TS, add methanol to make

1000 mL. To this solution, add diluted phosphoric acid (7 in 200) and adjust pH to 5.5.

Flow rate: Adjust the flow rate so that the retention time of colchicine is about 7 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the test solution and add diluted methanol (1 in 2) to make exactly 50 mL. Confirm that the peak area of colchicine obtained from 20 mL of this solution is equivalent to 1.4% to 2.6% of the peak area of colchicine obtained from the test solution.

System performance: Proceed with 20 μL of the test solution under the above conditions; the number of theoretical plates and symmetry factor of the peak of colchicine are NLT 6000 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times according to the above conditions with 20 μL each of the test solution; the relative standard deviation of the peak area of colchicine is NMT 2.0%.

Time span of measurement: About 2 times the retention time of colchicine after the solvent peak.

Water NMT 2.0% (0.5 g, volumetric titration, back titration).

Assay Weigh accurately about 0.4 g of Colchicine, dissolve in 25 mL of acetic anhydride and titrate with 0.05 mol/L perchloric acid (potentiometric titration under Titrimetry). Perform a blank test in the same way and make necessary correction.

Each mL of 0.05 mol/L perchloric acid VS
= 19.97 mg of $C_{22}H_{25}NO_6$

Packaging and storage Preserve in light-resistant, tight containers.

Colchicine Tablets
콜키신 정

Colchicine Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of colchicine ($C_{22}H_{25}NO_6$: 399.44).

Method of preparation Prepare as directed under Tablets, with Colchicine.

Identification Weigh an amount of Colchicine Tablets, previously powdered, equivalent to 20 mg of colchicine, mix with 20 mL of water, allow the insoluble matter to settle, filter the clear supernatant, and place the filtrate in a separatory funnel. Extract the filtrate with 30 mL of chloroform, and evaporate the chloroform extracts to dryness. Determine the infrared spectra of this residue and colchicine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Dissolution Perform the test with 1 tablet of Colchicine Tablets at 100 revolutions per minute according to Method 1 under the Dissolution, using 500 mL of water as the dissolution medium. Filter the dissolved solution through a membrane filter with a pore size NMT 0.8 μm 30 minutes after starting the Dissolution, pipet *V* mL of the filtrate, and extract three times with 15 mL each of chloroform. Combine the extracts, evaporate to dryness, dissolve in chloroform to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of colchicine RS, previously dried at 105 ℃ for 3 hours, dissolve in the dissolution medium to make the same concentration with the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using chloroform as a control solution, and determine the ultraviolet absorbance at the absorbance maximum wavelength at about 350 nm.

It meets the requirements if the dissolution rate of Colchicine Tablets in 30 minutes is NLT 75%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Colchicine Tablets, and powder. Weigh accurately about 0.6 mg of colchicine ($C_{22}H_{25}NO_6$), add 50 mL of a mixture of methanol and water (1 : 1), and shake using a shaker for 15 minutes. Add a mixture of methanol and water (1 : 1) to make exactly 100 mL, and filter to use the filtrate as the test solution. (Prepare this solution immediately before use.) Separately, weigh accurately an appropriate amount of colchicine RS, previously dried at 105 °C for 3 hours, add a mixture of methanol and water (1 : 1) to make a solution containing 6 μg per mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of colchicine, in each solution.

Amount (mg) of colchicine ($C_{22}H_{25}NO_6$)
$$= 0.1\times C \times \frac{A_T}{A_S}$$

C: Concentration of the standard solution (μg/mL)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Add water to 45 mL of 0.5 mol/L potassium dihydrogen phosphate solution to make 450 mL. Add 530 mL of methanol to this solution, mix, cool

to room temperature, and add methanol to make 1000 mL. Add 0.5 mol/L phosphoric acid to adjust pH to 5.5 ± 0.05.

Flow rate: 1 mL/min

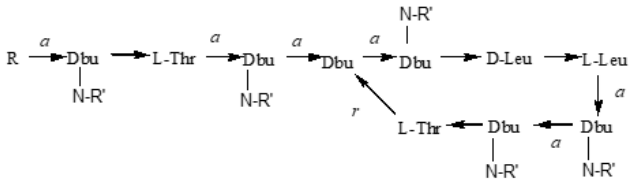
System suitability

System performance: Proceed with 20 µL of the standard solution under the above conditions; the retention time of colchicine is 5.5 to 9.5 minutes and the number of theoretical plates is NLT 4500.

System repeatability: Repeat the test 6 times according to the above conditions with 20 µL each of the standard solution; the relative standard deviation of the peak area is NMT 2.0%.

Packaging and storage Preserve in light-resistant, well-closed containers.

Colistin Sodium Methanesulfonate
콜리스틴메탄설포네이트나트륨



Colistin A: R = 6-methyloctanoic acid
R' = Sodium methanesulfonate
Colistin B: R = Methylheptanoic acid
R' = Sodium methanesulfonate
Dbu : L-α,γ-diaminobutyric acid
Thr : Threonine Leu : Leucine

$C_{58}H_{105}N_{16}Na_5O_{28}S_5$ (Colistin A) : 1749.82
$C_{57}H_{105}N_{16}Na_5O_{28}S_5$ (Colistin B) : 1735.80

Colistin A
Pentasodium [2-[(2*S*,5*R*,8*S*,11*S*,14*S*,17*S*,22*S*)-17-[(1*R*)-1-hydroxyethyl]-22-[[(2*S*)-2-[[(2*S*,3*R*)-3-hydroxy-2-[[(2*S*)-2-[[(6*R*)-6-methyloctanoyl]amino]-4-(sulfonatomethyl-amino)butanoyl]amino]butanoyl]amino]-4-(sulfonatomethylamino)butanoyl]amino]-5,8-*bis*(2-methylpropyl)-3,6,9,12,15,18,23-heptaoxo-11,14-*bis*[2-(sulfonatomethylamino)ethyl]-1,4,7,10,13,16,19-heptazacyclotricos-2-yl]ethylamino]methanesulfonate
Colistin B
Pentasodium [2-[(2*S*,5*R*,8*S*,11*S*,14*S*,17*S*,22*S*)-17-[(1*R*)-1-hydroxyethyl]-22-[[(2*S*)-2-[[(2*S*,3*R*)-3-hydroxy-2-[[(2*S*)-2-(6-methylheptanoylamino)-4-(sulfonatomethylamino)butanoyl]amino]butanoyl]amino]-4-(sulfonatomethyl-amino)butanoyl]amino]-5,8-*bis*(2-methylpropyl)-3,6,9,12,15,18,23-heptaoxo-11,14-*bis*[2-(sulfonatomethylamino)ethyl]-1,4,7,10,13,16,19-heptazacyclotricos-2-yl]ethylamino]methanesulfonate
[*8068-28-8*]

Colistin Sodium Methanesulfonate is a derivative sodium salt of colistin. Colistin Sodium Methanesulfonate is a mixture of colistin A sodium methanesulfonate and colistin B sodium methanesulfonate.

Colistin Sodium Methanesulfonate, when dried, contains NLT 11500 units per mg. However, the potency of Colistin Sodium Methanesulfonate indicates the amount of colistin A (R=6-methyloctanoic acid, R′=H, $C_{53}H_{100}N_{16}O_{13}$: 1169.46) in units.

Description Colistin Sodium Methanesulfonate occurs as a white to pale yellowish white powder. It is freely soluble in water and practically insoluble in ethanol(95).

Identification (1) Dissolve 20 mg of Colistin Sodium Methanesulfonate in 2 mL of water, add 0.5 mL of sodium hydroxide TS, shake to mix, and add 5 drops of copper(II) sulfate TS; the resulting solution exhibits a bluish purple color.

(2) Dissolve 40 mg of Colistin Sodium Methanesulfonate in 1 mL of 1 mol/L hydrochloric acid TS and add 0.5 mL of dilute iodine TS; the color of the iodine solution disappears.

(3) Determine the infrared spectra of Colistin Sodium Methanesulfonate and colistin sodium methanesulfonate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) Colistin Sodium Methanesulfonate responds to the Qualitative Analysis (1) for sodium salt.

pH Dissolve 0.1 g of Colistin Sodium Methanesulfonate in 10 mL of water and allow to stand for 30 minutes; the pH of this solution is between 6.5 and 8.5.

Purity (1) ***Clarity and color of solution***—Dissolve 0.16 g of Colistin Sodium Methanesulfonate in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Colistin Sodium Methanesulfonate according to Method 4 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Colistin Sodium Methanesulfonate according to Method 4 and perform the test (NMT 2 ppm).

(4) ***Free colistin***—Dissolve 80 mg of Colistin Sodium Methanesulfonate in 3 mL of water, add 0.05 mL of silicon dioxide-tungstic acid hydrate (1 in 10) and immediately compare against the reference distillate of the test for pharmaceutical plastic containers; the turbidity of the solution is not more intense than that of the control solution (NMT 0.25%).

Loss on drying NMT 3.0% (0.1 g, in vacuum, 60 ℃, 3 hours).

Sterility It meets the requirements when used in a sterile preparation. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins It is less than 0.67 EU per 10000 units of colistin when used in the manufacturing of sterile preparations.

Assay Cylinder plate method (1) Test bacterium: Use *Escherichia coli* NIHJ or NCCP 14134 as the test bacterium.

(2) Medium: Weigh 10.0 g of peptone, 30.0 g of sodium chloride, 3.0 g of meat extract and 20.0 g of agar, add 1000 mL of water, then add sodium hydroxide TS to adjust pH to 6.5 to 6.6 after sterilization, and sterilize. Use this medium as the agar medium for the seed and base layer.

(3) Weigh accurately an appropriate amount of Dry Colistin Sodium Methanesulfonate, previously dried, dissolve in the phosphate buffer solution (pH 6.0) to obtain a solution containing about 100000 units per mL, and use this solution as the test stock solution. Take exactly an appropriate amount of the test stock solution, add 0.1 mol/L phosphate buffer solution (pH 6.0) to obtain solutions that contain 10000 units and 2500 units per mL, and use these solutions as the high concentration test solution and low concentration test solution, respectively. Separately dry colistin sodium methanesulfonate RS, weigh accurately an accurate amount, and dissolve in phosphate buffer solution (pH 6.0) to obtain a solution that contains 100,000 units per mL. Use this solution as the standard stock solution. Store the standard stock solution below 10 °C and use it within 7 days. For the Assay, pipet an appropriate amount of this standard stock solution and dilute with phosphate buffer solution (pH 6.0) to prepare solutions that contain 10000 units and 2500 units per mL, and use these solutions as the high-concentration standard solution and low-concentration standard solution, respectively. With these solutions, perform the test according to A) (8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in tight containers.

Colistin Sodium Methanesulfonate for Injection
주사용 콜리스틴메탄설포네이트나트륨

Colistin Sodium Methanesulfonate for Injection is a preparation for injection, which is dissolved before use. It contains NLT 90.0% and NMT 120.0% of the labeled amount of colistin.

Method of preparation Prepare as directed under Injections, with Colistin Sodium Methanesulfonate.

Description Colistin Sodium Methanesulfonate for Injection occurs as a white to pale yellowish white powder.

Identification Perform the test as directed under the Identification of Colistin Sodium Methanesulfonate.

pH Dissolve 0.1 g of Colistin Sodium Methanesulfonate in 10 mL of water and allow to stand for 30 minutes; the pH of this solution is between 6.0 and 8.0.

Purity ***Heavy metals***—Proceed with 1.0 g of Colistin Sodium Methanesulfonate for Injection according to Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

Loss on drying NMT 5.0% (0.1 g, 0.7 kPa, 60 ℃, 3 hours).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.67 EU per 10000 units of Colistin Sodium Methanesulfonate for Injection.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay of Colistin Sodium Methanesulfonate. However, weigh accurately an appropriate amount of Colistin Sodium Methanesulfonate for Injection, dilute with 1% phosphate buffer solution (pH 6.0) to prepare a solution containing 100000 units (potency) per mL. Pipet an appropriate amount of this solution, and dilute with 1% phosphate buffer solution (pH 6.0) to contain 10000 and 2500 units per mL, and use these solutions as the high-dose test solution and the low-dose test solution, respectively.

Packaging and storage Preserve in hermetic containers.

Compound Acetaminophen, Cyanocobalamin and Pyridoxine Hydrochloride Tablets
복방아세트아미노펜·시아노코발라민·피리독신염산염 정

Compound Acetaminophen, Cyanocobalamin and Pyridoxine Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of acetaminophen ($C_8H_9NO_2$: 151.16), NLT 90.0% and NMT 150.0% of the labeled amount of cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$: 1355.37), pyridoxine hydrochloride ($C_8H_{11}NO_3 \cdot HCl$: 205.64), and thiamine nitrate ($C_{12}H_{17}N_5O_4S$: 327.36).

Method of preparation Prepare as directed under Tablets, with Acetaminophen, Cyanocobalamin, Pyridoxine Hydrochloride, and Thiamine Nitrate.

Identification The major peaks obtained from the test solution and standard solution under the Assay are the same in the retention time.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Acetaminophen, pyridoxine hydrochloride, and thiamine nitrate—***Weigh accurately the mass of NLT 20 Compound Acetaminophen, Cyanocobalamin and Pyridoxine Hydrochloride Tablets, and powder. Weigh accurately an amount, equivalent to about 250 mg of acetaminophen ($C_8H_9NO_2$) [about 50 mg of pyridoxine hydrochloride ($C_8H_{11}NO_3$·HCl), about 25 mg of thiamine nitrate ($C_{12}H_{17}N_5O_4S$)], add methanol to make exactly 50 mL, sonicate for 20 minutes, and centrifuge for 5 minutes at 1000 rpm. Pipet 1 mL of the supernatant, evaporate to dryness, add water to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of acetaminophen RS, about 10 mg of pyridoxine hydrochloride RS, and 5 mg of thiamine nitrate RS, respectively, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to conditions from (2), and determine the peak areas of acetaminophen, pyridoxine hydrochloride, and thiamine nitrate, A_{T1}, A_{T2}, A_{T3}, A_{S1}, A_{S2}, and A_{S3}, in each solution.

$$\text{Amount (mg) of acetaminophen } (C_8H_9NO_2) = \text{Amount (mg) of acetaminophen RS} \times \frac{A_{T1}}{A_{S1}} \times 5$$

$$\text{Amount (mg) of pyridoxine hydrochloride } (C_8H_{11}NO_3\cdot HCl) = \text{Amount (mg) of pyridoxine hydrochloride RS} \times \frac{A_{T2}}{A_{S2}} \times 5$$

$$\text{Amount (mg) of thiamine nitrate } (C_{12}H_{17}N_5O_4S) = \text{Amount (mg) of thiamine nitrate RS} \times \frac{A_{T3}}{A_{S3}} \times 5$$

(2) ***Cyanocobalamin—***Weigh accurately the mass of NLT 20 Compound Acetaminophen, Cyanocobalamin and Pyridoxine Hydrochloride Tablets, and powder. Weigh accurately an amount, equivalent to about 2 mg of cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$), add methanol to make exactly 20 mL, sonicate for 20 minutes, and centrifuge for 5 minutes at 1000 rpm. Pipet 1 mL of the supernatant, evaporate to dryness, add water to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of cyanocobalamin RS, and add water to make exactly 100 mL. Pipet 1 mL of this solution, add water to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of cyanocobalamin, A_T and A_S, in each solution.

$$\text{Amount (mg) of cyanocobalamin } (C_{63}H_{88}CoN_{14}O_{14}P) = \text{Amount (mg) of cyanocobalamin RS} \times \frac{A_T}{A_S} \times \frac{1}{5}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 275 nm, but 210 nm for cyanocobalamin).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Control the gradient by mixing the mobile phases A and B as directed under the following table.

Mobile phase A: Dissolve 0.25 mL of trifluoroacetic acid in 1000 mL of water, and adjust the pH to 2.6 with ammonium acetate.

Mobile phase B: Methanol

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0.0 - 5.0	100	0
5.0 - 11.0	100 → 75	0 → 25
11.0 - 19.0	75 → 60	25 → 40
19.0 - 19.1	60 → 100	40 → 0
19.1 - 30.0	100	0

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution from (1) according to the above conditions; thiamine nitrate, pyridoxine hydrochloride, and acetaminophen peaks are eluted in this order with the resolution between the thiamine nitrate peak and the pyridoxine hydrochloride peak being NLT 10.0.

System repeatability: Repeat the test 6 times with 20 μL of the standard solutions from (2) according to the above conditions; the relative standard deviation of the peak area of cyanocobalamin is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Compound Acetaminophen, Ethenzamide and Chlorpheniramine Maleate Tablets
복방아세트아미노펜·에텐자미드·클로르페니라민말레산염 정

Compound Acetaminophen, Ethenzamide and Chlorpheniramine Maleate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of acetaminophen ($C_8H_9NO_2$: 151.16), ethenzamide ($C_9H_{11}NO_2$: 165.19), anhydrous caffeine ($C_8H_{10}N_4O_2$: 194.19), and chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$: 390.86).

Method of preparation Prepare as directed under Tablets, with Acetaminophen, Ethenzamide, Anhydrous Caffeine, and Chlorpheniramine Maleate.

Identification (1) The major peaks of the test solution and the standard solution obtained under the Assay are the same in the retention time.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tables of Compound Acetaminophen, Ethenzamide and Chlorpheniramine Maleate Tablets, and powder. Weigh accurately an amount equivalent to about 100 mg of acetaminophen ($C_8H_9NO_2$) [about 50 mg of ethenzamide ($C_9H_{11}NO_2$), about 15 mg of anhydrous caffeine ($C_8H_{10}N_4O_2$), about 1 mg of chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$)], add methanol to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 100 mg of acetaminophen RS, about 50 mg of ethenzamide RS, and about 15 mg of anhydrous caffeine RS, and transfer into the 100-mL volumetric flask. Separately, add about 10 mg of chlorpheniramine maleate RS in methanol to make exactly 10 mL, pipet 1 mL of this solution, transfer into the same 100-mL volumetric flask, add methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of acetaminophen, ethenzamide, anhydrous caffeine, and chlorpheniramine maleate, A_{T1}, A_{T2}, A_{T3}, A_{T4}, A_{S1}, A_{S2}, A_{S3}, and A_{S4}, of each solution.

Amount (mg) of acetaminophen ($C_8H_9NO_2$)
= Amount (mg) of acetaminophen RS $\times \frac{A_{T1}}{A_{S1}}$

Amount (mg) of ethenzamide ($C_9H_{11}NO_2$)
= Amount (mg) of ethenzamide RS $\times \frac{A_{T2}}{A_{S2}}$

Amount (mg) of anhydrous caffeine ($C_8H_{10}N_4O_2$)
= Amount (mg) of anhydrous caffeine RS $\times \frac{A_{T3}}{A_{S3}}$

Amount (mg) of chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$)
= Amount (mg) of chlorpheniramine maleate RS $\times \frac{A_{T4}}{A_{S4}} \times \frac{1}{10}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Use mobile phases A and B to control a stepwise or gradient elution-wise as follows.

Mobile phase A: Dissolve 1.361 g of potassium dihydrogen phosphate in 1000 mL of water, and add phosphoric acid or potassium hydroxide to adjust the pH to 3.0.

Mobile phase B: Methanol

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0.0 - 7.0	90 → 85	10 → 15
7.0 - 15.0	85 → 75	15 → 25
15.0 - 32.0	75 → 50	25 → 50
32.0 - 40.0	50 → 40	50 → 60
40.0 - 40.1	40 → 90	60 → 10
40.1 - 50.0	90	10

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the anhydrous caffeine, acetaminophen, chlorpheniramine maleate, and ethenzamide peaks are eluted in this order with the resolution between the chlorpheniramine maleate peak and the ethenzamide peak being NLT 10.7.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions under the above conditions; the relative standard deviation of the peak area of chlorpheniramine maleate is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Compound Dried Aluminum Hydroxide Gel and Sodium Bicarbonate Tablets
복방건조수산화알루미늄겔·탄산수소나트륨 정

Compound Dried Aluminum Hydroxide Gel and Sodium Bicarbonate Tablets contain NLT 47.0% of aluminum oxide (Al_2O_3: 101.96) for the labeled amount of dried aluminum hydroxide gel, NLT 38.0% and NMT 46.0% of magnesium oxide (MgO: 40.30) for magnesium carbonate, and NLT 90.0% and NMT 110.0% of the labeled amount of sodium bicarbonate ($NaHCO_3$: 84.01) and precipitated calcium carbonate ($CaCO_3$: 100.09).

Method of preparation Prepare as directed under Tablets, with Dried Aluminum Hydroxide Gel, Magnesium Carbonate, Sodium Bicarbonate, and Precipitated Calcium Carbonate.

Identification (1) ***Dried aluminum hydroxide gel***—Weigh 1 g of Compound Dried Aluminum Hydroxide Gel and Sodium Bicarbonate Tablets, previously powdered, and carbonize. After cooling, add 30 mL of dilute hydrochloric acid to the residue, warm on a steam bath for 10 minutes, add water to make 50 mL, and filter. To the filtrate, add 1 drop of methyl orange TS, and slowly add ammonia TS until the color of the solution changes to yellow. A precipitate formed by warming on a steam bath responds to the Qualitative Analysis (1) and (4) for aluminum salt.

(2) ***Magnesium carbonate***—Warm the filtrate from (1) on a steam bath, add 5 mL of saturated ammonium hydroxide TS, and allow to stand on a steam bath for 1 hour to complete the precipitation. Filter when warm, and wash with warm water. Combine the washings with the filtrate. This solution responds to the Qualitative Analysis for magnesium salt.

(3) ***Precipitated calcium carbonate—***A precipitate from (2) responds to the Qualitative Analysis (3) for calcium salt.

(4) ***Sodium bicarbonate***—Weigh 1 g of Compound Dried Aluminum Hydroxide Gel and Sodium Bicarbonate Tablets, previously powdered, add 30 mL of water, dissolve at between 30 and 40 ℃, and filter. The filtrate responds to the Qualitative Analysis for sodium salt and hydrogen carbonate.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Dried aluminum hydroxide gel***—Weigh accurately the mass of NLT 20 Compound Dried Aluminum Hydroxide Gel and Sodium Bicarbonate Tablets, and powder. Weigh accurately an amount equivalent to about 0.5 g of dried aluminum hydroxide gel, and carbonize. After cooling, add 30 mL of dilute hydrochloric acid to the residue, and warm on a steam bath for 10 minutes. After cooling, add water to make 100 mL. Filter and use the filtrate as the test solution. Take 10 mL of the test solution, add 30.0 mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt solution, add 20 mL of pH 4.8 acetic acid-ammonium acetate buffer solution, and then boil for 5 minutes. After cooling, add 55 mL of ethanol, and titrate with 0.05 mol/L zinc acetate VS (indicator: 2 mL of dithizone TS). However, the endpoint of the titration is when the pale dark green color of the solution changes to pale red. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.5490 mg of Al_2O_3

(2) ***Magnesium carbonate***—Take 50.0 mL of the test solution from (1), add 1 drop of methyl orange TS and 2 g of ammonium chloride, and slowly add ammonia TS until the color of the solution changes to yellow. Warm on a steam bath, filter, and wash with water. Combine the filtrate and the washings, warm on a steam bath, add 5 mL of hot saturated ammonium hydroxide TS, and allow to stand on a steam bath for 1 hour to complete the precipitation. Filter when warm, add barium chloride TS to the washings, and wash with warm water until no white precipitate forms (the formed precipitation is used to quantify the precipitated calcium carbonate). To the filtrate and the washings, add 3 mL triethanolamine, 2 mL of potassium cyanide TS (5 in 100), and 10 mL of pH 10.7 ammonia-ammonium chloride buffer solution, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 40 mg of eryochrome black T-sodium chloride indicator). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.0152 mg of MgO

(3) ***Precipitated calcium carbonate—***Dissolve the precipitate from (2) in 50 mL of dilute sulfuric acid, warm at between 60 and 80 ℃, and titrate with 0.1 mol/L potassium permanganate VS. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.02 mol/L potassium permanganate VS
= 5.005 mg of $CaCO_3$

(4) ***Sodium bicarbonate—***Weigh accurately the mass of NLT 20 Compound Dried Aluminum Hydroxide Gel and Sodium Bicarbonate Tablets, and powder. Weigh accurately an amount equivalent to about 0.1 g of sodium bicarbonate, add 50 mL of water, warm at between 35 and 40 ℃, and shake to mix for 10 minutes to dissolve. Filter the solution, wash 3 times each with 20 mL of water. Combine the filtrate and the washings, and titrate with 0.05 mol/L sulfuric acid VS (potentiometric titration

under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L sulfuric acid VS
= 8.401 of $NaHCO_3$

Packaging and storage Preserve in well-closed containers.

Compound Ascorbic Acid, Lysozyme Hydrochloride and Carbazochrome Capsules
복방아스코르브산·리소짐염산염·카르바조크롬 캡슐

Compound Ascorbic Acid, Lysozyme Hydrochloride and Carbazochrome Capsules contain NLT 90.0% and NMT 130.0% of lysozyme hydrochloride, NLT 90.0% and NMT 150.0% of ascorbic acid ($C_6H_8O_6$: 176.12) and tocopherol calcium succinate ($C_{66}H_{106}CaO_{10}$: 1099.62), NLT 90.0% and NMT 110.0% of carbazochrome ($C_{10}H_{12}N_4O_3$: 236.23), respectively, according to the labeled amount.

Method of preparation Prepare as directed under Capsules, with Ascorbic Acid, Lysozyme Hydrochloride, Carbazochrome and Tocopherol Calcium Succinate.

Identification (1) ***Lysozyme hydrochloride*—**Weigh an amount of Compound Ascorbic Acid, Lysozyme Hydrochloride and Carbazochrome Capsules, equivalent to about 50 mg of lysozyme hydrochloride, add 5 mL of 0.4 mol/L sodium chloride solution, shake enough to mix, and then centrifuge. Take the clear supernatant, add 5 mL of acetic acid-sodium acetate buffer solution, pH 5.4, and shake to mix. To 5 mL of this solution, add 1 mL of ninhydrin TS, and then heat; the resulting solution exhibits a reddish purple color.

(2) ***Carbazochrome*—**The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

(3) ***Tocopherol calcium succinate and ascorbic acid*—**Perform the test with Compound Ascorbic Acid, Lysozyme Hydrochloride and Carbazochrome Capsules as directed under the Analysis for Vitamins.

Disintegration Meets the requirements.

Uniformity of dosage units Meet requirements.

Assay (1) ***Ascorbic acid, lysozyme hydrochloride and carbazochrome*—**Weigh accurately the mass of NLT 20 capsules of Compound Ascorbic Acid, Lysozyme Hydrochloride and Carbazochrome Capsules. Weigh accurately an amount of Compound Ascorbic Acid, Lysozyme Hydrochloride and Carbazochrome Capsules, equivalent to about 75 mg of ascorbic acid ($C_6H_8O_6$), about 15 mg of lysozyme hydrochloride and about 1 mg of carbazochrome ($C_{10}H_{12}N_4O_3$), add 0.1% trifluoroacetic acid solution to make exactly 200 mL, sonicate for 30 minutes, and filter through a membrane filter with a pore size of NMT 0.45 μm. Use this solution as the test solution. Separately, weigh accurately about 75 mg of ascorbic acid RS, about 15 mg of lysozyme hydrochloride RS and about 1 mg of carbazochrome RS, add 0.1% trifluoroacetic acid solution to make exactly 200 mL, sonicate for 30 minutes, and filter through a membrane filter with a pore size of NMT 0.45 μm. Use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_{T1}, A_{T2}, A_{T3}, A_{S1}, A_{S2}, and A_{S3}, of ascorbic acid, lysozyme hydrochloride and carbazochrome in each solution.

$$\text{Amount (mg) of ascorbic acid } (C_6H_8O_6) = \text{Amount (mg) of ascorbic acid RS} \times \frac{A_{T1}}{A_{S1}}$$

$$\text{Amount (mg) of lysozyme hydrochloride} = \text{Amount (mg) of lysozyme hydrochloride RS} \times \frac{A_{T2}}{A_{S2}}$$

$$\text{Amount (mg) of carbazochrome } (C_{10}H_{12}N_4O_3) = \text{Amount (mg) of carbazochrome RS} \times \frac{A_{T3}}{A_{S3}}$$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: 0.1% trifluoroacetic acid solution

Mobile phase B: To 1000 mL of acetonitrile, add 1 mL of trifluoroacetic acid.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0.0	100	0
0.0 - 2.0	100 → 95	0→ 5
2.0 - 7.0	95 → 50	5 → 50
7.0 - 15.0	50	50

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 10 μL of the

standard solution according to the above conditions; ascorbic acid, carbazochrome and lysozyme hydrochloride are eluted in this order with the resolution between the carbazochrome peak and the lysozyme hydrochloride peak being NLT 8.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of ascorbic acid, carbazochrome and lysozyme hydrochloride is NMT 1.0%

(2) ***Tocopherol calcium succinate*—**Weigh accurately the mass of NLT 20 capsules of Compound Ascorbic Acid, Lysozyme Hydrochloride and Carbazochrome Capsules. Weigh accurately an amount of Compound Ascorbic Acid, Lysozyme Hydrochloride and Carbazochrome Capsules, equivalent to about 17 mg of tocopherol calcium succinate ($C_{66}H_{106}CaO_{10}$), add a mixture of anhydrous ethanol and diluted acetic acid(100) (1 in 5) (9 : 1) to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately an amount equivalent to about 17 mg of tocopherol calcium succinate RS, add a mixture of anhydrous ethanol and diluted acetic acid(100) (1 in 5) (9 : 1) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of tocopherol succinate in each solution.

Amount (mg) tocopherol calcium succinate ($C_{66}H_{106}CaO_{10}$)
= Amount (mg) of tocopherol calcium succinate RS
$\times \frac{A_T}{A_S} \times 1.0358$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 284 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: Room temperature

Mobile phase: A mixture of methanol, water and acetic acid(100) (97 : 2 : 1).

Flow rate: Adjust the flow rate so that the retention time of tocopherol succinate is about 8 minutes.

System suitability

System performance: Weigh 17 mg each of tocopherol calcium succinate and tocopherol, and dissolve in a mixture of anhydrous ethanol and diluted acetic acid(100) (1 in 5) (9 : 1) to make 50 mL. Proceed with 20 μL of this solution under the above operating conditions; tocopherol succinate and tocopherol are eluted in this order with the resolution being 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of tocopherol succinate is NMT 0.8%.

Packaging and storage Preserve in tight containers.

Compound Berberine Tannate, Bismuth Subnitrate and Ursodeoxycholic Acid Capsules
복방베르베린탄닌산염·비스무트차질산염·우르소데옥시콜산 캡슐

Compound Berberine Tannate, Bismuth Subnitrate and Ursodeoxycholic Acid Capsules contain NLT 90.0% and NMT 110.0% of the labeled amounts of berberine ($C_{20}H_{19}NO_5$: 357.37) in berberine tannate, bismuth (Bi : 208.98) in bismuth subnitrate and ursodeoxycholic acid ($C_{24}H_{40}O_4$: 392.57), and NLT 90.0% and NMT 130.0% of the labeled amounts of scopolia extract acid (total alkaloid [hyoscyamine ($C_{17}H_{23}NO_3$: 289.37) and scopolamine ($C_{17}H_{21}NO_4$: 303.35)]).

Method of preparation Prepare as directed under Capsules, with Berberine Tannate, Bismuth Subnitrate, Ursodeoxycholic Acid, and Scopolia Extract Acid.

Identification (1) ***Berberine tannate***—The retention time of major peak of the test solution correspond to that of the standard solution, as obtained in the Assay.

(2) ***Bismuth subnitrate***—Compound Berberine Tannate, Bismuth Subnitrate and Ursodeoxycholic Acid Capsules respond to the Qualitative Analysis for bismuth salt and nitrate.

(3) ***Ursodeoxycholic acid***—The retention time of major peak of the test solution correspond to that of the standard solution, as obtained in the Assay.

(4) ***Scopolia extract acid*—**(i) Put 2.0 g of the contents of Compound Berberine Tannate, Bismuth Subnitrate and Ursodeoxycholic Acid Capsules in a stoppered centrifuge tube, add 30 mL of ammonia TS, sonicate for 5 minutes, and centrifuge the filtrate. Put the clear supernatant in a separatory funnel, add 40 mL of ethyl acetate, shake and mix, and take the ethyl acetate layer separately. Add 3 g of anhydrous sodium sulfate, shake to mix, and filter after the ethyl acetate layer becomes clear. Evaporate ethyl acetate in vacuum, dissolve the residue in 1 mL of ethanol, and use this solution as the test solution. Separately, dissolve 2 mg of atropine sulfate hydrate RS and 1 mg of scopolamine hydrobromide hydrate RS each in 1 mL of ethanol, and use these solutions as the standard solution (1) and the standard solution (2), respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of acetone, water and

strong ammonia water (90 : 7 : 3) as the developing solvent to a distance of about 10 cm, and dry the plate at 80 ºC for 10 minutes. After cooling, spray evenly Dragendorff's TS for spray on the plate the Rf values and colors of the two principal spots of the test solution correspond to those of the standard solution.

(ii) The retention time of major peak of the test solution correspond to that of the standard solution, as obtained in the Assay.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Berberine***—Weigh accurately the contents of NLT 20 capsules of Compound Berberine Tannate, Bismuth Subnitrate and Ursodeoxycholic Acid Capsules. Weigh accurately an amount equivalent to about 50 mg of berberine ($C_{20}H_{19}NO_5$), add 2 mL of 1 mol/L hydrochloric acid and 50 mL of methanol, and sonicate to extract for 30 minutes to make 100 mL. Filter to take 2 mL of the filtrate, add methanol to make 50 mL, and use this solution as the test solution. Separately, weigh accurately 50 mg of berberine chloride hydrate RS (measure the water in advance), dissolve in 2 mL of 1 mol/L hydrochloric acid, and add methanol to make 100 mL. Pipet 2 mL of this solution, add methanol to make 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of berberine in each solution.

Amount (mg) of berberine ($C_{20}H_{19}NO_5$)
= Amount (mg) of berberine chloride RS, calculated on the anhydrous basis$\times \frac{A_T}{A_S} \times 0.9504$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of 0.01 mol/L phosphoric acid and acetonitrile (620 : 380).

Flow rate: 1.3 mL/min

(2) ***Bismuth subnitrate***—Weigh accurately the contents of NLT 20 capsules of Compound Berberine Tannate, Bismuth Subnitrate and Ursodeoxycholic Acid Capsules. Weigh accurately the amount equivalent to about 0.2 g of bismuth subnitrate, add 25 mL of nitric acid (2 in 5), warm and shake to dissolve, and add water to make 100 mL. Pipet 50 mL of this solution, add 200 mL of water, and titrate with 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 1 mL of xylenol orange TS). However, the endpoint of the titration when the color of the solution changes from reddish purple to yellow. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 4.180 mg of Bi

(3) ***Ursodeoxycholic acid***—Weigh accurately the contents of NLT 20 capsules of Compound Berberine Tannate, Bismuth Subnitrate and Ursodeoxycholic Acid Capsules. Weigh accurately an amount equivalent to about 10 mg of ursodeoxycholic acid ($C_{24}H_{40}O_4$), add methanol, sonicate to extract for 30 minutes and make 50 mL, and use the filtrate as the test solution. Separately, weigh accurately about 10 mg of ursodeoxycholic acid RS, add methanol to make 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of ursodeoxycholic acid in each solution.

Amount (mg) of ursodeoxycholic acid ($C_{24}H_{40}O_4$)
= Amount (mg) of ursodeoxycholic acid RS$\times \frac{A_T}{A_S}$

Operating conditions

Detector: A differential refractometer

Column: A stainless steel column about 3.9 mm in internal diameter and about 150 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μ*m* to 10 μm in particle diameter).

Mobile phase: A mixture of water, acetonitrile and acetic acid (60 : 40 : 1).

Flow rate: 1.0 mL/min

(4) ***Scopolia extract acid***—Weigh accurately the mass of contents of NLT 20 capsules of Compound Berberine Tannate, Bismuth Subnitrate and Ursodeoxycholic Acid Capsules. Weigh accurately an amount equivalent to about 0.1 g of scopolia extract acid, put in a glass-stoppered centrifuge tube, add 15 mL of ammonia TS, and shake to mix. To the mixture, add 25 mL of ether, stopper, shake for 15 minutes, and take the ether layer separately. Repeat this procedure 3 times for the water layer with 25 mL of ether. Combine all the extracts and evaporate ether on a steam bath. Dissolve the residue in the mobile phase to make 25 mL, and use this solution as the test solution. Separately, weigh accurately 25 mg of hiyoscyamine RS and 25 mg of scopolamine hydrobromide hydrate RS, add the mobile phase to make 25 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions to calculate the peak areas A_{T1} $A_{T2,}$ A_{S1} and A_{S2} for hiyoscyamine and scopolamine hydrobromide in each solution.

Amount (mg) of hiyoscyamine ($C_{17}H_{23}NO_3$)
= Amount (mg) of hiyoscyamine RS× $\frac{A_{T1}}{A_{S1}} \times \frac{1}{5}$

Amount (mg) of scopolamine ($C_{17}H_{21}NO_4$)
= Amount (mg) of scopolamine hydrobromide hydrate RS× $\frac{A_{T2}}{A_{S2}} \times \frac{1}{5} \times 0.789$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 150 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μ*m* to 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and a solution prepared by dissolving 6.8 g of potassium dihydrogen phosphate in 900 mL of water, adding 10 mL of triethylamine, adjusting the pH to 3.5 with phosphoric acid, and adding water to make 1000 mL (9 : 1).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in well-closed containers.

Compound Bilberry Fruit Dried Extract, Aceglutamide and DL-Phosphoserine Capsules
복방빌베리건조엑스·아세글루타미드·DL-포스포세린 캡슐

Compound Bilberry Fruit Dried Extract, Aceglutamide and DL-Phosphoserine Capsules contain NLT 90.0% of the labeled amount of total anthocyanosides in bilberry fruit dried extract and NLT 90.0% and NMT 130.0% of the labeled amounts of aceglutamid ($C_7H_{12}N_2O_4$: 188.18), cobamamide ($C_{72}H_{100}CoN_{18}O_{17}P$: 1579.58) and Dl-phosphoserine ($C_3H_8NO_6P$: 185.07).

Method of preparation Prepare as directed under Capsules, with Bilberry Fruit Dried Extract, Aceglutamid, Cobamamide and DL-Phosphoserine.

Identification (1) ***Bilberry fruit dried extract***—Weigh an amount of Compound Bilberry Fruit Dried Extract, Aceglutamide and DL-Phosphoserine Capsules equivalent to about 0.1 g of bilberry fruit dried extract according to the labeled amount, add 25 mL of a mixture of methanol, hydrochloric acid, and water (80 : 15 : 5), heat on a steam bath for 3 hours with a reflux condenser, and centrifuge. Warm on a steam bath to evaporate the clear supernatant, dissolve the residue in 5 mL of anhydrous ethanol, and use this solution as the test solution. Separately, weigh about 0.1 g of Bilberry Fruit Dried Extract, proceed in the same manner with the test solution, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of cellulose MN_{300}. Develop the plate with a mixture of water, acetic acid(100) and hydrochloric acid (82 : 15 : 3) as the developing solvent, and air-dry the plate. Develop the plate again with 60% acetic acid as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 365 nm); the colors and R_f values of the several spots obtained from the test solution and the spots from the standard solution are the same.

(2) ***Aceglutamide***—Dissolve 1 capsule of Compound Bilberry Fruit Dried Extract, Aceglutamide and DL-Phosphoserine Capsule in water to make 100 mL to filter, and use the filtrate as the test solution. Separately, weigh about 10 mg of aceglutamide RS in 10 mL of water, and use the solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of cellulose MN_{300}. Develop the plate with the mixture of 1-butanol, acetone, water and diethylamine (45 : 45 : 22.5 : 9) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly 0.2% ninhydrin-ethanol solution evenly on the plate; the R_f values and colors of the spots obtained from the test solution and the standard solution are the same.

(3) ***Cobamamide***—Dissolve the contents of 1 capsule of Compound Bilberry Fruit Dried Extract, Aceglutamide and DL-Phosphoserine Capsule in 2 mL of water to centrifuge, and use the clear supernatant as the test solution. Separately, add cobamamide RS to water to contain 500 μg per mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of 0.07 mol/L potassium dihydrogen phosphate solution, 1-butanol, acetic acid(100), and methanol (36 : 36 : 18 : 10) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light; the R_f values and colors of the spots from the test solution and the standard solution are the same.

(4) ***DL-phosphoserine***—Dissolve the contents of 1 Compound Bilberry Fruit Dried Extract, Aceglutamide and DL-Phosphoserine Capsule in 50 mL of water to filter, and use the filtrate as the test solution. Separately, weigh about 50 mg of DL-phosphoserine RS, dissolve in 50 mL of water, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of 1-propanol and strong ammonia water (7 : 3) as a developing solvent to a distance of

about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light; the R_f values and colors of the spots from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Total anthocyanosides in bilberry fruit dried extract***—Weigh accurately the contents of NLT 20 capsules of Compound Bilberry Fruit Dried Extract, Aceglutamide and DL-Phosphoserine Capsules. Weigh accurately an amount of Compound Bilberry Fruit Dried Extract, Aceglutamide and DL-Phosphoserine Capsules equivalent to about 20 mg of bilberry fruit dried extract according to the labeled amount, and dissolve in a mixture of anhydrous ethanol and 1.5 mol/L hydrochloric acid (17 : 3) to make 200 mL. Take 5 mL of this solution, add a mixture of anhydrous ethanol and 1.5 mol/L hydrochloric acid (17 : 3) to make 50 mL, and filter. Discard about 20 mL of the first filtrate, and use the next filtrate as the test solution. Separately, weigh accurately about 20 mg of bilberry fruit dried extract with a known content of anthocyanidin, proceed in the same manner with the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 541 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of total anthocyanosides in bilberry fruit dried extract
= Amount (mg) of anthocyanidin RS$\times \frac{A_T}{A_S} \times 1.475$

(2) ***Cobamamide***—Weigh accurately the contents of NLT 20 capsules of Compound Bilberry Fruit Dried Extract, Aceglutamide and DL-Phosphoserine Capsules. Weigh accurately the amount of Compound Bilberry Fruit Dried Extract, Aceglutamide and DL-Phosphoserine Capsules equivalent to about 5 mg of cobamamide ($C_{72}H_{100}CoN_{18}O_{17}P$) according to the labeled amount, add water to make 50 mL, and filter. Then, put 10 mL of the filtrate in an ion exchange resin column, and elute it. Wash the column with 100 mL of water and 1 mol/L hydrochloric acid until no absorbance is detected at 240 to 370 nm, then add a mixture of 1 mol/L hydrochloric acid, water, and tetrahydrofuran (60 : 30 : 10) to the column, and elute it. The red band of cobamamide reaches the bottom of the column; connect a 50-mL volumetric flask to the outlet to receive the dissolved solution. Elute until the effluent exhibits no red color, then evaporate the tetrahydrofuran by heating on a steam bath, add water to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of cobamamide RS, and dissolve in water to make 100 mL. Take 10.0 mL of this solution, add water to make 50 mL, and take 10 mL of this solution to place in an ion exchange resin column. Proceed in the same manner with the test solution below, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 525 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of cobamamide ($C_{72}H_{100}CoN_{18}O_{17}P$)
= Amount (mg) of cobamamide RS$\times \frac{A_T}{A_S} \times \frac{1}{10}$

(3) ***Aceglutamid and DL-Phosphoserine—***Weigh accurately the contents of NLT 20 capsules of Compound Bilberry Fruit Dried Extract, Aceglutamide and DL-Phosphoserine Capsules, and perform the test as directed under the Identification and Assay for Amino Acids.

Packaging and storage Preserve in well-closed containers.

Compound Bilberry Fruit Dried Extract 3.0%, Riboflavin Sodium Phosphate and Retinol Palmitate Capsules
복방빌베리건조엑스3.0%·리보플라빈포스페이트나트륨·레티놀팔미테이트 캡슐

Compound Bilberry Fruit Dried Extract 3.0%, Riboflavin Sodium Phosphate and Retinol Palmitate Capsules contain NLT 90.0% and NMT 150.0% of the labeled amount of retinol palmitate ($C_{36}H_{60}O_2$: 524.86), NLT 90.0% and NMT 130.0% of the labeled amount of riboflavin sodium phosphate ($C_{17}H_{20}N_4NaO_9P$: 478.33), NLT 90.0% of bilberry fruit dried extract 3.0% and total anthocyanosides in bilberry fruit dried powder.

Method of preparation Prepare as directed under Capsules, with Bilberry Fruit Dried Extract 3.0%, Bilberry Fruit Dried powder, Riboflavin Sodium Phosphate and Retinol Palmitate.

Identification (1) ***Retinol palmitate and riboflavin sodium phosphate***—Perform the test under the Analysis for Vitamins.

(2) ***Bilberry fruit dried powder and bilberry fruit dried extract 3.0%***—Wash the contents of 5 capsules of Compound Bilberry Fruit Dried Extract 3.0%, Riboflavin Sodium Phosphate and Retinol Palmitate Capsules twice with 20 mL each of chloroform, then add the residue to 25 mL of a mixture of methanol, hydrochloric acid, and water (80 : 15 : 5), heat for 1 hour in a reflux condenser, and filter. Evaporate the filtrate to dryness on a steam bath, dissolve the residue in 5 mL of anhydrous ethanol, and warm it slightly. Use the filtrate as the test solution if necessary. Separately, weigh 0.1 g of Bilberry Fruit Dried Extract 3.0% and 0.2 g of Bilberry Fruit Dried Powder, proceed in the same manner as in the test solution, and

use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of cellulose Mn_{300} with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of water, acetic acid(100) and hydrochloric acid (82 : 15 : 3) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Develop the plate again with 60% acetic acid as the secondary developing solvent to a distance of about 10 cm, and air-dry the plate; the colors and R_f values of the several spots obtained from the test solution and the spots from the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Retinol palmitate and riboflavin sodium phosphate—***Weigh accurately the contents of NLT 20 capsules of Compound Bilberry Fruit Dried Extract 3.0%, Riboflavin Sodium Phosphate and Retinol Palmitate Capsules, and perform the test as directed under the Analysis for Vitamins.

(2) ***Bilberry fruit dried extract 3.0% and total anthocyanosides in bilberry fruit dried powder—***Weigh accurately The mass of content of NLT 20 capsules of Compound Bilberry Fruit Dried Extract 3.0%, Riboflavin Sodium Phosphate and Retinol Palmitate Capsules. Weigh accurately an amount equivalent to about 20 mg of anthocyanosides, add a mixture of anhydrous ethanol and 1.5 mol/L hydrochloric acid (17 : 3) to make 50 mL, and shake to mix. Then, filter, discard the first 20 mL, and use the filtrate as the test solution. Separately, weigh accurately Bilberry Fruit Dried Extract 3.0% equivalent to about 20 mg of anthocyanosides, and add a mixture of anhydrous ethanol and 1.5 mol/L hydrochloric acid (17 : 3) to make 200 mL. Take 5 mL of this solution, add a mixture of anhydrous ethanol and 1.5 mol/L hydrochloric acid (17 : 3) to make 50 mL, and use this solution as the standard solution. Determine the absorbances, A_S and A_T, of the test solution and the standard solution, respectively, at the wavelength of 535 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of anthocyanosides} = \text{Amount (mg) of anthocyanosides RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in well-closed containers.

Compound DL-Carnitine Hydrochloride, Cyanocobalamin and L-Lysine Hydrochloride Tablets

복방DL-카르니틴염산염·시아노코발라민·L-리신염산염 정

Compound DL-Carnitine Hydrochloride, Cyanocobalamin and L-Lysine Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of cyproheptadine orotate hydrate ($C_{26}H_{25}N_3O_4 \cdot H_2O$: 461.51), NLT 90.0% and NMT 130.0% of L-lysine hydrochloride ($C_6H_{14}N_2O_2 \cdot HCl$: 182.65), and NLT 90.0% and NMT 150.0% of cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$: 1355.37) and DL-carnitine hydrochloride ($C_7H_{16}NO_3Cl$: 197.66).

Method of preparation Prepare as directed under Tablets, with DL-Carnitine Hydrochloride, Cyanocobalamin, L-Lysine Hydrochloride, and Cyproheptadine Orotate Hydrate.

Identification (1) ***Cyproheptadine orotate hydrate—***Weigh an amount of Compound DL-Carnitine Hydrochloride, Cyanocobalamin and L-Lysine Hydrochloride Tablets equivalent to 25 mg of cyproheptadine orotate hydrate according to the labeled amount, add 25 mL of ethyl acetate, shake to dissolve, filter, and use the filtrate as the test solution. Separately, dissolve 10 mg of cyproheptadine orotate hydrate RS in 10 mL of ethyl acetate and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, diethylamine, and cyclohexane (18 : 1 : 1) as the developing solvent, and air-dry the plate with hot air. Examine the plate under ultraviolet light; the R_f values of the spots obtained from the test solution and the standard solution are the same.

(2) ***L-Lysine hydrochloride—***Weigh an amount of Compound DL-Carnitine Hydrochloride, Cyanocobalamin and L-Lysine Hydrochloride Tablets equivalent to 100 mg of L-lysine hydrochloride according to the labeled amount, dissolve in 10 mL of water, filter, and use the filtrate as the test solution. Separately, use 1% aqueous solution of L-lysine hydrochloride RS as the standard solution. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of 1-propanol and strong ammonia water (60 : 30) as the developing solvent, and air-dry the plate with hot air. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values of the spots obtained from

the test solution and the standard solution are the same.

(3) ***Cyanocobalamin, DL-carnitine hydrochloride***—With Compound DL-Carnitine Hydrochloride, Cyanocobalamin and L-Lysine Hydrochloride Tablets, perform the test as directed under the Analysis for Vitamins.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Cyproheptadine orotate hydrate*—**Weigh accurately the mass of NLT 20 tablets of Compound DL-Carnitine Hydrochloride, Cyanocobalamin and L-Lysine Hydrochloride Tablets, and powder. Weigh accurately an amount equivalent to 1.5 mg of cyproheptadine orotate hydrate ($C_{26}H_{25}N_3O_4 \cdot H_2O$), transfer into a separatory funnel, add 5 mL of water, and extract with chloroform, previously warmed, repeat the extraction until total volume of chloroform reaches 80 mL. To the filtrate, add chloroform to make 100 mL. Filter if necessary, discard the first 20 mL of the filtrate, take 10 mL of the subsequent filtrate, and transfer into a separatory funnel. Add 20 mL of chloroform, 10 mL of pH 5.4 phosphate buffer solution, and 5 mL of 0.05% bromocresol green TS, and extract by shaking to mix vigorously. Next, take chloroform filtrate in another separatory funnel, wash the water layer with 15 mL of chloroform, combine the washings with chloroform filtrate, and add 50 mL of 0.1 mol/L sodium hydroxide TS. Shake to mix, take the water layer, and use this solution as the test solution. Separately, weigh accurately about 15 mg of cyproheptadine orotate hydrate RS, make the same concentration as the test solution, proceed in the same manner as the test solution, and use this solution as the standard solution. Perform the test using the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, and measure the absorbances, A_T and A_S, at a wavelength of 615 nm.

$$\text{Amount (mg) of cyproheptadine orotate hydrate } (C_{26}H_{25}N_3O_4 \cdot H_2O) = \text{Amount (mg) of cyproheptadine orotate hydrate RS} \times \frac{A_T}{A_S} \times \frac{1}{10}$$

(2) ***L-l-lysine hydrochloride*—**Weigh accurately the mass of NLT 20 tablets of Compound DL-Carnitine Hydrochloride, Cyanocobalamin and L-Lysine Hydrochloride Tablets, and powder. Weigh accurately an amount equivalent to 0.2 g of L-lysine hydrochloride, and add pH 2.2 buffer solution for dilution to make 100 mL. Filter this solution, discard the initial 20 mL of the filtrate, take 5 mL of the subsequent filtrate, add pH 2.2 buffer solution for dilution to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.2 g of L-lysine hydrochloride RS, and add pH 2.2 buffer solution for dilution to make 100 mL. Take 5 mL of this solution, proceed in the same manner as the test solution, use this solution as the standard solution, and perform the test as directed under the Identification and Assay for Amino Acids.

$$\text{Amount (mg) of L-lysine hydrochloride } (C_6H_{14}N_2O_2 \cdot HCl) = \frac{H \times W}{C} \times M \times dilution\ factor \times \frac{1}{10^3}$$

H: Peak height of the test solution
W: Peak full width at half maximum of the test solution
C: H·W coefficient
M: Radius

(3) ***Cyanocobalamin and DL-carnitine hydrochloride*—**Weigh accurately the mass of NLT 20 Compound DL-Carnitine Hydrochloride, Cyanocobalamin and L-Lysine Hydrochloride Tablets, powder, and perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in well-closed containers.

Compound β-Carotene Suspension 30%, Ascorbic Acid and Selenium in Dried Yeast Capsules
복방β-카로틴현탁액30%·아스코르브산·셀레늄함유건조효모 캡슐

Compound β-Carotene Suspension 30%, Ascorbic Acid and Selenium in Dried Yeast Capsules contain NLT 90.0% and NMT 150.0% of the labeled amounts of *β*-carotene ($C_{40}H_{56}$: 536.87), selenium in dried yeast (Se : 78.96), ascorbic acid ($C_6H_8O_6$: 176.12) and tocopherol ($C_{29}H_{50}O_2$: 430.71).

Method of preparation Prepare as directed under Capsules, with selenium in dried yeast, *β*-Carotene Suspension 30%, Ascorbic Acid and Tocopherol.

Identification (1) ***Selenium in dried yeast***—Perform the test as directed under the Analysis for Minerals.

(2) ***β-carotene, ascorbic acid and tocopherol***—Perform the test as directed under the Analysis for Vitamins.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Selenium*—**Weigh accurately the contents of NLT 20 capsules of Compound β-Carotene Suspension 30%, Ascorbic Acid and Selenium in Dried Yeast Cap-

sules and perform the test as directed under the Analysis for Minerals.

(2) ***β-Carotene, ascorbic acid and tocopherol—*** Weigh accurately the contents with NLT 20 capsules of Compound β-Carotene Suspension 30%, Ascorbic Acid and Selenium in Dried Yeast Capsules and perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in well-closed containers.

Compound Cyanocobalamin, Taurine and Ergocalciferol Tablets
복방시아노코발라민·타우린·에르고칼시페롤 정

Compound Cyanocobalamin, Taurine and Ergocalciferol Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of total calcium (Ca: 40.08), NLT 90.0% and NMT 130.0% of taurine ($C_2H_7NO_3S$: 125.15), L-lysine hydrochloride ($C_6H_{14}N_2O_2$ ·HCl: 182.65), NLT 90.0% and NMT 150.0% of the thiamine nitrate ($C_{12}H_{17}N_5O_4S$: 327.36), pyridoxine hydrochloride ($C_8H_{11}NO_3$·HCl: 205.64), ergocalciferol ($C_{28}H_{44}O$: 396.65), and cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$: 1355.37).

Method of preparation Prepare as directed under Tablets, with Cyanocobalamin, Taurine, Ergocalciferol, L-Lysine Hydrochloride, Pyridoxine Hydrochloride, Dibasic Calcium Phosphate Hydrate, Calcium Lactate Hydrate, and Thiamine Nitrate.

Identification (1) ***Cyanocobalamin, ergocalciferol, pyridoxine hydrochloride, and thiamine nitrate—***Perform the test with Compound Cyanocobalamin, Taurine and Ergocalciferol Tablets as directed under the Analysis for Vitamins.

(2) ***Taurine, L-lysine hydrochloride—***Perform the test with Compound Cyanocobalamin, Taurine and Ergocalciferol Tablets as directed under the Identification and Assay for Amino Acids.

(3) ***Dibasic calcium phosphate hydrate and calcium lactate hydrate—***Perform the test with Compound Cyanocobalamin, Taurine and Ergocalciferol Tablets as directed under the Analysis for Minerals.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Total calcium—***Weigh accurately the mass of NLT 20 Compound Cyanocobalamin, Taurine and Ergocalciferol Tablets, and powder. Weigh accurately an amount equivalent to about 0.1 g of calcium (Ca), and perform the test as directed under the Analysis for Minerals.

(2) ***Taurine, L-lysine hydrochloride—***Weigh accurately the mass of NLT 20 Compound Cyanocobalamin, Taurine and Ergocalciferol Tablets, powder, and perform the test as directed under the Identification and Assay for Amino Acids.

(3) ***Cyanocobalamin, ergocalciferol, pyridoxine hydrochloride, and thiamine nitrate—***Weigh accurately the mass of NLT 20 Compound Cyanocobalamin, Taurine and Ergocalciferol Tablets, powder, and perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in tight containers.

Compound Cyproheptadine Orotate, L-Lysine Hydrochloride and DL-Carnitine Hydrochloride Capsules
복방시프로헵타딘오로트산염·L-리신염산염·DL-카르니틴염산염 캡슐

Compound Cyproheptadine Orotate, L-Lysine Hydrochloride and DL-Carnitine Hydrochloride Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of cyproheptadine orotate ($C_{26}H_{25}N_3O_4$: 443.50), NLT 90.0% and NMT 130.0% of the labeled amounts of L-lysine hydrochloride ($C_6H_{14}N_2O_2$·HCl : 182.65) and cobamamide ($C_{72}H_{100}CoN_{18}O_{17}P$: 1579.58), and NLT 90.0% and NMT 150.0% of the labeled amount of DL-carnitine hydrochloride ($C_7H_{16}O_3NCl$: 197.66).

Method of preparation Prepare as directed under Capsules, with Cyproheptadine Orotate, L-Lysine Hydrochloride, DL-Carnitine Hydrochloride and Cobamamide.

Identification (1) ***Cyproheptadine orotate hydrate***—Weigh the contents of 1 capsule of Compound Cyproheptadine Orotate, L-Lysine Hydrochloride and DL-Carnitine Hydrochloride Capsule, shake, dissolve in 10 mL of methanol, and filter. Use the filtrate as the test solution. Separately, use a 0.015% solution of cyproheptadine orotate RS in methanol as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform and acetone (100 : 1.5) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light; the Rf value and color of the major spot of the test solution correspond to those of the standard solution.

(2) ***L-lysine hydrochloride***—Perform the test with L-Aspartate-L-Arginine Hydrate as directed under the Identification and Assay for Amino Acids.

(3) ***DL-carnitine hydrochloride***—Perform the test with Compound Cyproheptadine Orotate, L-Lysine Hy-

drochloride and DL-Carnitine Hydrochloride Capsules as directed under the Analysis for Vitamins.

(4) ***Aceglutamide***—Dissolve the contents of 5 capsules of Compound Bilberry Fruit Dried Extract, Aceglutamide and DL-Phosphoserine Capsule in water to make 5 mL, and filter. Use the filtrate as the test solution. Separately, use 0.1% acetic acid(100) of cobamamide RS as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography or alumina. Next, develop the plate with a mixture of benzene, methanol, acetic acid(100) and acetone (70 : 20 : 5 : 5) as the developing solvent to a distance of about 10 cm, air-dry the plate, and observe it with the naked eye; the Rf value and color of the major spot of the test solution correspond to those of the standard solution.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Cyproheptadine orotate*—**Weigh accurately the mass of content of NLT 20 capsules of Compound Cyproheptadine Orotate, L-Lysine Hydrochloride and DL-Carnitine Hydrochloride Capsules. Weigh accurately an amount equivalent to about 1.5 mg of cyproheptadine orotate ($C_{26}H_{25}N_3O_4$) and transfer to a separatory funnel. Add 5 mL of water, extract several times with 80 mL of warmed chloroform, and add chloroform to make 100 mL. If necessary, filter to discard the first 20 mL of the filtrate, take 10.0 mL of the next filtrate, transfer it to a separatory funnel, and add 20 mL of chloroform, 10 mL of phosphate buffer solution, pH 5.4, and 5 mL of 0.05% bromocresol green TS. Shake vigorously to mix, and pour the chloroform extract into another funnel. Transfer it in a separatory funnel, wash the water layer with 15 mL of chloroform, and combine the washed solution with the chloroform extract. Add 50 mL of 0.1 mol/L sodium hydroxide solution, shake to mix, take the water layer, and use this solution as the test solution. Separately, weigh accurately about 15 mg of cyproheptadine orotate RS to make the same concentration as the test solution, proceed in the same manner as in the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 615 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of cyproheptadine orotate } (C_{26}H_{25}N_3O_4) = \text{Amount (mg) of cyproheptadine orotate RS} \times \frac{A_T}{A_S} \times \frac{1}{10}$$

(2) ***L-lysine hydrochloride*—**Weigh accurately the contents of NLT 20 capsules of Compound Cyproheptadine Orotate, L-Lysine Hydrochloride and DL-Carnitine Hydrochloride Capsules, and perform the test as directed under the Identification and Assay for Amino Acids.

(3) ***DL-carnitine hydrochloride*—**Weigh accurately the contents of NLT 20 capsules of Compound Cyproheptadine Orotate, L-Lysine Hydrochloride and DL-Carnitine Hydrochloride Capsules, and perform the test as directed under the Analysis for Vitamins.

(4) ***Cobamamide*—**Proceed quickly all the operations under the light-resistant condition. Weigh accurately the mass of NLT 20 xxx Capsules, take out all of the content, and weigh accurately the mass of the empty capsules. Weigh accurately about 2 mg of cobamamide ($C_{72}H_{100}O_{17}N_{18}PCo$), transfer to a separatory funnel, add about 50 to 70 mL of ether to mix thoroughly, and extract 3 times sequentially by adding 20, 15, and 10 mL of hydrochloric acid-potassium chloride buffer solution, pH 2.0. Combine all extracts to place in a 50-mL volumetric flask, add hydrochloric acid-potassium chloride buffer solution, pH 2.0, and fill to the mark. Filter this solution, discard the first 10 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately about 20 mg of cobamamide RS, add hydrochloric acid-potassium chloride buffer solution, pH 2.0, and use this solution as the standard solution. Determine the absorbances, A_S and A_T, of the test solution and the standard solution, respectively, at the wavelength of 460 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of cobamamide } (C_{72}H_{100}CoN_{18}O_{17}P) = \text{Amount (mg) of cobamamide RS} \times \frac{A_T}{A_S} \times \frac{1}{10}$$

Packaging and storage Preserve in tight containers.

Compound Diastase·protease 100, Magnesium Carbonate and Sodium Bicarbonate Tablets
복방디아스타제·프로테아제100·탄산마그네슘·탄산수소나트륨 정

Compound Diastase·protease 100, Magnesium Carbonate and Sodium Bicarbonate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of sodium bicarbonate ($NaHCO_3$: 84.01) and magnesium carbonate ($MgCO_3$: 84.31), NLT 90.0% and NMT 130.0% of total alkaloids in scopolia extract [hyoscyamine ($C_{17}H_{23}NO_3$: 289.37) and scopolamine ($C_{17}H_{21}NO_4$: 303.35)], and NLT 90.0% of *α*-amylase, *β*-amylase, and protease in diastase·protease 100.

Method of preparation Prepare as directed under Tablets, with Diastase·Protease 100, Magnesium Carbonate, Sodium Bicarbonate, and Scopolia Extract.

Identification (1) ***Magnesium carbonate*—**Weigh an amount of Compound Diastase·protease 100, Magnesium Carbonate and Sodium Bicarbonate Tablets, equivalent to 0.54 g of magnesium carbonate according to the labeled

amount, dissolve in 50 mL of water, filter, and wash the precipitate in the filter paper 3 times each with 10 mL of water. Completely dissolve the residue in 15 mL of dilute hydrochloric acid, filter, wash the residue on the filter paper 3 times each with 10 mL of water, and combine the filtrate and the washings. Add enough hot ammonium hydroxide TS until no precipitate forms, combine the alkaline filtrate and the washings with ammonia water and make the solution acidic; the solution does not produce a precipitate when ammonium chloride TS is added, but produces a white crystalline precipitate when dibasic sodium phosphate TS is added. This precipitate is insoluble in ammonia TS.

(2) ***Sodium bicarbonate*—**Weigh an amount of Compound Diastase·protease 100, Magnesium Carbonate and Sodium Bicarbonate Tablets equivalent to 1.4 g of sodium bicarbonate according to the labeled amount, dissolve in 30 mL of water, and filter. This filtrate responds to the Qualitative Analysis for sodium salt and bicarbonate.

(3) ***Scopolia extract*—**Weigh an amount of Compound Diastase·protease 100, Magnesium Carbonate and Sodium Bicarbonate Tablets, equivalent to 20 mg of scopolia extract according to the labeled amount, extract 3 times with 50 mL each of ether in an ammonia alkaline solution, combine the filtrates to concentrate on a steam bath, and dissolve in 10 mL of ethanol. Use this solution as the test solution. Separately, weigh about 20 mg of scopolia extract RS, proceed in the same manner as in the test solution, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Next, develop the plate using a mixture of chloroform, acetone, and diethylamine (5 : 4 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray Dragendorff's TS evenly onto the plate; the spot of the test solution exhibits an Rf value and color corresponding to that of the standard solution.

(4) ***α-Amylase, β-amylase, and protease in diastase·protease 100*—**Perform the test as directed under the Assay; each exhibits a positive reaction.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Magnesium carbonate*—**(i) Weigh accurately the mass of NLT 20 Compound Diastase·protease 100, Magnesium Carbonate and Sodium Bicarbonate Tablets, and powder. Weigh an amount equivalent to 0.18 g of magnesium carbonate ($MgCO_3$), transfer into a crucible, and ignite. After cooling, add 20 mL of water and 10 mL of hydrochloric acid, and evaporate on a steam bath. Concentrate, and dry the solution, dissolve in 10 mL of water and 4 mL of dilute hydrochloric acid, and add water to make 100 mL. Take 25.0 mL of this solution, add 50 mL of water and 5 mL of pH 10.7 ammonia-ammonium chloride buffer solution, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS to determine the consumed amount (indicator: 40 mg of eryochrome black T-sodium chloride indicator). Perform a blank test in the same manner and make any necessary correction.

From the consumed amount of the 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS, subtract the amount of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS that is equivalent to calcium oxide (CaO) obtained as directed under the following (B).

(ii) Separately, weigh accurately about 0.25 g of Compound Diastase·protease 100, Magnesium Carbonate and Sodium Bicarbonate Tablets, previously ignited, add 6 mL of dilute hydrochloric acid, and dissolve by heating. After cooling, add 300 mL of water and 3 mL of L-tartaric acid solution (1 in 5), put 10 mL of triethanolamine solution (3 in 10) and 10 mL of 8 mol/L potassium hydroxide TS, allow it to stand for 5 minutes, and titrate with 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 0.1 g of NN indicator). The end-point of titration is when the color of the solution changes from reddish purple to blue. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 4.2159 mg of MgCO3

Each mg of calcium oxide (CaO)
= 0.36 mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS

(2) **Sodium bicarbonate** Weigh accurately the mass of NLT 20 Compound Diastase·protease 100, Magnesium Carbonate and Sodium Bicarbonate Tablets, and powder. Weigh accurately an amount equivalent to about 0.1 g of sodium bicarbonate ($NaHCO_3$), add 50 mL of water, warm at between 35 and 40 °C, and shake for 10 minutes to dissolve. After filtering, wash 3 times each with 20 mL of water. Combine the filtrate and the washings, and titrate with 0.05 mol/L sulfuric acid VS as directed in the potentiometric titration under the Titrimetry. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sulfuric acid VS
= 8.401 mg of $NaHCO_3$

(3) ***Total alkaloids in scopolia extract (hyoscyamine and scopolamine)*—**Weigh accurately the mass of NLT 20 Compound Diastase·protease 100, Magnesium Carbonate and Sodium Bicarbonate Tablets, and powder. Weigh accurately an amount, equivalent to 0.2 mg of total alkaloids [hyoscyamine ($C_{17}H_{23}NO_3$: 289.37) and scopolamine ($C_{17}H_{21}NO_4$: 303.35)], and perform the test according to the Assay as directed under the Scopolia extract of the Korean Pharmacopoeia.

(4) ***Diastase·protease 100***—(i) α-Amylase Weigh accurately the mass of NLT 20 Compound Diastase·protease 100, Magnesium Carbonate and Sodium Bicarbonate Tablets, and powder. Weigh accurately an amount equivalent to 0.5 g of diastase·protease 100, dilute with 0.1% sodium chloride to make 40,000 to 80,000 times the concentration, and use this solution as the test solution. To 5 mL of 1% soluble starch TS, add 3 mL of McIlvaine buffer (pH 5.6) and 1 mL of 0.1% calcium chloride, allow it to stand at 37 ℃ for 5 minutes, add 1 mL of the test solution, and shake well to mix. Allow it to stand at 37 ℃ for 30 minutes, take 0.2 mL of the solution, and add to 10 mL of iodine TS. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy using water as the control solution, and determine the absorbance, OD_1, at a wavelength of 660 nm. Proceed according to the above using water instead of the test solution, and determine the absorbance, OD_{ST}. Proceed according to the above by heating the test solution at 100 ℃ for 30 minutes to deactivate the solution, and determine the absorbance, OD_0. Calculate the amount of starch digested in mg using the following equation.

$$\text{Potency (unit/tab) of } \alpha\text{-amylase} = \frac{OD_0 - OD_1}{OD_{ST}} \times 50 \times \frac{1}{10} \times D \times \frac{Average\ weight\ (g)\ of\ 1\ tablet}{Amount\ (g)\ of\ sample\ taken}$$

D: Dilution factor

Definition of potency—Set the unit as 1 when 10 mg of starch is digested according to the above conditions for 30 minutes.

(ii) *β*-Amylase Weigh accurately about 1.0 g of Compound Diastase·protease 100, Magnesium Carbonate and Sodium Bicarbonate Tablets, add 0.1% sodium chloride to dilute so that the solution becomes 30000 times the concentration, and use this solution as the test solution. Transfer 10 mL of 2% soluble starch TS to a 100-mL Erlenmeyer flask, allow it to stand at 40 ℃ for 30 minutes, and add 2 mL of Fehling's alkaline copper TS to stop the enzyme action. Add 2 mL of Ferring's copper TS, and boil on fire for 2 minutes. After cooling with running water, add 2 mL of 30% potassium iodide and 2 mL of 25% sulfuric acid, and titrate free iodine with 0.05 mol/L sodium thiosulfate VS. Separately, add water instead of the test solution, proceed according to the above, perform a blank test, and determine the mg of the produced reducing sugar.

$$\text{Potency of (unit/tab) } \beta\text{-amylase} = 1.62 \times (\text{consumed amount of the blank test solution} - \text{Consumed amount of the test solution}) \times \frac{1}{10} \times \frac{Average\ weight\ (g)\ of\ 1\ tablet}{Amount\ (g)\ of\ sample\ taken} \times f \times D$$

f: Normality factor of 0.05 mol/L sodium thiosulfate VS

D: Dilution factor

Definition of potency—Set the activation unit as 1 when 10 mg of glucose is created according to the above conditions.

(iii) Protease Weigh accurately 0.5 g of Compound Diastase·protease 100, Magnesium Carbonate and Sodium Bicarbonate Tablets, dilute with 0.1% sodium chloride to obtain a concentration of 5000 to 10000 times, and use this solution as the test solution. Transfer 1mL of 0.6% casein solution in a test tube, previously warmed at 37 ℃ in a constant temperature water bath, add 1.0 mL of the test solution, and shake to mix well. Allow it to stand in a 37 ℃ constant temperature water bath for exactly 10 minutes, add 2 mL of 0.4 mol/L trichloroacetic acid TS, allow it to stand at 37 ℃ for 20 minutes, and filter. Transfer 1.0 mL of the filtrate into a test tube, add 5 mL of 0.4 mol/L sodium carbonate and 1 mL of Folin TS (1 in 3), and shake to mix well. Allow it to stand at 37 ℃ for 20 minutes, perform the test with the colored solution as directed under the Ultraviolet-visible Spectroscopy using water as the control solution, and determine the absorbance E at the wavelength of 660 nm. Separately transfer 1.0 mL of the test solution into a test tube, add 2 mL of 0.4 mol/L trichloroacetic acid TS, add 1 mL of 0.6% casein solution, and filter after 10 minutes. With 1 mL of the filtrate, proceed in the same manner, and determine the absorbance, E_0. Separately, weigh accurately 50 mg of tyrosine RS, add 0.02 mol/L hydrochloric acid TS to make 100 mL, take 10.0 mL of this solution, and add 0.02 mol/L hydrochloric acid to make 100 mL. Use this solution as the standard solution. Take 1 mL of this standard solution, color like the test solution, and determine the absorbance, E_S.

$$\text{Potency (unit/tab) of protease} = \frac{E - E_0}{E_S} \times 50 \times \frac{4}{10} \times D \times \frac{Average\ weight\ (g)\ of\ 1\ tablet}{Amount\ (g)\ of\ sample\ taken}$$

D: Dilution factor

Definition of potency—Set the unit as 1 for potency creating non-protein material that responds to 1 μg of tyrosine according to the above conditions.

Packaging and storage Preserve in tight containers.

Compound Diprophylline, Methoxyphenamine Hydrochloride and Noscapine Capsules
복방디프로필린·메톡시페나민염산염·노스카핀 캡슐

Compound Diprophylline, Methoxyphenamine Hydrochloride and Noscapine Capsules contain NLT 90.0% and NMT 110.0% of the labeled amounts of diprophylline ($C_{10}H_{14}N_4O_4$: 254.24), methoxyphenamine hydrochloride ($C_{11}H_{17}ON\cdot HCl$: 215.72), noscapine ($C_{22}H_{23}NO_7$: 413.42) and chlorpheniramine maleate ($C_{16}H_{19}ClN_2\cdot C_4H_4O_4$: 390.86).

Method of preparation Prepare as directed under Capsules, with Diprophylline, Methoxyphenamine Hydrochloride, Noscapine and Chlorpheniramine Maleate.

Identification ***Diprophylline, chlorpheniramine maleate, methoxyphenamine hydrochloride, and noscapine—***The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay ***Diprophylline, chlorpheniramine maleate, methoxyphenamine hydrochloride, and noscapine—***Weigh accurately the contents of NLT 20 capsules of Compound Diprophylline, Methoxyphenamine Hydrochloride and Noscapine Capsules Weigh accurately an amount equivalent to 0.1 g of diprophylline $C_{10}H_{14}N_4O_4$) [20 mg of noscapine ($C_{22}H_{23}NO_7$), 8 mg of chlorpheniramine maleate ($C_{16}H_{19}ClN_2\cdot C_4H_4O_4$), and 0.1 g of methoxyphenamine hydrochloride ($C_{11}H_{17}ON\cdot HCl$)], dissolve in a mixture of methanol and chloroform (2 : 1), sonicate for 20 minutes, and add a mixture of methanol and chloroform (2 : 1) to make 100 mL, and filter. Use the filtrate as the test solution. Separately, weigh accurately about 0.1 g of diprophylline RS, about 20 mg of noscapine RS, about 8 mg of chlorpheniramine maleate RS, and about 0.1 g of methoxyphenamine hydrochloride RS, add a mixture of methanol and chloroform (2:1) and sonicate it for 20 minutes to dissolve, add a mixture of methanol and chloroform (2:1) to make 100 mL, and filter. Use the filtrate as the standard solution. Perform the test as directed under the Liquid Chromatography according to the following conditions with the test solution and the standard solution; determine the peak areas of A_{T1}, A_{T2}, A_{T3}, A_{T4}, A_{S1}, A_{S2}, A_{S3}, and A_{S4} of diprophylline, methoxyphenamine hydrochloride, chlorpheniramine maleate, and noscapine in each solution.

Amount (mg) of diprophylline ($C_{10}H_{14}N_4O_4$)

$$= \text{Amount (mg) of diprophylline RS} \times \frac{A_{T1}}{A_{S1}}$$

Amount (mg) of methoxphenamine hydrochloride ($C_{11}H_{17}ON\cdot HCl$)

$$= \text{Amount (mg) of methoxphenamine hydrochloride RS} \times \frac{A_{T2}}{A_{S2}}$$

Amount (mg) of chlorpheniramine maleate ($C_{16}H_{19}ClN_2\cdot C_4H_4O_4$)

$$= \text{Amount (mg) of chlorpheniramine maleate RS} \times \frac{A_{T3}}{A_{S3}}$$

Amount (mg) of noscapine ($C_{22}H_{23}NO_7$)

$$= \text{Amount (mg) of noscapine RS} \times \frac{A_{T4}}{A_{S4}}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μ*m* to 10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of 0.1 mol/L potassium dihydrogen phosphate (pH 2.6) and acetonitrile (85 : 15).

Flow rate: 1 mL/min

Packaging and storage Preserve in tight containers.

Compound Dried Ergocalciferol, Calcium Gluconate and Calcium Lactate Tablets
복방건조에르고칼시페롤·글루콘산칼슘·락트산칼슘 정

Compound Dried Ergocalciferol, Calcium Gluconate and Calcium Lactate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of total calcium (Ca: 40.08) and NLT 90.0% and NMT 150.0% of ergocalciferol ($C_{29}H_{44}O$: 396.65).

Method of preparation Prepare as directed under Tablets, with Calcium Lactate Hydrate, Calcium Gluconate Hydrate, Precipitated Calcium Carbonate, and Dried Ergocalciferol.

Identification (1) ***Calcium lactate hydrate, calcium gluconate hydrate, and calcium in precipitated calcium carbonate—***Perform the test with Compound Dried Ergocalciferol, Calcium Gluconate and Calcium Lactate Tablets; it responds to the Qualitative Analysis for calcium salt.

(2) ***Lactate in calcium lactate hydrate—***Weigh an amount of Compound Dried Ergocalciferol, Calcium

Gluconate and Calcium Lactate Tablets equivalent to 20 mg of calcium lactate hydrate, add 20 mL of water, dissolve by shaking to mix, and filter. The filtrate responds to the Qualitative Analysis for lactate and calcium salt.

(3) ***Carbonate in precipitated calcium carbonate***—Perform the test with Compound Dried Ergocalciferol, Calcium Gluconate and Calcium Lactate Tablets; it responds to the Qualitative Analysis for carbonate.

(4) ***Gluconate in calcium gluconate hydrate***—Weigh 0.5 g of Compound Dried Ergocalciferol, Calcium Gluconate and Calcium Lactate Tablets, dissolve in 5 mL of water by heating, add 0.65 mL of acetic acid(100) and 1 mL of freshly distilled phenylhydrazine, and heat on a steam bath for 30 minutes. After cooling, rub the inner wall with the glass rod; a crystal precipitates. Filter and collect the crystal, dissolve in 10 mL of hot water, add a small amount of activated charcoal, and filter. After cooling, rub the inner wall with the glass rod, filter and collect the precipitating crystals under suction, wash 3 times each with 10 mL of cold water, and dry; the melting point is between 187 and 199 ℃ (with decomposition).
An aqueous solution of Compound Dried Ergocalciferol, Calcium Gluconate and Calcium Lactate Tablets (1 in 40) responds to the Qualitative Analysis for calcium salt.

(5) ***Ergocalciferol—***Perform the test with Compound Dried Ergocalciferol, Calcium Gluconate and Calcium Lactate Tablets as directed under the Analysis for Vitamins.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Total calcium in calcium lactate hydrate, precipitated calcium carbonate, and calcium gluconate hydrate—***Weigh accurately the mass of NLT 20 Compound Dried Ergocalciferol, Calcium Gluconate and Calcium Lactate Tablets, powder, and perform the test as directed under the Analysis for Minerals.

(2) ***Ergocalciferol***—Weigh accurately the mass of NLT 20 Compound Dried Ergocalciferol, Calcium Gluconate and Calcium Lactate Tablets, powder, and perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in well-closed containers.

Compound Fursultiamine, Pyridoxine Hydrochloride and Tocopherol Acetate Capsules

복방푸르설티아민·피리독신염산염·토코페롤아세테이트 캡슐

Compound Fursultiamine, Pyridoxine Hydrochloride and Tocopherol Acetate Capsules contain NLT 90.0% and NMT 110.0% of sodium chondroitin sulfate and γ-oryzanol ($C_{40}H_{58}O_4$: 602.89), NLT 90.0% and NMT 130.0% of fursultiamine ($C_{17}H_{26}N_4O_3S_2$: 398.54) and riboflavin butyrate ($C_{33}H_{44}N_4O_{10}$: 656.72), NLT 90.0% and NMT 150.0% of nicotinamide ($C_6H_6N_2O$: 122.13), pyridoxine hydrochloride ($C_8H_{11}NO_3$·HCl: 205.64), calcium pantothenate ($C_{18}H_{32}CaN_2O_{10}$: 476.53), cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$: 1355.37) and tocopherol acetate ($C_{31}H_{52}O_3$: 472.74), respectively, according to the labeled amount.

Method of preparation Prepare as directed under Capsules, with Sodium Chondroitin Sulfate, *Γ*-Oryzanol, Fursultiamine, Riboflavin Butyrate, Nicotinamide, Pyridoxine Hydrochloride, Calcium Pantothenate, Cyanocobalamin and Tocopherol Acetate.

Identification (1) ***γ-Oryzanol—***Weigh an amount of Compound Fursultiamine, Pyridoxine Hydrochloride and Tocopherol Acetate Capsules, equivalent to about 10 mg of γ-oryzanol, add 50 mL of n-heptane, shake to mix, and extract. Then, dehydrate with anhydrous sodium sulfate, filter, and use this filtrate as the test solution. Separately, weigh about 10 mg of γ-oryzanol RS, add n-heptane, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate using a mixture of n-heptane, ether and ethyl acetate (75 : 20 : 5) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly potassium permanganate TS on the plate; the R_f values and the colors of the spots obtained from the sample and the standard solutions are the same.

(2) ***Sodium chondroitin sulfate—***(i) Weigh an amount of Compound Fursultiamine, Pyridoxine Hydrochloride and Tocopherol Acetate Capsules, equivalent to about 1 g of sodium chondroitin sulfate according to the labeled amount, add 60 mL of water, shake well to mix, extract, and filter. Extract and filter the residue 2 times each with 20 mL of water, combine these filtrates with the above filtrate, and add 1 mL of acriflavine solution (1 in 100); an orangey yellow acidic precipitate immediately forms, and this precipitate does not dissolve in dilute sodium hydroxide or dilute hydrochloric acid.

(ii) Weigh an amount of Compound Fursultiamine, Pyridoxine Hydrochloride and Tocopherol Acetate Capsules, equivalent to about 0.2 g of sodium chondroitin sulfate according to the labeled amount, and filter 2 times each with 20 mL of water while shaking to mix. Combine all the filtrates, add 50 mL of 3 mol/L hydrochloric acid TS, and react under evolving conditions with a reflux condenser for 2 hours. After cooling, neutralize with 3 mol/L potassium hydroxide TS, and use this solution as the test solution. Separately, weigh about 0.2 g of sodium chondroitin sulfate RS, proceed in the same manner as in the preparation of the test solution to make a neutralized solution having a concentration of about 5%, and use this solution as the standard solution. With these

solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of water, methanol and ammonia water (50 : 50 : 50) as a developing solvent to a distance of about 10 cm, air-dry the plate, and spray evenly potassium dichromate-sulfuric acid TS or naphthoresorcin-sulfuric acid TS; the R_f values and colors of the spots obtained from the test solution and standard solution are the same.

(3) ***Riboflavin butyrate, fursultiamine, nicotinamide, pyridoxine hydrochloride, calcium pantothenate, cyanocobalamin and tocopherol acetate***—Perform the test with Compound Fursultiamine, Pyridoxine Hydrochloride and Tocopherol Acetate Capsules as directed under the Analysis for Vitamins.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***γ-Oryzanol***—Weigh accurately the mass of NLT 20 capsules of Compound Fursultiamine, Pyridoxine Hydrochloride and Tocopherol Acetate Capsules. Weigh accurately an amount of these capsules, equivalent to about 5 mg of γ-oryzanol ($C_{40}H_{58}O_4$), add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 5 mg of γ-oryzanol RS, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20 mL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of γ-oryzanol in each solution.

$$\text{Amount (mg) of } \gamma\text{-oryzanol } (C_{40}H_{58}O_4) = \text{Amount (mg) of } \gamma\text{-oryzanol RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 280 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with aminopropylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Mobile phase: A mixture of cyclohexane, ethyl acetate and acetic acid (730 : 270 : 1).

Flow rate: 1.0 mL/min

(2) ***Sodium chondroitin sulfate***—Weigh accurately the mass of NLT 20 capsules of Compound Fursultiamine, Pyridoxine Hydrochloride and Tocopherol Acetate Capsules. Weigh accurately an amount of these capsules, equivalent to about 80 mg of sodium chondroitin sulfate, add 150 mL of water, sonicate for 10 minutes, and add water to make exactly 200 mL. Then, centrifuge. Pipet 5 mL of the clear supernatant, add 5 mL of 6 mol/L hydrochloric acid TS, fill nitrogen, then close the stopper, and warm at 100 ± 1 ℃ for 16 hours. After cooling, adjust the pH to 3.5 with sodium hydroxide TS, transfer into a 100-mL volumetric flask (wash the stoppered Erlenmeyer flask with water, and combine the washings into the volumetric flask), add 5 mL of the internal standard solution, and then add water to make exactly 100 mL. Use this solution as the test solution. Separately, weigh accurately about 80 mg of sodium chondroitin sulfate RS, and add water to make exactly 200 mL. Pipet 5 mL of this solution, transfer into a stoppered Erlenmeyer flask, add 5 mL of 6 mol/L hydrochloric acid TS, and fill nitrogen. Then, proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of the peak area of sodium chondroitin sulfate to the peak area of the internal standard, respectively.

$$\text{Amount (mg) of sodium chondroitin sulfate} = \text{Amount (mg) of sodium chondroitin sulfate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—*dl*-3-amino-*n*-butyric acid solution (1 in 12500).

Operating conditions

Detector: A fluorometer (excitation wavelength 345 nm, fluorescence wavelength 445 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with strongly acidic ion-exchange resin composed of sulfonated polystyrene (about 10 μm in particle diameter).

Column temperature: A constant temperature of about 50 °C.

Reaction vessel temperature: A constant temperature about 50 ℃ (use a reaction coil with about 0.5 mm in internal diameter and about 2 m in length).

Mobile phase: Citrate buffer solution

Reaction regent: o-phthalaldehyde solution

Flow rate: Adjust the flow rate so that the peak retention time of the substance derived from sodium chondroitin sulfate is about 6 minutes.

Flow rate of reaction regent: About 1.0 mL/min.

Selection of column: Proceed with 10 μL of the standard solution according to the above conditions; internal standard and the substance derived from sodium chondroitin sulfate are eluted in this order, and each peak is completely separated.

(3) ***Riboflavin butyrate, fursultiamine, nicotinamide, pyridoxine hydrochloride, calcium pantothenate, cyanocobalamin and tocopherol acetate***—Weigh accurately the mass of NLT 20 capsules of Compound Fursultiamine, Pyridoxine Hydrochloride and Tocopherol Acetate Capsules, and perform the test as directed under the

Analysis for Vitamins.

Packaging and storage Preserve in light-resistant, tight containers.

Compound Fursultiamine, Pyridoxine Hydrochloride and γ-Oryzanol Capsules
복방푸르설티아민·피리독신염산염·γ-오리자놀 캡슐

Compound Fursultiamine, Pyridoxine Hydrochloride and γ-Oryzanol Capsules contain NLT 90.0% and NMT 110.0% of sodium chondroitin sulfate and γ-oryzanol ($C_{40}H_{58}O_4$: 602.89), NLT 90.0% and NMT 130.0% of fursultiamine ($C_{17}H_{26}N_4O_3S_2$: 398.54) and riboflavin butyrate ($C_{33}H_{44}N_4O_{10}$: 656.72), NLT 90.0% and NMT 150.0% of nicotinamide ($C_6H_6N_2O$: 122.13), pyridoxine hydrochloride ($C_8H_{11}NO_3$·HCl: 205.64), calcium pantothenate ($C_{18}H_{32}CaN_2O_{10}$: 476.53), cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$: 1355.37) and inositol ($C_6H_{12}O_6$: 180.16), respectively, according to the labeled amount.

Method of preparation Prepare as directed under Capsules, with Sodium Chondroitin Sulfate, *Γ*-Oryzanol, Fursultiamine, Riboflavin Butyrate, Nicotinamide, Pyridoxine Hydrochloride, Calcium Pantothenate, Cyanocobalamin and Inositol.

Identification (1) ***γ-Oryzanol*—**Weigh an amount of Compound Fursultiamine, Pyridoxine Hydrochloride and γ-Oryzanol Capsules, equivalent to about 10 mg of γ-oryzanol according to the labeled amount, add 50 mL of 1-heptane, shake to mix, and extract. Then, dehydrate with anhydrous sodium sulfate, filter, and use this filtrate as the test solution. Separately, weigh about 10 mg of γ-oryzanol RS, add n-heptane, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of 1-heptane, ether and ethyl acetate (75 : 20 : 5) (as the developing solvent) to a distance of about 10 cm, and air-dry the plate. Spray evenly a potassium permanganate TS onto the plate; the R_f values and colors of the spots obtained from the test solution and the standard solution are the same.

(2) ***Sodium chondroitin sulfate*—**(i) Weigh an amount of Compound Fursultiamine, Pyridoxine Hydrochloride and γ-Oryzanol Capsules, equivalent to about 1 g of sodium chondroitin sulfate according to the labeled amount, add 60 mL of water, shake well to mix, extract, and filter. Extract and filter the residue 2 times each with 20 mL of water, combine these filtrates with the above filtrate, and add 1 mL of acriflavine solution (1 in 100); a orangey yellow acidic precipitate immediately forms, and this precipitate does not dissolve in dilute sodium hydroxide or dilute hydrochloric acid.

(ii) Perform the test as directed under the Assay (2); the retention times of the major peaks obtained from the test solution and the standard solution are the same.

(3) ***Riboflavin butyrate, fursultiamine, nicotinamide, pyridoxine hydrochloride, calcium pantothenate, cyanocobalamin and inositol*—**Perform the test with Compound Fursultiamine, Pyridoxine Hydrochloride and γ-Oryzanol Capsules as directed under the Analysis for Vitamins.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***γ-Oryzanol*—**Weigh accurately the mass of NLT 20 capsules of Compound Fursultiamine, Pyridoxine Hydrochloride and γ-Oryzanol Capsules. Weigh accurately an amount of these capsules, equivalent to about 5 mg of γ-oryzanol ($C_{40}H_{58}O_4$), add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 5 mg of γ-oryzanol RS, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area, A_T and A_S, of γ-oryzanol in each solution.

$$\text{Amount (mg) of } \gamma\text{-oryzanol } (C_{40}H_{58}O_4) = \text{Amount (mg) of } \gamma\text{-oryzanol} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 280 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with aminopropylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Mobile phase: A mixture of cyclohexane, ethyl acetate, and acetic acid (730 : 270 : 1).

Flow rate: 1.0 mL/min

(2) ***Sodium chondroitin sulfate*—**Weigh accurately the mass of NLT 20 capsules of Compound Fursultiamine, Pyridoxine Hydrochloride and γ-Oryzanol Capsules. Weigh accurately an amount of these capsules, equivalent to about 80 mg of sodium chondroitin sulfate, add 150 mL of water, sonicate for 10 minutes, and add water to make exactly 200 mL. Then, centrifuge. Take 5 mL of the clear supernatant, add 5 mL of 6 mol/L hydrochloric acid TS, fill nitrogen, then close the stopper, and warm at 100 ± 1 °C for 16 hours. After cooling, adjust the pH to 3.5 with sodium hydroxide TS, transfer into a 100-mL volumetric flask (wash the stoppered Erlenmeyer flask with water, and combine the washings into the vol-

umetric flask), add 5 mL of the internal standard solution, and then add water to make exactly 100 mL. Use this solution as the test solution. Separately, weigh accurately about 80 mg of sodium chondroitin sulfate RS, and add water to make exactly 200 mL. Transfer 5 mL of this solution into a stoppered Erlenmeyer flask, add 5 mL of 6 mol/L hydrochloric acid TS, then proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of the peak area of sodium chondroitin sulfate to the peak area of the internal standard, respectively.

$$\text{Amount (mg) of sodium chondroitin sulfate} = \text{Amount (mg) of sodium chondroitin sulfate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—*dl*-3-amino-n-butyric acid solution (1 in 12500).

Operating conditions

Detector: A fluorometer (excitation wavelength: 345 nm, emission wavelength: 445 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with strongly acidic ion-exchange resin composed of sulfonated polystyrene (about 10 μm in particle diameter).

Column temperature: A constant temperature of about 50 °C.

Reaction vessel temperature: A constant temperature of about 50 ℃ (use a reaction coil with about 0.5 mm in internal diameter and about 2 m in length).

Mobile phase: Citrate buffer solution

Reaction regent: *O*-phthalaldehyde solution

Flow rate: Adjust the flow rate so that the peak retention time of sodium chondroitin sulfate is about 6 minutes.

Flow rate of reaction regent: About 1.0 mL/min.

Selection of column: Proceed with 10 μL of the standard solution according to the above conditions; internal standard and sodium chondroitin sulfate are eluted in this order, and each peak is completely separated.

(3) ***Nicotinamide, pyridoxine hydrochloride, fursultiamine and riboflavin butyrate***—Weigh accurately the mass of NLT 20 capsules of Compound Fursultiamine, Pyridoxine Hydrochloride and γ-Oryzanol Capsules. Weigh accurately an amount of these capsules, equivalent to about 50 mg of nicotinamide ($C_6H_5N_2O$), about 25 mg of pyridoxine hydrochloride ($C_8H_{11}NO_3 \cdot HCl$), about 50 mg of fursultiamine ($C_{17}H_{26}N_4O_3S_2$) and about 6 mg of riboflavin butyrate ($C_{33}H_{44}N_4O_{10}$), and add 20% methanol to make exactly 100 mL. Sonicate this solution at 60 ℃ for about 20 minutes, filter through a membrane filter with a pore size of NMT 0.45 μm, discard the first 2 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately about 50 mg of nicotinamide RS, about 25 mg of pyridoxine hydrochloride RS, about 50 mg of fursultiamine RS, and about 6 mg of riboflavin butyrate RS, add 20% methanol to make exactly 100 mL, sonicate at 60 ℃ for about 20 minutes, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_{T1}, A_{S1}, A_{T2}, A_{S2}, A_{T3}, A_{S3}, A_{T4}, and A_{S4}, of nicotinamide, pyridoxine hydrochloride, fursultiamine and riboflavin butyrate in each solution.

$$\text{Amount (mg) of nicotinamide } (C_6H_5N_2O) = \text{Amount (mg) of nicotinamide RS} \times \frac{A_{T1}}{A_{S1}}$$

$$\text{Amount (mg) of pyridoxine hydrochloride } (C_8H_{11}NO_3 \cdot HCl) = \text{Amount (mg) of pyridoxine hydrochloride RS} \times \frac{A_{T2}}{A_{S2}}$$

$$\text{Amount (mg) of fursultiamine } (C_{17}H_{26}N_4O_3S_2) = \text{Amount (mg) of fursultiamine RS} \times \frac{A_{T3}}{A_{S3}}$$

$$\text{Amount (mg) of riboflavin butyrate } (C_{33}H_{44}N_4O_{10}) = \text{Amount (mg) of riboflavin butyrate RS} \times \frac{A_{T4}}{A_{S4}}$$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 270 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: Dissolve 1.9 g of sodium 1-hexanesulfonate in 800 mL of water, add 1.0 mL of formic acid, and then add water to make 1000 mL. Add 100 mL of methanol to 900 mL of this solution.

Mobile phase B: Methanol

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 3	100	0
3 - 10	100 → 0	0 → 100
10 - 15	0	100

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; nicotinamide, pyridoxine hydrochloride, fursultiamine and

riboflavin butyrate are eluted in this order with the resolution between the pyridoxine hydrochloride peak and the fursultiamine peak being NLT 13.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above conditions; the relative standard deviation of the peak areas of nicotinamide, pyridoxine hydrochloride, fursultiamine and riboflavin butyrate is NMT 1.0%.

(4) ***Cyanocobalamin***—Weigh accurately the mass of NLT 20 capsules of Compound Fursultiamine, Pyridoxine Hydrochloride and γ-Oryzanol Capsules. Weigh accurately an amount of these capsules, equivalent to about 150 μg of cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$), and add water to make exactly 10 mL. Sonicate this solution for about 20 minutes, centrifuge at 13,000 rpm for 5 minutes, filter the lower layer through a membrane filter with a pore size of NMT 0.45 μm, and discard the first 2 mL of the filtrate. Use the subsequent filtrate as the test solution. Separately, weigh accurately about 15 mg of cyanocobalamin RS, and add water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of cyanocobalamin in each solution.

Amount (mg) of cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$)
= Amount (mg) of cyanocobalamin RS× $\frac{A_T}{A_S} \times \frac{1}{100}$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 360 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: 10% methanol
Mobile phase B: 90% methanol

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 1	90	10
1 - 4	90 → 10	10 → 90
4 - 5	10	90

Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of cyanocobalamin is NMT 1.0%

(5) ***Calcium pantothenate***—Weigh accurately the mass of NLT 20 capsules of Compound Fursultiamine, Pyridoxine Hydrochloride and γ-Oryzanol Capsules. Weigh accurately an amount of these capsules, equivalent to about 15 mg of calcium pantothenate ($C_{18}H_{32}CaN_2O_{10}$), and add water to make exactly 100 mL. Sonicate this solution for about 20 minutes, filter through a membrane filter with a pore size of NMT 0.45 μm, discard the first 2 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately about 15 mg of calcium pantothenate RS, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of calcium pantothenate in each solution.

Amount (mg) of calcium pantothenate ($C_{18}H_{32}CaN_2O_{10}$)
= Amount (mg) of calcium pantothenate RS× $\frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of methanol and 0.1% phosphoric acid (80 : 20).

Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of calcium pantothenate is NMT 1.0%

(6) ***Inositol***—Weigh accurately the mass of NLT 20 capsules of Compound Fursultiamine, Pyridoxine Hydrochloride and γ-Oryzanol Capsules and perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in tight containers.

Compound Ginkgo Biloba Leaf Extract, Heptaminol Hydrochloride and Troxerutin Tablets

복방은행엽엑스·헵타미놀염산염·트록세루틴 정

Compound Ginkgo Biloba Leaf Extract, Heptaminol Hydrochloride and Troxerutin Tablets contain heptaminol hydrochloride ($C_8H_{20}NOCl$: 181.70) and troxerutin ($C_{33}H_{42}O_{19}$: 742.70) equivalent to 22.0% to 27.0% of the total gingoflavone glycosides in ginkgo leaf extract (total amount of quercetin glycoside, kaempferol glycoside, and isorhamnetin glycoside, average molecular weight 756.7) and 90.0% to 110.0% of the labeled amount.

Method of preparation Prepare as directed under Tablets, with Ginkgo Biloba Extract, Heptaminol Hydrochloride, and Troxerutin.

Identification (1) ***Ginkgo leaf extract***—Perform the test as directed under the identification for ginkgo leaf extract tablets, with Compound Ginkgo Biloba Leaf Extract, Heptaminol Hydrochloride and Troxerutin Tablets.

(2) ***Heptaminol hydrochloride***—(i) Put 1 mL of 10% aqueous solution of Compound Ginkgo Biloba Leaf Extract, Heptaminol Hydrochloride and Troxerutin Tablets, previously powdered, in a test tube, and add 8 mL of water, 1 mL of nitric acid, and 0.5 mL of silver nitrate solution; a white precipitate that is insoluble in nitric acid but soluble in ammonia water (chloride) is formed.

(ii) Weigh an amount of Powder Compound Ginkgo Biloba Leaf Extract, Heptaminol Hydrochloride and Troxerutin Tablets, previously powdered, equivalent to 200 mg of heptaminol hydrochloride according to the labeled amount, add 10 mL of methanol, and use the solution as the test solution. Separately, weigh 0.2 g of heptaminol hydrochloride RS, add 10 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, isopropanol, and ammonia water (50 : 50 : 10) as the developing solvent to a distance of about 10 cm and air-dry the plate. Spray evenly iodine vapor onto plate, cool, and examine it under ultraviolet light (main wavelength 254 nm); the R_f value and the color of the spots obtained from the test solution and the standard solutions are the same.

(3) ***Troxerutin***—Weigh an amount of Compound Ginkgo Biloba Leaf Extract, Heptaminol Hydrochloride and
Troxerutin Tablets, previously powdered, equivalent to 100 mg of troxerutin, add in 100 mL of water, and use this solution as the test solution. Separately, weigh about 0.1 g of troxerutin RS, add water to make 100 mL and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of 1-propanol, water, ethyl acetate (100), and acetoc acod (100) (40 : 30 : 30 :1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength 254 nm) or spray 0.5% methanol solution of diphenyl boric acid aminoethyl ester; the test solution and the standard solution exhibit yellow spots at the same R_f value.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Ginkgo leaf extract***—Weigh accurately the mass of NLT 20 Compound Ginkgo Biloba Leaf Extract, Heptaminol Hydrochloride and Troxerutin Tablets, and power. Perform the test as directed in the paragraph (1) under the Assay of Ginkgo Leaf Extract Tablet.

(2) ***Heptaminol hydrocholride***—Weigh accurately the mass of NLT 20 Compound Ginkgo Biloba Leaf Extract, Heptaminol Hydrochloride and Troxerutin Tablets, and powder. Weigh accurately an amount equivalent to about 150 mg of heptaminol hydrochloride, put it in a beaker, dissolve in 45 mL of acetic acid(100) for non-aqueous titration, add 5 mL of mercury(II) acetate TS for non-aqueous titration, and titrate with 0.1 mol/L perchloric acid solution as directed in the potentiometric titration method under the Titration. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 18.170 mg of $C_8H_{19}NO \cdot HCl$

(3) ***Troxerutin***—Weigh accurately the mass of NLT 20 tablets of Compound Ginkgo Biloba Leaf Extract, Heptaminol Hydrochloride and Troxerutin Tablets, and powder. Weigh accurately an amount equivalent to about 0.2 g of troxerutin and add water to make 100 mL. Take 5.0 mL of this solution and add ethanol to make 100 mL, take 5.0 mL of this solution, and add 12.5 mL of a mixture of 0.1 mol/L sodium hydroxide solution, 0.05 mol/L sodium bicarbonate solution, and methanol (1 : 1 : 1) and ethanol to make 25 mL. Use the solution as the test solution. Separately, weigh accurately about 0.2 g of troxerutin RS, proceed in the same manner as in the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 248 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of troxerutin ($C_{33}H_{42}O_{19}$)
$= \text{Amount (mg) of troxerutin RS} \times \frac{A_T}{A_S}$

Packaging and storage Preserve in tight containers.

Compound Glycine, L-Leucine and L-Cysteine Hydrochloride Injection
복방글리신·L-류신·L-시스테인염산염 주사액

Compound Glycine, L-Leucine and L-Cysteine Hydrochloride Injection contains NLT 90.0% and NMT 130.0% of the labeled amount of L-leucine ($C_6H_{13}NO_2$: 131.17), L-methionine ($C_5H_{11}NO_2S$: 149.21), L-valine ($C_5H_{11}NO_2$: 117.15), L-serine ($C_3H_7NO_3$: 105.09), L-arginine ($C_6H_{14}N_4O_2$: 174.20), glycine ($C_2H_5O_2N$: 75.07), L-alanine ($C_3H_7NO_2$: 89.09), L-cysteine hydrochloride hydrate ($C_3H_7NO_2S \cdot HCl \cdot H_2O$: 175.64), L-isoleucine ($C_6H_{13}NO_2$: 131.17), L-lysine acetate ($C_6H_{14}N_4O_4 \cdot C_2H_4O_2$: 206.24), L-threonine ($C_6H_{14}N_4O_4 \cdot C_2H_4O_2$: 206.24), L-tryptophan ($C_{11}H_{12}N_2O_2$: 204.23), L-phenylalanine ($C_9H_{11}NO_2$: 165.19), L-proline ($C_5H_9NO_2$: 115.13) and L-histidine ($C_6H_9N_3O_2$: 155.16).

Method of preparation Prepare as directed under Injections, with L-Leucine, L-Methionine, L-Valine, L-Serine, L-Arginine, Glycine, L-Alanine, L-Cysteine Hydrochloride Hydrate, L-Isoleucine, L-Lysine Acetate, L-Threonine, L-Tryptophan, L-Phenylalanine, L-Proline and L-Histidine.

Identification (1) ***Amino acids***—Perform the test with Compound Glycine, L-Leucine and L-Cysteine Hydrochloride Injection as directed under the Identification and Assay for Amino Acids.

(2) ***Chloride and acetate***—Compound Glycine, L-Leucine and L-Cysteine Hydrochloride Injection responds to the Qualitative Analysis for chloride and acetate.

pH Between 5.5 and 7.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.5 EU per mL of Compound Glycine, L-Leucine and L-Cysteine Hydrochloride Injection.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets requirements.

Extractable volume of injections Meets the requirements.

Assay Take exactly an amount of Compound Glycine, L-Leucine and L-Cysteine Hydrochloride Injection, and perform the test as directed under the Identification and Assay for Amino Acids.

Packaging and storage Preserve in hermetic containers.

Compound Lysozyme Hydrochloride, Ascorbic Acid and Tocopherol Acetate Capsules
복방리소짐염산염·아스코르브산·토코페롤아세테이트 캡슐

Compound Lysozyme Hydrochloride, Ascorbic Acid and Tocopherol Acetate Capsules contain NLT 90.0% and NMT 130.0% of the labeled amount of lysozyme hydrochloride, NLT 90.0% and NMT 150.0% of the labeled amounts of ascorbic acid ($C_6H_8O_6$: 176.12) and tocopherol acetate ($C_{31}H_{52}O_3$: 472.74), and NLT 90.0% and NMT 110.0% of the labeled amount of chlorophylline copper complex sodium.

Method of preparation Prepare as directed under Capsules, with Lysozyme Hydrochloride, Ascorbic Acid, Tocopherol Acetate, and Chlorophyllin Copper Complex Sodium.

Identification (1) ***Lysozyme hydrochloride*—**Weigh an amount of Compound Lysozyme Hydrochloride, Ascorbic Acid and Tocopherol Acetate Capsules equivalent to about 50 mg of lysozyme hydrochloride, add 5 mL of 0.4 mol/L sodium chloride solution, shake to mix well, and centrifuge the solution. Take the clear supernatant, add 5 mL of acetic acid and sodium acetate buffer solution (pH 5.4), and shake to mix to. Add 1 mL of ninhydrin TS to 5 mL of this solution, and heat; this solution exhibits a reddish-purple color.

(2) ***Ascorbic acid, tocopherol acetate*—**Perform the test with Compound Lysozyme Hydrochloride, Ascorbic Acid and Tocopherol Acetate Capsules as directed under the Analysis for Vitamins.

(3) ***Chlorophylline copper complex sodium*—**Add 60 mL of acetic acid(100) to Compound Lysozyme Hydrochloride, Ascorbic Acid and Tocopherol Acetate Capsules, shake to dissolve, take 2 mL of the filtrate, and add acetic acid(100) to make 100 mL. Use acetic acid(100) as a control solution and determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum absorbance around a wavelength of 405 nm.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Lysozyme hydrochloride, ascorbic acid***—Weigh accurately the contents of NLT 20 capsules of Compound Lysozyme Hydrochloride, Ascorbic Acid and Tocopherol Acetate Capsules. Weigh accurately the amount equivalent to about 15 mg of lysozyme hydro-

chloride and about 75 mg of ascorbic acid ($C_6H_6O_6$), add 0.1% trifluoroacetic acid solution to make 100 mL, sonicate for 30 minutes, and filter through a membrane filter with a pore size of NMT 0.45 μm. Use this solution as the test solution. Separately, weigh accurately 15 mg of lysozyme hydrochloride RS and 75 mg of ascorbic acid RS, add 0.1% trifluoroacetic acid solution to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions.

$$\text{Amount (mg) of lysozyme hydrochloride} = \text{Amount (mg) of lysozyme hydrochloride RS} \times \frac{A_{T1}}{A_{S1}}$$

$$\text{Amount (mg) of ascorbic acid } (C_6H_6O_6) = \text{Amount (mg) of ascorbic acid RS} \times \frac{A_{T3}}{A_{S3}}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Control the gradient elution by modifying the mixing ratio of mobile phases A and B as follows.

Mobile phase A: 0.1% trifluoroacetic acid solution

Mobile phase B: Add 1 mL of trifluoroacetic acid to 1000 mL of acetonitrile.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 2	100 → 95	0 → 5
2 - 7	95 → 50	5 → 50
7 - 15	50	50

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; Ascorbic acid and lysozyme hydrochloride are eluted in this order with the resolution being NLT 21.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of lysozyme is NMT 1.0%.

(2) ***Tocopherol acetate*—**Weigh accurately the contents of NLT 20 capsules of Compound Lysozyme Hydrochloride, Ascorbic Acid and Tocopherol Acetate Capsules. Weigh accurately the amount equivalent to about 50 mg of tocopherol acetate ($C_{31}H_{52}O_3$), add methanol to make 100 mL, sonicate for 30 minutes, filter through a membrane filter of NMT 0.45 μm, and use this solution as the test solution. Separately, weigh accurately the amount equivalent to about 50 mg of tocopherol acetate RS and add methanol to make 100 mL and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of tocopherol acetate A_T and A_S, in each solution.

$$\text{Amount (mg) of tocopherol acetate } (C_{31}H_{52}O_3) = \text{Amount (mg) of tocopherol acetate} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Methanol

Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of tocopherol acetate is NMT 1.0%.

(3) ***Chlorophylline copper complex sodium*—**Weigh accurately the contents of NLT 20 Compound Lysozyme Hydrochloride, Ascorbic Acid and Tocopherol Acetate Capsules, and powder. Weigh accurately the amount equivalent to about 20 mg of chlorophylline copper complex sodium, add 30 mL of hexane, and shake to mix, discard the hexane layer, add 40 mL of a mixture of methyl cellosolve and dilute hydrochloric acid (50 : 2) to the residue, shake to mix, and perform the centrifuge. Pipet 1.0 mL of the clear supernatant, and add phosphate buffer solution (pH 7.5) to make 50 mL. Separately, weigh accurately about 20 mg of chlorophylline copper complex salt RS and prepare it in the same manner as the test solution. Use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, at a wavelength of 405 nm as directed under the Ultraviolet-visible Spectroscopy, using phosphate buffer solution (pH 7.5) as the control solution.

$$\text{Amount (mg) of chlorophylline copper complex sodium} = \text{Amount (mg) of chlorophylline copper complex sodium RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers.

Compound Miconazole Nitrate, Lidocaine and Crotamiton Cream
복방미코나졸질산염·리도카인·크로타미톤 크림

Compound Miconazole Nitrate, Lidocaine and Crotamiton Cream contains NLT 90.0% and NMT 110.0% of the labeled amount of miconazole nitrate ($C_{18}H_{14}Cl_4N_2O \cdot HNO_3$: 479.14), lidocaine ($C_{14}H_{22}N_2O$: 234.34), crotamiton ($C_{13}H_{17}NO$: 203.28) and dipotassium glycyrrhizinate ($C_{42}H_{60}K_2O_{16}$: 899.11).

Method of preparation Prepare as directed under Creams, with Miconazole Nitrate, Lidocaine, Crotamiton and Dipotassium Glycyrrhizinate.

Identification The major peaks obtained from the test solution and standard solution under the Assay are the same in retention time.

Assay Weigh accurately an amount of Compound Miconazole Nitrate, Lidocaine and Crotamiton Cream, equivalent to about 10 mg of miconazole nitrate ($C_{18}H_{14}Cl_4N_2O \cdot HNO_3$) [about 20 mg of lidocaine ($C_{14}H_{22}N_2O$), about 100 mg of crotamiton ($C_{13}H_{17}NO$) and about 5 mg of dipotassium glycyrrhizinate ($C_{42}H_{60}K_2O_{16}$)], add methanol to make exactly 100 mL, sonicate for 30 minutes, then filter with a membrane filter of pore size 0.45 μm, and use the filtrate as the test solution. Separately, weigh accurately about 10 mg of miconazole nitrate RS, about 20 mg of lidocaine RS, about 100 mg of crotamiton RS, and about 5 mg of dipotassium glycyrrhizinate RS, respectively, add methanol to make exactly 100 mL, and use these solutions as the standard solutions. With exactly 10 μL each of the test solution and the standard solutions, perform the test as directed under the Liquid Chromatography according to the following conditions, and measure the peak areas of miconazole nitrate, lidocaine, crotamiton and dipotassium glycyrrhizinate, A_{T1}, A_{T2}, A_{T3}, A_{T4}, A_{S1}, A_{S2}, A_{S3} and A_{S4}, from each solution.

Amount (mg) of miconazole nitrate ($C_{18}H_{14}Cl_4N_2O \cdot HNO_3$)
= Amount (mg) of miconazole nitrate RS × $\frac{A_{T1}}{A_{S1}}$

Amount (mg) of lidocaine ($C_{14}H_{22}N_2O$)
= Amount (mg) of lidocaine RS × $\frac{A_{T2}}{A_{S2}}$

Amount (mg) of crotamiton ($C_{13}H_{17}NO$)
= Amount (mg) of crotamiton RS × $\frac{A_{T3}}{A_{S3}}$

Amount (mg) of dipotassium glycyrrhizinate ($C_{42}H_{60}K_2O_{16}$)
= Amount (mg) of dipotassium glycyrrhizinate RS × $\frac{A_{T4}}{A_{S4}}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm, but 220 nm for miconazole nitrate).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution.

Mobile phase A: Dissolve 1.361 g of potassium dihydrogen phosphate in 1000 mL of water and add phosphoric acid to adjust pH to 2.5.

Mobile phase B: Methanol

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0.0 - 20.0	100 → 0	0 → 100
20.0 - 25.0	0	100
25.0 - 25.1	0 → 100	100 → 0
25.1 - 35.0	100	0

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the lidocaine, crotamiton, dipotassium glycyrrhizinate and miconazole nitrate peaks are eluted in this order with the resolution between crotamiton and dipotassium glycyrrhizinate peaks being NLT 5.3.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of dipotassium glycyrrhizinate is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Compound Milk-thistle Fruit Extract, Nicotinamide and Riboflavin Capsules
복방밀크시슬엑스·니코틴산아미드·리보플라빈 캡슐

Compound Milk-thistle Fruit Extract, Nicotinamide, and Riboflavin Capsules contain NLT 90.0% and NMT 150.0% of the labeled amounts of thiamine hydrochloride ($C_{12}H_{17}ClN_4OS \cdot HCl$: 337.27), nicotinic acid amide ($C_6H_6N_2O$: 122.13), riboflavin ($C_{17}H_{20}N_4O_6$: 176.13), and pyridoxine hydrochloride ($C_{17}H_{20}N_4O_6$: 176.13), pantothenate ($C_{18}H_{32}CaN_2O_{10}$: 476.54), and cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$: 1,355.38), NLT 90.0% and

NMT 110.0% of the labeled amounts of silymarin [as silybin ($C_{25}H_{22}O_{10}$: 482.40)] in milk thistle extract. (However, among the content of silymarin, the sum of silydianin ($C_{25}H_{22}O_{10}$: 482.40) and silycristine ($C_{25}H_{22}O_{10}$: 482.40) is NLT 20.0% and NMT 45.0%, the sum of silybcin A ($C_{25}H_{22}O_{10}$: 482.40), and silybin B ($C_{25}H_{22}O_{10}$: 482.40) is NLT 40.0% and NMT 65.0%, and the sum of isosilybin A ($C_{25}H_{22}O_{10}$: 482.40) and isosilybin B ($C_{25}H_{22}O_{10}$: 482.40) is NLT 10.0% and NMT 20.0%.)

Method of preparation Prepare as directed under Capsules, with Milk Thistle Extract, Thiamine Hydrochloride, Nicotinic Acid Amide, Riboflavin, Pyridoxine Hydrochloride, Calcium Pantothenate, Cyanocobalamin.

Identification (1) ***Milk-thistle Fruit Extract*—**(i) Weigh an amount of Compound Milk-thistle Fruit Extract, Nicotinamide and Riboflavin Capsules equivalent to about 30 mg of milk thistle extract, shake to mix with 10 mL of methanol, sonicate for 10 minutes, and use this solution as the test solution. Allow the test solution to stand for at least 15 minutes before use. Separately, weigh 2 mg of silibin RS, 5 mg of taxifolin RS, add 10 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate using a mixture of dichloromethane, acetone, and formic acid (75 : 16.5 : 8.5) as the developing solvent to a distance of about 10 cm, dry the plate between 100 and 105 ℃. Spray evenly 1% methanolic diphenylboric acid 2-aminoethyl ester solution on the plate, spray evenly 5% methanolic PEG 400 solution on to the plate, and examine it under ultraviolet light (main wavelength 365 nm); the R_f values and the light green fluorescence of the silybin spots obtained from the test solution and the standard solution are the same, and the test solution exhibits a relatively weakly fluorescent area above the silybin spot. The R_f values and yellowish brown fluorescence of taxifolin spots obtained from the test solution correspond to those of the standard solution, and in the test solution, a light green fluorescent spot (silicristin) exhibits below taxifolin.

(ii) Perform the test as directed under the Assay (1) with Compound Milk-thistle Fruit Extract, Nicotinamide and Riboflavin Capsules; the peaks of silycristine, silydianine, silybin A, silybin B, isosilybin A, and isosilybin B are appeared in this order in the test solution.

(2) ***Thiamine hydrochloride, nicotinic acid amide, riboflavin, pyridoxine hydrochloride, calcium pantothenate, cyanocobalamin*—**Perform the test as directed under the Analysis for Vitamins, with Compound Milk-thistle Fruit Extract, Nicotinamide and Riboflavin Capsules.

Disintegration Meets the requirements.

Uniformity of dosage units Meets requirements.

Assay (1) ***Silymarin (as silybin) in milk thistle extract*—**Weigh accurately the mass of NLT 20 capsules of Compound Milk-thistle Fruit Extract, Nicotinamide and Riboflavin Capsules equivalent to about 10 mg of silybin, add 90 mL of methanol, perform ultrasonic extraction for 20 minutes, cool to 20 °C, an filter. Add methanol to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of silybin RS (previously dried in a silica gel desiccator for 24 hours) and milk thistle extract control solution equivalent to about 10 mg of silybin, add methanol to make exactly 100 mL, and use these solutions as the standard solution and the milk thistle extract control solution, respectively. Perform the test as directed under the Liquid Chromatography according to the following conditions with 10 μL each of the test solution, standard solution, and control solution and determine the peak area of the test solution and the standard solution using the peaks of silicristin, silydianine, silybin A, silybin B, isosilybin A, and isosilybin B confirmed in the milk thistle extract control solution.

$$\text{Content (\%) of silymarin [as silybin } (C_{25}H_{22}O_{10})] = \frac{(F_1 + F_2 + F_3 + F_4 + F_5 + F_6) \times m_1}{F_7 + F_8 \times m_2} \times 100$$

$$\text{Amounts (\%) of silychristin } (C_{25}H_{22}O_{10}) \text{ and silydianin} (C_{25}H_{22}O_{10}) = \frac{F_1 + F_2}{(F_1 + F_2 + F_3 + F_4 + F_5 + F_6)} \times 100$$

$$\text{Amounts (\%) of silybin A } (C_{25}H_{22}O_{10}) \text{ and silybin B} (C_{25}H_{22}O_{10}) = \frac{F_3 + F_4}{(F_1 + F_2 + F_3 + F_4 + F_5 + F_6)} \times 100$$

$$\text{Amounts (\%) isosilybin A } (C_{25}H_{22}O_{10}) \text{ and isosilybin B } (C_{25}H_{22}O_{10}) = \frac{F_5 + F_6}{(F_1 + F_2 + F_3 + F_4 + F_5 + F_6)} \times 100$$

F_1 = Peak area of silicristin in the test solution
F_2 = Peak area of silidianine in the test solution
F_3 = Peak area of silybin A in the test solution
F_4 = Peak area of silybin B in the test solution
F_5 = Peak area of iosilybin A in test solution
F_6 = Peak area of isosilybin B in the test solution
F_7 = Peak area of silybin A in the standard solution
F_8 = Peak area of silybin B in the standard solution
m_1 = Mass (g) of silybin standard
m_2 = Mass (g) of milk thistle extract

Operating conditions

Detector: UV spectrophotometer (wavelength: 288 nm).

Column: A stainless steel column about 4 mm to 6

mm in internal diameter and 12 cm to 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Use mobile phases A and B to control a stepwise or gradient elution-wise as follows.

Mobile phase A: A mixture of water, methanol, and 85% phosphoric acid (65 : 35 : 0.5).

Mobile phase B: A mixture of water, methanol, and 85% phosphoric acid (50 : 50 : 0.5).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 28	100 → 0	0 → 100
28 - 35	0	100
35 - 36	0 → 100	100 → 0
36 - 51	100	0

Flow rate: 0.8 mL/min

Injection volume: 10 μL

System suitability: At least 1.8 minutes (difference in retention time between peaks of silybin A and silybin B). The retention time of silybin B should be about 30 minutes. If necessary, change the gradient elution of the mobile phase.

(2) ***Thiamine hydrochloride, nicotinic acid amide, riboflavin, pyridoxine hydrochloride, calcium pantothenate, cyanocobalamin*—**Weigh accurately the Mass of the content of NLT 20 capsules of Compound Milk-thistle Fruit Extract, Nicotinamide and Riboflavin Capsules and perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in light-resistant, tight containers.

Compound Nicotinamide, *d*-Biotin and Pyridoxine Hydrochloride Capsules
복방니코틴산아미드·*d*-비오틴·피리독신염산염 캡슐

Compound Nicotinamide, *d*-Biotin and Pyridoxine Hydrochloride Capsules contain NLT 90.0% and NMT 150.0% of the labeled amounts of nicotinamide ($C_6H_6N_2O$: 122.13), *d-biotin* ($C_{10}H_{16}N_2O_3S$: 244.31), pyridoxine hydrochloride ($C_8H_{11}NO_3 \cdot HCl$: 205.64), and NLT 90.0% and NMT 130.0% of the labeled amount of riboflavin butyrate ($C_{33}H_{44}N_4O_{10}$: 656.72) and NLT 90.0% and NMT 110.0% of the labeled amount of ursodeoxycholic acid (UDCA) ($C_{24}H_{40}O_4$: 392.57).

Method of preparation Prepare as directed under Capsules, with Nicotinamide, *D*-Biotin, Pyridoxine Hydrochloride, Ursodeoxycholic Acid, and Riboflavin Butyrate.

Identification (1) ***Pyridoxine hydrochloride, nicotinamide, d-biotin, riboflavin butyrate*—**Perform the test with Compound Nicotinamide, *d*-Biotin and Pyridoxine Hydrochloride Capsules as directed under the Analysis for Vitamins.

(2) ***Ursodeoxycholic acid*—**Weigh accurately an amount of Compound Nicotinamide, *d*-Biotin and Pyridoxine Hydrochloride Capsules equivalent to 10 mg of ursodeoxycholic acid according to the labeled amount, add 20 mL of ethanol, extract, and filter. Evaporate the filtrate on a steam bath to dryness, dissolve in 10 mL of ethanol, and use this solution as the test solution. Separately, weigh 10 mg of ursodeoxycholic acid RS, dissolve in 10 mL of ethanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, acetic acid(100), isooctane (40 : 30 : 30) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly phosphomolybdic acid in 50% saturated sulfuric acid solution on the plate; the R_f values and the colors of the spots obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Pyridoxine hydrochloride, nicotinamide, d-biotin, riboflavin butyrate*—**Weigh accurately the mass of NLT 20 capsules of Compound Nicotinamide, *d*-Biotin and Pyridoxine Hydrochloride Capsules and perform the test as directed under the Analysis for Vitamins.

(2) ***Ursodeoxycholic acid*—**Weigh accurately the contents of NLT 20 capsules of Compound Nicotinamide, *d*-Biotin and Pyridoxine Hydrochloride Capsules. Weigh accurately 50.0 mg of ursodeoxycholic acid ($C_{24}H_{40}O_4$), add 40 mL of methanol, shake well to mix for 30 minutes, and dissolve. Add 5.0 mL of the internal standard solution and 50 mL of methanol and use this solution as the test solution. Separately, weigh accurately 50.0 mg of ursodeoxycholic acid, dissolve in 40 mL of methanol, add 5.0 mL of the internal standard solution and methanol to make 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S of the peak area of ursodeoxycholic acid to that of the internal standard.

$$\text{Amount (mg) of ursodeoxycholic acid } (C_{24}H_{40}O_4) = \text{Amount (mg) of ursodeoxycholic acid RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh accurately 0.5 g

of cholic acid and dissolve in methanol to make 50 mL.

Operating conditions

Detector: A differential refractometer

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm to 30 cm in length, packed with octasilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A solution adjusted to pH 3.5 with phosphoric acid added to 500 mL of a mixture of methanol and water (70 : 30).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Compound Nicotinamide, Cyanocobalamin and Pyridoxine Hydrochloride Capsules
복방니코틴산아미드·시아노코발라민·피리독신염산염 캡슐

Compound Nicotinamide, Cyanocobalamin and Pyridoxine Hydrochloride Capsules contain NLT 90.0% and NMT 150.0% of the labeled amounts of nicotinamide ($C_6H_6N_2O$:122.13), cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$: 1355.37), pyridoxine hydrochloride ($C_8H_{11}NO_3 \cdot HCl$: 205.64), and thiamine nitrate ($C_{12}H_{17}N_5O_4S$: 327.36), and NLT 90.0% and NMT 110.0% of the labeled amounts of calcium pantothenate ($C_{18}H_{32}CaN_2O_{10}$: 476.53), silymarin [Silybin ($C_{25}H_{22}O_{10}$: 482.40)] in milk thistle extract. (However, among the content of silymarin, the sum of silydianin ($C_{25}H_{22}O_{10}$: 482.40) and silicristin ($C_{25}H_{22}O_{10}$: 482.40) is 20.0% to 45.0%, the sum of silybin A ($C_{25}H_{22}O_{10}$: 482.40) and silybin B ($C_{25}H_{22}O_{10}$: 482.40) is 40.0% to 65.0%, and the sum of isosilybin A ($C_{25}H_{22}O_{10}$: 482.40) and isosilybin B ($C_{25}H_{22}O_{10}$: 482.40) is 10.0% to 20.0%.

Method of preparation Prepare as directed under Capsules, with Nicotinamide, Cyanocobalamin, Pyridoxine Hydrochloride, Thiamine Nitrate, Calcium Pantothenate and Milk Thistle Extract.

Identification (1) ***Milk thistle extract*—**(i) Weigh an amount of Compound Nicotinamide, Cyanocobalamin and Pyridoxine Hydrochloride Capsules equivalent to about 30 mg of milk thistle extract according to the labeled amount, shake to mix with 10 mL of methanol, sonicate for 10 minutes, and use this solution as the test solution. Allow the test solution to stand for at least 15 minutes before use. Separately, weigh 2 mg of silibin RS and 5 mg of taxifolin RS, dissolve in 10 mL of methanol, and use this solution as the standard solution (1) and the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate using a mixture of dichloromethane, acetone, and formic acid (75 : 16.5 : 8.5) as the developing solvent to a distance of about 10 cm, dry the plate between 100 and 105 ℃, and air-dry the plate. Spray evenly 1% methanolic diphenylboric acid 2-aminoethyl ester solution on the plate, then spray evenly 5% methanolic polyethylene glycol 400 solution on the plate, and examine under ultraviolet light (main wavelength: 365 nm); the R_f values and pale green fluorescence of the silybin spot obtained from the test solution and the standard solution are the same, and the test solution exhibits a relatively weakly fluorescent area above the silybin spot. The R_f values and yellowish brown fluorescence of taxifolin spots obtained from the test solution and the standard solution are the same, and in the test solution, a light green fluorescent spot (silicristin) exhibits below taxifolin.

(ii) With Compound Nicotinamide, Cyanocobalamin and Pyridoxine Hydrochloride Capsules, perform the test as directed under the Assay (1); silycristine, silydianine, silybin A, silybin B, isosilybin A, and isosilybin B are eluted in this order in the test solution.

(2) ***Nicotinamide, cyanocobalamin, pyridoxine hydrochloride, thiamine nitrate, calcium pantothenate*—**Perform the test as directed under the Assay; the retention times of the major peak of each principal component obtained from the test solution and standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meet requirements.

Assay (1) ***Silymarin (as silybin) in milk thistle extract*—**Weigh accurately the mass of NLT about 20 capsules of Compound Nicotinamide, Cyanocobalamin and Pyridoxine Hydrochloride Capsules Weigh accurately an amount equivalent to about 10 mg of silybin, add 90 mL of methanol, sonicate for 20 minutes, cool to 20 ℃, filter, and add methanol to make exactly 100 mL. Use this solution as the test solution. Separately, silibin standard RS (dried in a silica gel desiccator for 24 hours in advance) Weigh accurately Milk Thistle Extract equivalent to about 10 mg and about 10 mg of silybin, add methanol to make exactly 100 mL, and use these solutions as the standard solution and milk thistle extract control solution, respectively. With each 10 μL of the test solution, the standard solution, and the control solution, perform the test as directed under the Liquid Chromatography according to the following conditions; determine the peak area of the test solution and the standard solution using the peaks of silicristin, silydianin, silybin A, silybin B, isosilybin A, and isosilybin B confirmed in the milk thistle extract control solution.

$$\text{Content (\%) of silymarin [as silybin } (C_{25}H_{22}O_{10})] = \frac{(F_1 + F_2 + F_3 + F_4 + F_5 + F_6) \times m_1}{(F_7 + F_8) \times m_2} \times 100$$

Content (%) of silicristine ($C_{25}H_{22}O_{10}$) and silidianin ($C_{25}H_{22}O_{10}$)

$$= \frac{F_1 + F_2}{(F_1 + F_2 + F_3 + F_4 + F_5 + F_6)} \times 100$$

Content (%) of silybin A ($C_{25}H_{22}O_{10}$) and silybin B ($C_{25}H_{22}O_{10}$)

$$= \frac{F_3 + F_4}{(F_1 + F_2 + F_3 + F_4 + F_5 + F_6)} \times 100$$

Content (%) of isosilybin A ($C_{25}H_{22}O_{10}$) and isosilybin B ($C_{25}H_{22}O_{10}$)

$$= \frac{F_5 + F_6}{(F_1 + F_2 + F_3 + F_4 + F_5 + F_6)} \times 100$$

F_1 = Peak area of silicristin in the test solution
F_2 = Peak area of silidianine in the test solution
F_3 = Peak area of silybin A in the test solution
F_4 = Peak area of silybin B in the test solution
F_5 = Peak area of iosilybin A in test solution
F_6 = Peak area of isosilybin B in the test solution
F_7 = Peak area of silybin A in the standard solution
F_8 = Peak area of silybin B in the standard solution
m_1 = Mass (g) of silybin standard
m_2 = Mass (g) of milk thistle extract

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 288 nm).

Column: A stainless steel column about 4 mm to 6 mm in internal diameter and about 12 cm to 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Use mobile phases A and B to control a stepwise or gradient elution-wise as follows.

Mobile phase A: A mixture of water, methanol, and 85% phosphoric acid (65 : 35 : 0.5).

Mobile phase B: A mixture of water, methanol, and 85% phosphoric acid (50 : 50 : 0.5).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 28	100 → 0	0 → 100
28 - 35	0	100
35 - 36	0 → 100	100 → 0
36 - 51	100	0

Flow rate: 0.8 mL/min

System suitability: At least 1.8 minutes (difference in retention time between peaks of silybin A and silybin B). The retention time of silybin B should be about 30 minutes. If absolutely necessary, change the gradient elution of the mobile phase.

(2) ***Nicotiniamide, cyanocobalamin, pyridoxine hydrochloride, thiamine nitrate, calcium pantothenate—***Weigh accurately the mass of NLT 20 capsules of Compound Nicotinamide, Cyanocobalamin and Pyridoxine Hydrochloride Capsules and perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in light-resistant, tight containers.

Compound Nicotinamide, Riboflavin and Oyster Shell Powder Tablets
복방니코틴산아미드·리보플라빈·모려가루 정

Compound Nicotinamide, Riboflavin and Oyster Shell Powder Tablets contain NLT 90.0% and NMT 150.0% of the labeled amount of nicotinamide ($C_6H_6N_2O$: 122.13), riboflavin ($C_{17}H_{20}N_4O_6$: 376.36), ascorbic acid ($C_6H_8O_6$: 176.12), pyridoxine hydrochloride ($C_8H_{11}NO_3 \cdot HCl$: 205.64), thiamine nitrate ($C_{12}H_{17}N_5O_4S$: 327.36), tocopherol acetate ($C_{31}H_{52}O_3$: 472.74), cholecalciferol ($C_{27}H_{44}O$: 384.64), and retinol palmitate ($C_{36}H_{60}O_2$: 524.86), NLT 90.0% and NMT 150.0% of iron (Fe: 55.85) in ferrous fumarate ($C_4H_2FeO_4$: 169.90), magnesium (Mg: 24.31), manganese (Mn: 54.94) in manganese sulfate hydrate, zinc (Zn: 65.38) in zinc sulfate hydrate, and NLT 90.0% of calcium (Ca: 40.078) in oyster shell powder.

Method of preparation Prepare as directed under Tablets, with Nicotinamide, Riboflavin, Oyster Shell Powder, Magnesium Oxide, Ascorbic Acid, Pyridoxine Hydrochloride, Thiamine Nitrate, Tocopherol Acetate, Cholecalciferol, Retinol Palmitate, Ferrous Fumarate, Manganese Sulfate Hydrate, and Zinc Sulfate Hydrate.

Identification (1) ***Nicotinamide, riboflavin, ascorbic acid, pyridoxine hydrochloride, thiamine nitrate, tocopherol acetate, cholecalciferol, and retinol palmitate—***Perform the test with Compound Nicotinamide, Riboflavin and Oyster Shell Powder Tablets as directed under the Analysis for Vitamins. However, use retinol palmitate RS for vitamin A.

(2) ***Ferrous fumarate, magnesium oxide, manganese sulfate hydrate, and zinc sulfate hydrate—***Perform the test with Compound Nicotinamide, Riboflavin and Oyster Shell Powder Tablets as directed under the Analysis for Minerals.

(3) ***Calcium in oyster shell powder***—Weigh an amount of Compound Nicotinamide, Riboflavin and Oyster Shell Powder Tablets equivalent to about 0.5 g of oyster shell, add 20 mL of dilute hydrochloric acid, dissolve by warming, and filter. Wash the residue 2 times each with 10 mL of dilute hydrochloric acid, combine the filtrate and the washings, add ammonia water to make it alkaline, and add excess hot ammonium hydroxide solution; a white precipitate forms, and this precipitate is insoluble in dilute acetic acid, but it is soluble in dilute hydrochloric acid or dilute sulfuric acid.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Nicotinamide, riboflavin, ascorbic acid, pyridoxine hydrochloride, thiamine nitrate, tocopherol acetate, retinol palmitate, and cholecalciferol***—Weigh accurately the mass of NLT 20 Compound Nicotinamide, Riboflavin and Oyster Shell Powder Tablets, powder, and perform the test as directed under the Analysis for Vitamins.

(2) ***Iron, magnesium, manganese, and zinc***—Weigh accurately the mass of NLT 20 Compound Nicotinamide, Riboflavin and Oyster Shell Powder Tablets, powder, and perform the test as directed under the Analysis for Minerals.

(3) ***Calcium in oyster shell powder***—Weigh accurately the mass of NLT 20 Compound Nicotinamide, Riboflavin and Oyster Shell Powder Tablets, and powder. Weigh accurately an amount equivalent to about 0.5 g of calcium (Ca), add 20 mL of dilute hydrochloric acid, dissolve by warming, and filter. Wash the residue 2 times each with 10 mL of dilute hydrochloric acid, combine the filtrate and the washings, add ammonia water to make it alkaline, and add excess ammonium hydroxide solution to generate a white precipitate. Filter the precipitate, and heat. After cooling, add water to make 200 mL. Pipet 20 mL of this solution, add 40 mL of water, 2 mL of 8 mol/L potassium hydroxide TS, and 0.1 g of indicator, and immediately titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS. The endpoint of titration is when the color of the solution changes from reddish purple to blue. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.004 mg of Ca

Packaging and storage Preserve in well-closed containers.

Compound Nicotinamide, Royal Jelly and Riboflavin Capsules
복방니코틴산아미드·로얄젤리·리보플라빈 캡슐

Compound Nicotinamide, Royal Jelly and Riboflavin Capsules contain NLT 90.0% of the labeled amount of 10-hydroxy-2-decenoic acid ($C_{10}H_{18}O_3$: 186.25) in royal jelly, and NLT 90.0% and NMT 150.0% of the labeled amounts of ascorbic acid ($C_6H_8O_6$: 176.12), thiamine hydrochloride ($C_{12}H_{17}ClN_4OS \cdot HCl$: 337.27), tocopherol acetate ($C_{31}H_{52}O_3$: 472.74), riboflavin ($C_{17}H_{20}N_4O_6$: 376.36), nicotinamide ($C_6H_6N_2O$: 122.13), pyridoxine hydrochloride ($C_8H_{11}NO_3 \cdot HCl$: 205.64), and cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$: 1355.37).

Method of preparation Prepare as directed under Capsules, with Nicotinamide, Royal Jelly, Riboflavin, Cyanocobalamin, Ascorbic Acid, Thiamine Hydrochloride, Pyridoxine Hydrochloride, and Tocopherol Acetate.

Identification (1) ***Royal jelly***—(i) Weigh the contents of Compound Nicotinamide, Royal Jelly and Riboflavin Capsules, equivalent to 50 mg of royal jelly, add 50 mL of acetone, shake, extract, and filter. Evaporate to concentrate the filtrate under reduced pressure to make about 10 mL and use this solution as the test solution. Separately, weigh about 50 mg of Royal Jelly, add 50 mL of acetone, extract, and then filter. Evaporate to concentrate the filtrate under reduced pressure to make about 10 mL and use this solution as the test solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of 1-propanol and strong ammonia water (7 : 3) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light and evenly spray iodine vapor on the plate; the colors and R_f values of several spots from the test solution and the standard solution are the same.

(ii) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

(2) ***Ascorbic acid, thiamine hydrochloride, riboflavin, nicotinamide, pyridoxine hydrochloride, tocopherol acetate, and cyanocobalamin***—With the contents of Compound Nicotinamide, Royal Jelly and Riboflavin Capsules, perform the test according to the Analysis for Vitamins.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***10-hydroxy-2-decenoic acid in royal jelly***—Weigh accurately the contents of NLT 20 capsules of Compound Nicotinamide, Royal Jelly and Riboflavin Capsules. Weigh accurately about 5 mg of 10-hydroxy-2-decenoic acid, add 40 mL of methanol, sonicate for 20 minutes, and add methanol to make exactly 50 mL. Centrifuge this solution, pipet 2 mL of the clear supernatant, add 10 mL of methanol to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately about 5 mg of 10-hydroxy-2-decenoic acid RS and dissolve in methanol to make exactly 50 mL. Pipet 2 mL of this solution, add methanol to make 10 mL, use this solution as the test solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of in-

dobufen, A_T and A_S, in each solution.

Amount (mg) of 10-hydroxy-2-decenoic acid ($C_{10}H_{18}O_3$)
= Amount (mg) of 10-hydroxy-2-decenoic acid RS ($C_{10}H_{18}O_3$) $\times \frac{A_T}{A_S}$

Operating conditions

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Detector: An ultraviolet absorption spectrophotometer (wavelength: 214 nm).

Mobile phase: A mixture of 2.5 mmol/L potassium dihydrogen phosphate TS (pH 3.0) and methanol (1 : 1).

Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of 10-hydroxy-2-decenoic acid is NMT 1.0%.

2.5 mmol/L potassium dihydrogen phosphate TS (pH 3.0)—Dissolve 0.340 g of potassium dihydrogen phosphate in water to make 1000 mL and add phosphoric acid to adjust the pH to 3.0.

(2) **Tocopherol acetate, ascorbic acid, thiamine hydrochloride, riboflavin, nicotinic acid amide, pyridoxine hydrochloride and cyanocobalamin*n*—**Weigh accurately the contents of NLT 20 capsules of Compound Nicotinamide, Royal Jelly and Riboflavin Capsules, perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in well-closed containers.

Compound Pancreatin, Dimethicone and Hemicellulase Tablets
복방판크레아틴·디메티콘·헤미셀룰라제 정

Compound Pancreatin, Dimethicone and Hemicellulase Tablets contain starch digestion activity, fat digestion activity, protein digestion activity, and hemicellulase in pancreatin equivalent to more than 90.0% of the labeled amount, and cholic acid ($C_{24}H_{40}O_5$: 408.57) in ox-bile extract. Dimethicone is polydimethylsiloxane ([-(CH_3)-SiO-]$_n$) and contains 85.0% to 115.0% of the labeled amount.

Compound Pancreatin, Dimethicone and Hemicellulase Tablets are delayed-release preparations.

Method of preparation Prepare as directed under Tablets, with Pancreatin, Ox-Bile Extract, Dimethicone, and Hemicellulase.

Identification (1) ***Starch digestion activity, fat digestion activity, protein digestion activity in pancreatin—*** Perform the test with Compound Pancreatin, Dimethicone and Hemicellulase Tablets, previously powdered, as direct under the Assay; the result is positive.

(2) ***Hemicellulase—***Perform the test with Compound Pancreatin, Dimethicone and Hemicellulase Tablets, previously powdered, as direct under the Assay; the result is positive.

(3) ***Ox-bile extract***—According to the labeled amount of Compound Pancreatin, Dimethicone and Hemicellulase Tablets, previously powdered, pipet an amount equivalent to 50 mg of ox-bile extract, add ethanol to make 20 mL, and use this solution as the test solution. Separately, weigh about 25 mg of Ox-bile Extract, add ethanol to make 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Paper Chromatography. Spot 10 μL each of the test solution and the standard solution on Whatman filter paper No. 1 or similar filter paper (impregnated with 2 mol/L acetic acid(100), washed with water, and dried in the shade). Next, develop the plate using a mixture of isopropanol, hydrochloric acid, and water (170 : 41 : 39) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spay 50% of sulfuric acid solution evenly onto the plate; several spots from the test solution have the same color and R_f value as the spots from the standard solution.

(4) ***Dimethicone—***Powder Compound Pancreatin, Dimethicone and Hemicellulase Tablets and determine the absorption spectrum as directed under the Assay; the standard solution and the test solution exhibit similar intensities of absorption as the same wavenumbers.

Disintegration Meets the requirements.

Uniformity of dosage units Meet requirements.

Assay (1) ***Pancreatin—***(i) Starch digestibility power (α-amylase): Weigh accurately the mass of NLT 20 Compound Pancreatin, Dimethicone and Hemicellulase Tablets, and powder. Weigh accurately the amount equivalent to 110 to 130 mg of Compound Pancreatin, Dimethicone and Hemicellulase Tablets as pancreatin according to the potency, put it in a 200-mL volumetric flask, add 1/15 mol/L phosphate buffer solution (pH 6.8) to make exactly 200 mL, and stir it for 30 minutes. Each mL of this solution does not exceed 20 FIP units of starch digestibility power, and the test solution is used in the test immediately after preparation.

Take 25 mL of 1% soluble starch solution, put it in a test tube (about 22 mm × 200 mm), add 10 mL of 0.2 mol/L phosphate buffer solution (pH 6.8) and 1 mL of 0.2 mol/L sodium chloride solution, close with an elastomeric closure, and allow to stand in a constant temperature water bath at 25 ℃. When the temperature of the solution reaches 25 ℃, take exactly 1 mL of the test solution to add, and at the same time, a stopwatch and shake to mix well to a constant temperature. Exactly 10 minutes after

adding the test solution, add 2 mL of 1 mol/L hydrochloric acid solution to stop the reaction. Transfer this solution to a glass-stoppered 300-mL Erlenmeyer flask, wash the test tube with about 20 mL of water, and combine it to the Erlenmeyer flask. Add accurately 10 mL of 0.05 mol/L iodine solution while stirring well, immediately add 45 mL of 0.1 mol/L sodium hydroxide solution, allow to stand in the dark for 15 minutes, then add 4 mL of 20% sulfuric acid solution and titrate with 0.1 mol/L sodium thiosulfate solution. Separately, take 25 mL of 1% soluble starch solution, put it in a test tube, add 10 mL of 0.2 mol/L phosphate buffer solution (pH 6.8) and 1 mL of 0.2 mol/L sodium chloride solution, close an elastomeric closure, and allow to stand in a constant temperature water bath at 25 °C. When the temperature of the solution reaches 25 °C, add 2 mL of 1 mol/L hydrochloric acid solution, shake to mix, immediately add 1 mL of the test solution to mix, and then perform a blank test by following the same procedures as for the test solution.

Potency of starch digestibility power in one tablet of Compound Pancreatin, Dimethicone and Hemicellulase Tablets (FIP unit/tablet)

$$= \frac{5(\mathrm{b}-\mathrm{a})}{1-0.03(\mathrm{b}-\mathrm{a})} \times 200 \times \frac{\mathrm{W}}{\mathrm{S}}$$

a: Volume (mL) of 0.1 mol/L sodium thiosulfate solution consumed in determination of the test solution

b: Volume (mL) of 0.1 mol/L sodium thiosulfate solution consumed in the blank test

S: Amount (mg) of sample taken

w: Average (mg) mass of 1 tablet

0.03: Correction factor

200: Dilution factor

5: $0.1 \times 1000 \times \frac{1}{10} \times \frac{1}{2}$

Definition of potency—1 FIP starch digestion activity unit refers to the amount of enzyme required to decompose starch at a rate that hydrolyzes 1 microequivalent of glycoside for 1 minute.

(ii) Fat digestibility power: Weigh accurately the mass of NLT 20 Compound Pancreatin, Dimethicone and Hemicellulase Tablets, and powder. Weigh accurately 70 to 90 mg of Compound Pancreatin, Dimethicone and Hemicellulase Tablets, put it in a mortar, add 8 to 10 mL of water at 5 °C, grind well for 10 minutes, then put in a 200-mL volumetric flask, and add cold water to make exactly 200 mL. Each mL of this solution contains about 12 FIP fat digestion activity units. Shake to mix well this solution for several minutes, and store it at 4°C. Prepare the test solution and use it for each test. The temperature when used for the test is 20 °C.

Put 10 mL of olive oil emulsion in a glass container of about 50 mL, buffer it with 8 mL of tris buffer solution and 2 mL of 8 W/V% sodium taurocholate solution, and then dilute with water so that the total amount diluted with water is (30 - X) mL. Put in a constant temperature water bath at 37±0.1 °C so that the temperature of the solution is 37±0.1 °C. Adjust the pH to 9.05 with 0.05 to 0.1 mol/L sodium hydroxide solution, but adjust to pH with a microburet to 9.0, and then adjust the pH to 9.05 again with an automatic microburet. Add accurately X mL of the test solution (containing 8 to 16 FIP lipase units) to the solution adjusted to 9.05 and titrate it with 0.1 mol/L sodium hydroxide solution to maintain the pH of 9.0 using an automatic microburet. Determine the number of mL of 0.1 mol/L sodium hydroxide solution consumed per minute. Perform titration by stirring with a stirrer at a constant speed in a nitrogen stream or in a closed container. Repeat 4 to 5 times, discard the first one, and take the average of the remaining times. After completing the preliminary experiment, adjust the amount of the test solution so that the volume (mL) consumed per minute of 0.1 mol/L sodium hydroxide solution is 0.08 to 0.16 mL and then proceed again in the same manner as above. Separately, proceed with pancreatin RS in the same manner as above, and make any necessary correction.

Potency of fat digestion activity in one tablet of this medicine (FIP unit/tablet)

$$= \frac{\mathrm{b} \times 100{,}000}{\mathrm{a}} \times \frac{200}{\mathrm{X}} \times \mathrm{F} \times \mathrm{w}$$

a: Amount (mg) of sample taken

b: Volume (mL) of 0.1 mol/L sodium hydroxide solution consumed per minute

X: Volume (mL) of test solution taken

F: $\frac{Theoretical\ potency\ of\ RS}{Experimental\ potency\ of\ RS}$

w: Average weight (mg) of 1 tablet

100,000: 0.1 × 1000 ×1000

200: Dilution factor

Definition of potency—The amount of enzyme that liberates 1 microequivalent of fatty acid per minute under the conditions of temperature 37 °C and pH 9.0 is considered as 1 FIP fat digestion activity unit.

(iii) Protein digestion activity: Weigh accurately the mass of NLT 20 Compound Pancreatin, Dimethicone and Hemicellulase Tablets, and powder. Weigh accurately about 0.1 g of Compound Pancreatin, Dimethicone and Hemicellulase Tablets, put it in a cooled mortar, add cold 0.02 mol/L calcium hydrochloride solution, and grind and shake to mix well to make 100 mL. Add 10 mL of enterokinase solution to 10 mL of this solution, activate it, shake to mix well, and allow to stand at 35 °C for 90 minutes. Add 30 to 40 μ*g* of pancreatin per mL diluted with borate buffer solution, pH 7.5, in this solution.
Separately, weigh accurately about 0.1 of the pancreatin RS (1.65 FIP protease unit/mg), put it in the cooled mortar, add 0.02 mol/L calcium chloride solution, grind and shake to mix well, add to a 100-mL volumetric flask, and wash with 0.02 mol/L calcium chloride solution to make 100 mL. Pipet 3 to 4 mL of this solution, put it in a 100-

mL volumetric flask, add cold borate buffer solution, pH 7.5, and shake to mix to make 100 mL. Each mL of this solution contains 30 to 40 μg of pancreatin, and the absorbance is 0.15 to 0.60.
Prepare 8 test tubes, divide them into 2 groups of 4 each, and test as follows.

Blank test solution group—S_1B, S_2B, S_3B, UB

Test solution group—S_1, S_2, S_3, U

The blank test solution group is operated as follows.

Test tube	Borate Buffer solution	Standard solution	Test solution	5% of trichloroacetic add solution	Casein solution of pH 8.0
S_1B	2 mL	1 mL	-	5 mL	2 mL
S_2B	1 mL	2 mL	-	5 mL	2 mL
S_3B	-	3 mL	-	5 mL	2 mL
UB	1 mL	-	2 mL	5 mL	2 mL

Add boate buffer solution, standard solution, and test solution to each test tube in the blank test solution group as above, add 5% of trichloroacetic acid again, shake to mix well, maintain 35 °C in a constant temperature water bath, and then add accurately 2 mL each of casein solution, pH 8.0. Shake to mix well, remove from a constant temperature water bath, cool, and filter to use as blank test solution. The test solution group is operated as follows.

Test tube	Borate Buffer solution	Standard solution	Test solution	Casein solution of pH 8.0	5% of trichloroacetic add solution
S_1	2 mL	1 mL	-	2 mL	5 mL
S_2	1 mL	2 mL	-	2 mL	5 mL
S_3	-	3 mL	-	2 mL	5 mL
U	1 mL	-	2 mL	2 mL	5 mL

Add the borate buffer solution, standard solution, and test solution to each test tube in the test solution group as above, maintain the temperature at 35 °C in a constant temperature water bath, add 2 mL each of casein solution, pH 8.0, allow to stand for exactly 30 minutes, and then add 5 mL each of 5% trichloroacetic acid solution. Remove from the water bath, allow to stand at room temperature for about 20 minutes to completely precipitate the protein, and then filter twice with the same filter paper. For the blank test solution group and the filtrate of the test solution group, determine each absorbance at a layer length of 1 cm and a wavelength of 280 nm using the reagent blank test solution as a control. Shake to mix 3 mL of borate buffer solution, 5 mL of 5% trichloroacetic acid solution, and 2 mL of casein solution, pH 8.0, to prepare the reagent blank test solution.

Potency of protein digestion activity in one tablet of Compound Pancreatin, Dimethicone and Hemicellulase Tablets (FIP unit)

$$= \frac{\mathrm{UA}}{\mathrm{SA}} \times \mathrm{C} \times Amount\ (mg)\ of\ RS \times \frac{Dilution\ factor\ of\ test\ solution}{Dilution\ factor\ of\ standard\ solution} \times \frac{Average\ mass\ (mg)\ of\ 1\ tablet}{Amount\ (mg)\ of\ sample\ taken}$$

UA: U-UB

SA: $\frac{(S_1-S_1B)+(S_2-S_2B)+(S_3-S_3B)}{3}$

C: Unit of protease of 1 mg of reference standard (FIP unit)

Definition of potency—Determine the unit by comparing it with pancreatin RS of NF. 1 FIP protein digestion activity unit is the amount of enzyme required to decompose casein to an absorbance equivalent to 1 micro tyrosine per minute.

Filter paper—Filter a 5% trichloroacetic acid solution through filter paper and determine the absorbance of the filtrate at 280 nm using an unfiltered 5% trichloroacetic acid solution as a control. Use filter paper whose absorbance does not exceed 0.04.

(2) ***Hemicellulase***—Weigh accurately the mass of NLT 20 tablets of Compound Pancreatin, Dimethicone and Hemicellulase Tablets, and powder. According to the potency, weigh accurately about 0.1 to 0.2 g of hemicellulase, put in a mortar, add with water, shake to mix well, then put in a 100-mL volumetric flask. Wash the mortar with water, and add the washed solutions to make 100 mL with water. Take 5 mL of this solution, put it in a 100-mL volumetric flask, and add water to make 100 mL. Before testing, filter with Whatman filter paper No. 1 and use the filtrate as the test solution. 1 mL of this solution should be able to change the relative fluidity of 0.18 to 0.22 for 5 minutes when tested under the test conditions. If not, the amount of the test is adjusted. Put the viscometer vertically in a constant temperature water bath (40 ± 1 ℃) and wash thoroughly with water. Add 20 mL of substrate solution and 4 mL of acetic acid and sodium acetate buffer solution (pH 4.5) to two 50 mL stoppered Erlenmeyer flasks for the test solution and one 50 mL stoppered Erlenmeyer flask for the test solution, and warm and allow to stand in a constant temperature water bath (40 ± 1°C) for 15 minutes.
Add 1 mL of the test solution to the flask for the test solution, immediately operate the stopwatch 1 and shake to mix the solution well. Immediately, take 10 mL of this solution and put it into the wide opening of the viscometer. After about 2 minutes, when the pressure is reduced through the rubber tube connected to the mouth side, and

when the reaction solution passes the upper half scale; operate stopwatch 2 and at the same time determine the reaction time (minutes) (Tr) of the stopwatch 1. When the meniscus of the reaction solution passes the lower scale, determine the time (seconds) (Tt) of the stopwatch 2. Immediately, re-aspirate the reaction solution, raise it to the upper half of the viscometer, and repeat the operation as above. The total reaction time (Tr) of these four tests should not exceed 15 minutes. Add 1 mL of water to the blank test substrate solution flask, take 10 mL of this solution, put it into the wide mouth of the viscometer, reduce the pressure through the rubber tube connected to the narrow mouth, bring this solution up to the upper half scale, and then let it flow naturally. When the meniscus passes the upper scale of the viscometer, operate the stopwatch, and determine the time (seconds) (Ts) until it passes the lower scale. Perform this test 5 times and determine the average value. Determine the time (seconds) (Tw) using 10 mL of equilibrated water and operate in the same manner as for the substrate solution for the blank test solution above. Perform this test 5 times as well and determine the average value.

$$T_N = 1/2\ (Tt/60\ \text{seconds/minutes}) + Tr$$

Fr: Relative flow rate for each reaction time

Ts: Average flow time (seconds) for substrate solution for blank test

Tw: Average flow time (seconds) for water for blank test

Tt: Flow time (seconds) of the reacted test solution

Tr: Time from when the test solution is added to the substrate solution until the flow time (Tt) is measured on the viscometer.

T_N: Response time (minutes) (Tr) plus 1/2 of the flow time converted to minutes

With the four Fr values and four T_N values obtained using the formula above, draw a calibration curve with the T_N values as the horizontal axis and the Fr values as the vertical axis. At the time, the calibration curve is a straight line. From this calibration curve, obtain the Fr value when the T_N value is 5 and 10 minutes and calculate the potency according to the following formula. At the time, the difference between the Fr values at 5 minutes of T_N value and 10 minutes of T_N value is 0.18 to 0.22.

One hemicellulase unit (HCU) per Compound Pancreatin, Dimethicone and Hemicellulase Tablet

$$= \frac{M(Fr_{10} - Fr_5) \times dilution\ factor}{W}$$

Fr_5: Relative fluidity after 5 minutes of reaction time

Fr_{10}: Relative fluidity after 10 minutes of reaction time

M: Average weight of 1 tablet (g)

W: Sample collection amount (g)

Definition of potency—When tested as directed under specified test conditions using locust bean gum as a substrate solution, the activity unit that gives a change in relative fluidity of 1.0 in 5 minutes is referred as 1 hemicellulase unit.

Substrate solution—Take 12.5 mL of 0.2 mol/L hydrochloric acid and 250 mL of warm water (72 to 75 °C) and put in a blender. Weigh accurately 2.0 g of locust bean gum, calculated on the anhydrous basis, add it slowly, and mix carefully at low speed not to let the solution flow out. Wipe the rim of the container with a small amount of warm water using a rubber spatula and shake to mix at high speed for 5 minutes. Transfer to a 1000-mL beaker, cool to room temperature, and adjust pH to 6.0 with 0.2 mol/L sodium hydroxide. Transfer this solution to a 1000-mL volumetric flask, add water to make 1000.0 mL, and shake to mix well. Filter through gauze before use.

(3) ***Bromelain***—Weigh accurately the mass of NLT 20 Compound Pancreatin, Dimethicone and Hemicellulase Tablets and Bromelain Tablets, and powder. Weigh accurately the amount equivalent to about 50 mg of cholic acid ($C_{24}H_{40}O_5$) and add 60% acetic acid solution to make exactly 100 mL. Filter, if necessary, and use the filtrate as the test solution. Separately, weigh accurately about 50 mg of the cholic acid RS, put it in a 100-mL volumetric flask, dissolve it in 60% acetic acid solution, and then add 60% acetic acid solution to make exactly 100 mL and use this solution as the standard solution. This solution can be used for several months if stored in a cool, dark place. Take 1 mL each of the standard solution and the test solution, put in glass-stopped test tubes, add 1 mL each of the newly prepared furfural solution (1 in 100) to each test tube, cool in an ice bath for about 5 minutes, and dissolve it in dilute sulfuric acid. (Dissolve 50 mL of sulfuric acid in 65 mL of water.) Add 13 mL each. Shake to mix the contents thoroughly in the test tube, react on a steam bath at 70 °C for 10 minutes, cool in an ice bath for 2 minutes, and then perform the test as directed under the Ultraviolet-visible Spectroscopy using a dilute sulfuric acid solution as a control and determine the absorbance A_T and A_S at a wavelength of 660 nm.

$$\text{Amount (mg) of cholic acid } (C_{24}H_{40}O_5) = \text{Amount (mg) of cholic acid RS} \times \frac{A_T}{A_S} \times 10$$

(4) ***Bromelain***—Weigh accurately the mass of NLT 20 Compound Pancreatin, Dimethicone and Hemicellulase Tablets, and powder. Hereinafter, perform the test as directed under the Assay of United States Pharmacopoeia simethicone.

Packaging and storage Preserve in tight containers.

Compound Polysaccharide Iron Complex, Folic Acid and Cyanocobalamin Capsules
복방폴리사카리드철착염·폴산·시아노코발라민 캡슐

Compound Polysaccharide Iron Complex, Folic Acid and Cyanocobalamin Capsules contain NLT 90.0% and NMT 110.0% of iron in polysaccharide iron complex (Fe: 55.85) and NLT 90.0% and NMT 150.0% of folic acid ($C_{19}H_{19}N_7O_6$: 441.40) and cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$: 1,355.37), respectively, according to the labeled amount.

Method of preparation Prepare as directed under Capsules, with Polysaccharide Iron Complex, Folic Acid and Cyanocobalamin.

Identification (1) ***Iron in polysaccharide iron complex*—**Weigh an amount of Compound Polysaccharide Iron Complex, Folic Acid and Cyanocobalamin Capsules, equivalent to 0.2 g of polysaccharide iron complex, and perform the test as directed under the Identification of Polysaccharide Iron Complex Tablets.

(2) ***Folic acid and cyanocobalamin***—Perform the test with Compound Polysaccharide Iron Complex, Folic Acid and Cyanocobalamin Capsules as directed under the Analysis for Vitamins.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Iron in polysaccharide iron complex*—**Weigh accurately the mass of NLT 20 capsules of Compound Polysaccharide Iron Complex, Folic Acid and Cyanocobalamin Capsules, and perform the test as directed under the Assay of Polysaccharide Iron Complex Tablets.

(2) ***Folic acid and cyanocobalamin*—**Weigh accurately the mass of NLT 20 capsules of Compound Polysaccharide Iron Complex, Folic Acid and Cyanocobalamin Capsules, and perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in tight containers.

Compound Ranitidine Hydrochloride, Magnesium Oxide and Magnesium Aluminosilicate Tablets
복방라니티딘염산염·산화마그네슘·규산알루민산마그네슘 정

Compound Ranitidine Hydrochloride, Magnesium Oxide and Magnesium Aluminosilicate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of ranitidine hydrochloride ($C_{13}H_{22}N_4O_3S$·HCl: 350.87). One tablet of Magnesium Oxide and Magnesium Aluminosilicate Tablet contains NLT 61.5 mg and NMT 75.1 mg of total aluminum oxide in magnesium aluminosilicate ($2MgO·Al_2O_3·SiO_2·xH_2O$) and magnesium aluminum hydrate (Al_2O_3: 101. 96), and NLT 99.1 mg and NMT 121.1 mg of magnesium aluminosilicate, magnesium aluminum hydrate, and magnesium oxide (MgO: 40.30).

Method of preparation Prepare as directed under Tablets, with Ranitidine Hydrochloride, Magnesium Oxide, Magnesium Aluminosilicate, and Magnesium Aluminum Hydrate.

Identification (1) ***Ranitidine hydrochloride*—**Perform the test with Compound Ranitidine Hydrochloride, Magnesium Oxide and Magnesium Aluminosilicate Tablets as directed under the Identification of ranitidine hydrochloride tablets under the United States Pharmacopeia.

(2) ***Aluminum oxide in magnesium aluminosilicate and magnesium aluminum hydrate*—**Weigh about 0.5 g of Compound Ranitidine Hydrochloride, Magnesium Oxide and Magnesium Aluminosilicate Tablets, add 10 mL of dilute hydrochloric acid, and dissolve by warming; the resulting solution responds to the Qualitative Analysis for aluminum salt and magnesium salt.

(3) ***Aluminum oxide in magnesium aluminosilicate, magnesium oxide, and magnesium aluminum hydrate*—**Weigh about 0.5 g of Compound Ranitidine Hydrochloride, Magnesium Oxide and Magnesium Aluminosilicate Tablets, add 10 mL of dilute hydrochloric acid, and dissolve by warming; the resulting solution responds to the Qualitative Analysis for aluminum salt and magnesium salt.

(4) ***Silicic acid*—**Mix Compound Ranitidine Hydrochloride, Magnesium Oxide and Magnesium Aluminosilicate Tablets by shaking well. To 0.125g of Compound Ranitidine Hydrochloride, Magnesium Oxide and Magnesium Aluminosilicate Tablets, add 5 mL of dilute sulfuric acid (1 in 3), and heat until white smoke is produced. After cooling, add 20 mL of water, and filter. Wash the residue with 30 mL of water, add 2 mL of methylene blue solution (1 in 10000), and then wash with 30 mL of water again; a precipitate exhibits a blue color.

Acid-neutralizing capacity For a daily dose of Compound Ranitidine Hydrochloride, Magnesium Oxide and Magnesium Aluminosilicate Tablets (2 tablets), the consumed amount of 0.1 mol/L hydrochloric acid is NLT 146 mL.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Ranitidine hydrochloride*—**Weigh accurately the mass of NLT 20 Compound Ranitidine Hydrochloride, Magnesium Oxide and Magnesium Aluminosilicate

Tablets, powder, and perform the test as directed under the Assay of ranitidine hydrochloride tablets under the United States Pharmacopeia.

(2) ***Aluminum oxide in magnesium aluminosilicate and magnesium aluminum hydrate (Al_2O_3)***—Weigh accurately the mass of NLT 20 Compound Ranitidine Hydrochloride, Magnesium Oxide and Magnesium Aluminosilicate Tablets, and powder. Weigh accurately an amount equivalent to about 4 Compound Ranitidine Hydrochloride, Magnesium Oxide and Magnesium Aluminosilicate Tablets (amount equivalent to 0.5 g of magnesium aluminosilicate and 0.4 g of magnesium aluminum hydrate), add 30 mL of dilute hydrochloric acid, dissolve by heating, and add water to make 250 mL. Use this solution as the test solution. Take 15.0 mL of the test solution, add 25 mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt and 20 mL of acetic acid-ammonium acetate buffer solution, pH 4.8, and boil for 5 minutes. After cooling, add 55 mL of ethanol, and titrate with 0.05 mol/L zinc sulfate VS (indicator: 2 mL of dithizone TS). The endpoint of titration is when the solution changes from pale dark green to pale purple. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.5490 mg of Al_2O_3

(3) ***Magnesium oxide (MgO) in magnesium aluminosilicate, magnesium oxide, magnesium aluminum hydrate***—Take 10.0 mL of the test solution prepared from the assay of aluminum oxide mentioned above, add a small amount of water, add 5 mL of triethanolamine solution (1 in 2), and shake to mix. With ammonia water, make the pH 10, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 40 mg of eriochrome black T-sodium chloride TS). The endpoint of titration is when the solution changes from reddish purple to blue. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.0152 mg of MgO

Packaging and storage Preserve in well-closed containers.

Compound Selenium in Dried Yeast, Retinol Palmitate and Ascorbic Acid Capsules
복방셀레늄함유건조효모·레티놀팔미테이트·아스코르브산 캡슐

Compound Selenium in Dried Yeast, Retinol Palmitate and Ascorbic Acid Capsules contain NLT 90.0% and NMT 150.0% of the labeled amounts of selenium (Se : 78.96) of selenium in dried yeast, retinol palmitate ($C_{36}H_{60}O_2$: 524.86), ascorbic acid ($C_6H_8O_6$: 176.12) and tocopheryl acetate ($C_{31}H_{52}O_3$: 472.74).

Method of preparation Prepare as directed under Capsules, with Selenium in Dried Yeast, Retinol Palmitate, Ascorbic Acid and Tocopheryl Acetate.

Identification (1) ***Selenium of selenium in dried yeast***—Weigh an amount of Compound Selenium in Dried Yeast, Retinol Palmitate and Ascorbic Acid Capsules, equivalent to 1 mg of selenium according to the labeled amount, and perform the test as directed under the Analysis for Minerals.

(2) ***Ascorbic acid, tocopheryl acetate and retinol palmitate***—Perform the test with Compound Selenium in Dried Yeast, Retinol Palmitate and Ascorbic Acid Capsules as directed under the Analysis for Vitamins.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Ascorbic acid, tocopheryl acetate and retinol palmitate***—Weigh accurately the contents of NLT 20 capsules of Compound Selenium in Dried Yeast, Retinol Palmitate and Ascorbic Acid Capsules, and perform the test as directed under the Analysis for Vitamins.

(2) ***Selenium***—Weigh accurately the contents of NLT 20 capsules of Compound Selenium in Dried Yeast, Retinol Palmitate and Ascorbic Acid Capsules, and perform the test as directed under the Analysis for Minerals.

Packaging and storage Preserve in tight containers.

Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets
복방트리메부틴말레산염·메타규산알루민산마그네슘·침강탄산칼슘 정

Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets contains trimebutine maleate ($C_{22}H_{29}O_5N \cdot C_4H_4O_4$: 503.54), sodium bicarbonate ($NaHCO_3$: 84.01), precipitated calcium carbonate ($CaCO_3$: 100.09), and magnesium oxide (MgO: 40.30) and aluminum oxide (Al_2O_3: 101.96) in magnesium aluminometasilicate equivalent to 90.0% to 110.0% of the labeled amount, contains total alKoids [hyoscyamine ($C_{17}H_{23}NO_3$: 289.37) and scopolamine ($C_{17}H_{21}NO_4$: 303.35)] in scopolia extract equivalent to 45.0 to 65.0 μ*g* per tablet, and glycyrrhizic acid ($C_{42}H_{62}O_{16}$: 822.93) in licorice powder equivalent to NLT 90.0%, and contains NLT 90.0% of starch saccharifying activity (pH 4.5) of 278 units, protein digestibility power (pH 3.0) of 170 units, and fat

digestion activity (pH 6.0) of 45 units.

Method of preparation Prepare as directed under Tablets, with Trimebutine Maleate, Magnesium Aluminome Tasilicate, Precipitated Calcium Carbonate, Sodium Bicarbonate, Powdered Glycyrrhiza, Scopolia Extract, Diastase, Protease, Cellulase 2000 IV and Lipase II.

Identification (1) ***Trimebutine maleate*—**Weigh an amount of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, equivalent to about 0.1 g of trimebutine maleate, according to the labeled amount, add 20 mL of chloroform, shake to mix, extract, and filter. Use the filtrate as the test solution. Separately, dissolve 0.1 g of trimebutine maleate RS in 20 mL of 95% ethanol and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol and water (8 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm) or spray Dragendorff's TS evenly; the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

(2) ***Magnesium metasilicate aluminate***—(i) Aluminum: Powder 2 tablets of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, add 30 mL of water, dissolve the soluble content, filter, and wash the residue with water. Add 10 mL of sodium hydroxide solution (1 in 6) to the residue, warm to dissolve, cool, filter, add hydrochloric acid to the filtrate to make it acidic, and filter again. Neutralize this filtrate with ammonia TS and responds to the Qualitative Analysis for aluminum salt.

(ii) Magnesium: Take 5 tablets of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, add 50 mL of water, dissolve the soluble content, filter, and wash the residue with water. Add 10 mL of hydrochloric acid to this residue, boil the solution for 1 minute, cool, filter, and add ammonia TS to the filtrate, and responds to the Chemical identification responds for magnesium salt.

(iii) Silicon: Take 2 tablets of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, add 30 mL of water, elute and filter the soluble content, wash the residue thoroughly with warm water, and then dry. Separately, round the platinum wire to create a melting hole for sodium ammonium hydrogen phosphate, and then apply the dried material to melt it again; it exhibits an insoluble part floating in the lump, and when cooling this melting hole, it becomes opaque.

(3) ***Scopolia extract***—Weigh an amount of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, equivalent to 0.6 g of scopolia extract, according to the labeled amount, add 30 mL of water, shake to mix evenly, add 200 mL of ether and 15 g of sodium chloride, seal, shake to mix for 2 hours, add 10 g of tragacantha powder, and shake to mix vigorously. Take 150 mL of the clearly separated ether layer, evaporate to dryness on a steam bath, then dissolve in 100 mL of ethanol and use the solution as the test solution. Separately, weigh 0.6 g of 10% Scopolia Extract Powder from the Korean Pharmacopoeia and treat it in the same manner as the above test solution to use this solution as the standard solution. However, during operation, add 200 mL of ether, add 15 mL of ammonia TS, and extract under alkalinity. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, ethanol, dimethylformamide, and diethylamie (2 : 1 : 1 : 1) as the developing solvent to a distance of about 10 cm and air-dry the plate. Spray Dragendorff's TS evenly onto the plate; the R_f value and the color of the spots obtained from the sample and the standard solutions are the same.

(4) ***Precipitated calcium carbonate***—Weigh 1 g of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets and carbonize. After cooling, add 30 mL of diluted hydrochloric acid to the residue, warm on a steam bath for 10 minutes, add water to make 50 mL, and filter. Allow this filtrate to stand on a steam bath for 1 hour to complete precipitation. (Precipitation responds to the Qualitative Analysis (3) for sodium salt.

(5) ***Sodium bicarbonate*—**Weigh 1 g of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, add 30 mL of water, dissolve at 30 to 40 °C, and filter. The filtrate responds to the Qualitative Analysis for sodium salt and hydrogen carbonate.

(6) ***Powdered licorice*—**Weigh the amount equivalent to about 1.0 g of licorice, add 100 mL of 80% ethanol, attach a reflux condenser, and extract under reflux on a steam bath for 1 hour. Add 20 mL of 10% sulfuric acid, attach a reflux condenser, and heat for 2 hours to hydrolyze. After cooling, extract with 30 mL of chloroform three times, filter, and concentrate under reduced pressure. Add 2 mL of a mixture of chloroform and methanol (1 : 1) to the residue and dissolve it. Use this solution as the test solution. Separately, weigh about 1.0 g of Licorice and proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform and methanol (19 : 1) as the developing solvent to a distance of about 10 cm and dry the plate at 105 ºC for 10 minutes. Spray 4-

methoxybenzaldehyde and sulfuric acid TS evenly onto the plate; the R_f value and the color of the spots obtained from the sample and the standard solutions are the same.

(7) ***Diastase, protease, cellulase 2000 IV and lipase II***—It exhibits a positive reaction when tested as directed under the Assay.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Acid-neutralizing capacity Take NLT 20 tablets of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, weigh accurately the mass, powder, and perform the test as directed under the Acid-neutralizing Capacity; the consumption of 0.1 mol/L hydrochloric acid per daily dose (6 tablets) is NLT 80 mL.

Assay (1) ***Trimebutine maleate***—Weigh accurately the mass of NLT 20 tablets of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, and powder. Weigh accurately an amount equivalent to about 0.1 g of trimebutine maleate ($C_{22}H_{29}NO_5 \cdot C_4H_4O_4$), dissolve in a mixture of 0.01 mol/L hydrochloric acid and acetonitrile (13 : 7) to make 100 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 0.1 g of trimebutine maleate RS, proceed in the same manner as the test solution, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of trimebutine and maleic acid, respectively.

$$\text{Amount (mg) of trimebutine maleate } (C_{22}H_{29}NO_5 \cdot C_4H_4O_4) = \text{Amount (mg) of trimebutine maleate RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Add ammonium acetate solution (1 in 1000) to dilute perchloric acid (17 in 20000) and adjust the pH to 3.0. Dissolve 1 g of sodium 1-pentanesulfonate in 650 mL of this solution and filter through a membrane filter. Add 350 mL of acetonitrile to 650 mL of the filtrate.

Flow rate: Adjust the flow rate so that the retention time of trimebutine is about 9 minutes.

Time span of area measurement: About 2 times the retention time of trimebutine following the maleic acid peak.

Selection of column: Dissolve 40 mg of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets and 20 mg of imipramine hydrochloride in a mixture of 0.01 mol/L hydrochloric acid TS and acetonitrile (13 : 7) to make 100 mL. Proceed with 20 μL of this solution under the above operating conditions; use a column from which trimebutine and imipramine are eluted in this order with the resolution being NLT 2.5.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of trimebutine obtained from 20 μL of the standard solution is between 2 mm and 6 mm.

(2) ***Aluminum oxide and magnesium oxide in magnesium metasilicate aluminate***—(i) Weigh accurately the mass of NLT 20 tablets of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, and powder. Weigh accurately the amount equivalent to 10 tablets, dissolve the soluble components in 50 mL of dilute hydrochloric acid, and evaporate to dryness on a steam bath. Add 30 mL of hydrochloric acid again to the residue, evaporate to dryness, add 25 mL of boiling water to the residue, filter it through quantitative filter paper, and wash the precipitate 4 times with 10 mL of hot water, respectively. Transfer the precipitate back to the evaporation dish, add 50 mL of water, boil on a steam bath for 15 minutes, filter through quantitative filter paper, and wash the precipitate with hot water. Combine the filtrate and washings, add water to make 500 mL, and use this solution as the test solution. Take 50.0 mL of the test solution, add 25.0 mL of 0.05 mol/L disodium ethylenediaminetetraacetate VS, add 25 mL of acetic acid and ammonium acetate buffer solution (pH 4.5), heat on a steam bath, cool, add 100 mL of ethanol and 2 mL of dithizone TS, and titrate with 0.05 mol/L zinc sulfate VS. However, the endpoint of titration is when the color changes from green to bright pink. Perform a blank test in the same manner and make any necessary correction.

$$\text{Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium VS} = 2.5490 \text{ mg of } Al_2O_3$$

(ii) Magnesium oxide: Take 50.0 mL of the test solution in (1), put it in a beaker, add water to make about 70 mL, add 10 mL of ammonium chloride solution (1 in 10) and 1 to 2 drops of methyl red TS and heat to boiling. Add ammonia water (10%) until the color of the solution changes form red to yellow, boil for about 1 hour, cool, filter, and wash the precipitate 3 times with ammonium chloride solution (1 in 50). Combine the filtrate and the washed solution, add 3 drops of triethanolamine, 2 mL of potassium cyanide solution (5 in 100), and strong ammonia water to adjust the pH to 10, and titrate with 0.01 mol/L disodium ethylenediaminetetraacetate VS. (indicator: Eriochrome black T) However, the endpoint of titra-

tion is when the color changes from purple to blue. Perform a blank test in the same manner and make any necessary correction.

Each mL 0.01 mol/L of ethylenediaminetetraacetic acid disodium VS
= 0.4030 mg of MgO

(3) ***Precipitated calcium carbonate—***Weigh accurately the mass of NLT 20 tablets of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, and powder. Weigh accurately an amount equivalent to about 0.5 g of dried aluminum hydroxide gel and carbonize. After cooling, add 30 mL of dilute hydrochloric acid to the residue, warm on a steam bath for 10 minutes, cool, and add water to make 100 mL. Filter and use the filtrate as the test solution. Take 50.0 mL of this test solution, add 1 drop of methyl orange TS and 2 g of ammonium chloride, and slowly add ammonia TS until the color changes to yellow. Warm on a steam bath, filter and wash with water. Warm the filtrate and washings on a steam bath, add 5 mL of heat-saturated ammonium oxalate TS, and allow to stand in the water bath for 1 hour to complete precipitation. Dissolve this precipitate in 50 mL of dilute sulfuric acid, warm to 60 to 80 °C, and titrate with 0.1 mol/L potassium permanganate VS. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.02 mol/L potassium permanganate VS
= 5.005 mg of $CaCO_3$

(4) ***Sodium bicarbonate—***Weigh accurately the mass of NLT 20 tablets of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, and powder. Weigh accurately the amount equivalent to about 0.1 g of sodium bicarbonate according to the labeled amount of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, add 50 mL of water, warm at 35 to 40 ℃, and shake for 10 minutes to dissolve. Filter and wash 3 times with 20 mL of water, respectively. Combine the filtrate and the washings and titrate with 0.05 mol/L sulfuric acid as directed in the potentiometric titration under the Titrimetry. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L sulfuric acid VS
= 8.401 of $NaHCO_3$

(5) ***Total alkoids (hyoscyamine and scopolamine) in scopolia extract—***Weigh accurately the mass of NLT 20 Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, and powder. Weigh accurately 0.4 g of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets and perform the test as directed under the Assay in the Korean Pharmacopoeia, 10% Scopolia Extract Powder.

(6) ***Glycyrrhizic acid in powdered licorice—***Weigh accurately the mass of NLT 20 tablets of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, and powder. Weigh accurately an amount equivalent to about 30 mg of glycyrrhizic acid ($C_{42}H_{62}O_{166}$), add 50 mL of water, attach a reflux condenser, extract under reflux on a steam bath for 3 hours, then add 50 mL of 3 mol/L sulfuric acid and hydrolyze on a steam bath for 1 hour. After cooling, add 50 mL of chloroform and reflux and extract on a steam bath for 30 minutes. After cooling, transfer to a separatory funnel to take the chloroform layer, extract again with 30 mL of chloroform 3 times, collect all chloroform layers, and filter through anhydrous sodium sulfate. Evaporate the filtrate to dryness and dissolve the residue in methanol to make exactly 50 mL. Separately, weigh about 30 mg of glycyrrhizic acid RS and proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas, A_T and A_S, for the test solution and the standard solution, respectively.

Amount (mg) of glycrrhizic acid ($C_{42}H_{62}O_{16}$)
= Amount (mg) of glycrrhizic acid RS $\times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 254 nm).

Column: A stainless steel column 4 to 6 mm in internal diameter and 15 to 20 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 mm in particle diameter).

Mobile phase: A mixture of methanol, water, and acetic acid(100) (78 : 19 : 3).

Flow rate: 1.0 mL/min

(7) ***Starch saccharifying activity, protein digestion activity and fat digestion activity in Diastase·Protease·Cellulase 2000 IV and Lipase II—***(i) Weigh accurately NLT 20 tablets of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, and powder. Weigh accurately an amount of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, equivalent to about 30 mg of diastase·protease·cellulase 2000 IV, add 50 mL of test solution (pH 4.5), shake to mix well for 10 minutes, and centrifuge. Take 5 mL of the clear supernatant, add water to make 100.0 mL, and use this solution as the test solution. Add 10 mL of 1% potato starch solution (pH 4.5) to a test tube, allow to stand at 37 ± 0.5 ℃ for 10 minutes, add 1.0 mL of the test solution, shake to mix, and make reaction at 37 ± 0.5 ℃ for 10 minutes. Next,

add 2 mL of alkaline tartrate solution in the Fehling's TS, immediately shake to mix, add 2.0 mL of copper solution in the Fehling's TS, heat on a steam bath for 15 minutes, cool, add 2.0 mL of potassium iodide TS and 2.0 mL of dilute sulfuric acid (1 in 6), and titrate with 0.05 mol/L sodium thiosulfate VS. Separately, proceed in the same manner as above and perform the test using 10 mL of water instead of 10 mL of 1% potato starch solution (pH 4.5).

Definition of potency—When amylase reacts with potato starch at 37 ℃, the amount of enzymes that bring about an increase in reducing power equivalent to 1 mg of glucose for the initial 1 minute of reaction is defined as 1 unit.

$$\text{Starch saccharifying activity (pH 4.5) (unit/g)} = (a - b)\times 1.6\times \frac{1}{10} \times \frac{1}{Amount\ (g)\ of\ sample\ in\ 1\ mL\ of\ test\ solution}$$

a: Amount (mL) of 0.05 mol/L sodium thiosulfate VS consumed in the blank test.

b: Amount (mL) of 0.05 mol/L sodium thiosulfate consumed in determination of the test solution.

c: Molarity factor of 0.05 mol/L sodium thiosulfate

(ii) Protein digestion activity (pH 3.0): Weigh accurately the mass of NLT 20 Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, and powder. Weigh accurately an amount of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, equivalent to about 100 mg of diastase·protease·cellulase 2000 IV, add 50 mL of the test solution (pH 4.5), shake to mix for 20 minutes, filter, and use the filtrate as the test solution. Take 5.0 mL of casein solution, pH 3.0, allow to stand at 37 ± 0.5 ℃ for 10 minutes, add 1.0 mL of the test solution, and shake to mix. Allow this solution to stand at 37 ± 0.5 ℃ for 10 minutes, add 5 mL, shake to mix, allow to stand again at 37 ± 0.5 ℃ for 30 minutes and filter. Take 2 mL of the filtrate, add 5.0 mL of 0.55 mol/L sodium carbonate solution and 1 mL of Folin's TS (1 in 3), allow to stand at 37 ± 0.5 ° C for 30 minutes, perform the test as directed under the Ultraviolet-visible Spectroscopy using water as a control solution, and determine the absorbance A_T at a wavelength of 660 nm. Separately, take 1.0 mL of the test solution, add 5 mL of trichloroacetic acid TS, shake to mix, and add 5 mL of pH 3.0 casein solution. Allow to stand at 37 ± 0.5 ℃ for 30 minutes, proceed in the same manner as above, and determine the absorbance A_B.

Definition of potency—The amount of enzymes that bring about an increase in non-protein, Folin TS readily carbonizable substances equivalent to 1 μg of tyrosine in the first minute of the reaction is defined as 1 unit under the above conditions.

Tyrosine calibration curve—Weigh accurately 0.500 g of tyrosine RS, previously dried at 105 °C for 3 hours, add 0.2 mol/L hydrochloric acid TS to make 500 mL. Take 1.0 mL, 2.0 mL, 3.0 mL, and 4.0 mL each of this solution, and add 0.2 mol/L hydrochloric acid TS to make 100 mL, respectively. Take 2.0 mL each of these solutions, add 5.0 mL of 0.55 mol/L sodium carbonate TS and 1.0 mL of Folin's TS (1 in 3), allow to stand at 37 ± 0.5 ℃ for 30 minutes. Perform the test as directed under the Ultraviolet-visible Spectroscopy and determine the absorbances A_1, A_2, A_3 and A_4 at the wavelength of 660 nm. Separately, proceed with 2.0 mL of 0.2 mol/L hydrochloric acid TS in the same manner as above and determine the absorbance A_0. Create a calibration curve with the absorbance differences A_1-A_0, A_2-A_0, A_3-A_0, and A_4-A_0 on the vertical axis and the amount of tyrosine (μg) in 2 mL on the horizontal axis. Calculate the amount of tyrosine (μg) when the absorbance difference is 1.000.

$$\text{Protein digestion activity (pH 3.0) (unit/g)} = (A_B\text{-}A_T)\times F\times \frac{11}{2} \times \frac{1}{10} \times \frac{1}{Amount\ (g)\ of\ sample\ in\ test\ solution}$$

F: Amount (μg) of tyrosine when the absorbance difference is 1.000 in the tyrosine calibration curve

(iii) Fat digestion activity (pH 6.0): Weigh accurately the mass of NLT 20 tablets of Compound Trimebutine Maleate, Magnesium Aluminometasilicate and Precipitated Calcium Carbonate Tablets, and powder. Weigh accurately about 30 mg of lipase II, add water to make 50 mL, and use the filtrate as the test solution. Put 0.5 mL of olive oil emulsion and 4 mL of phosphate buffer solution, pH 6.0, into a test tube (30 × 12 mm), shake to mix, allow to stand at 37 ± 0.5 ℃ for exactly 20 minutes, add 10 mL of a mixture of acetone and ethanol (1 : 1), and shake to mix. Titrate with 0.05 mol/L hydrochloric acid (b mL). Separately, put 5.0 mL of olive oil emulsion and 4.0 mL of phosphate buffer solution, pH 6.0, into a test tube, shake to mix, allow to stand at 37 ± 0.5 ℃ for 30 minutes, add 10 mL of a mixture of acetone and ethanol (1: 1), add 1.0 mL of test solution, and shake to mix. Proceed in the same manner as above and titrate (a mL).

$$\text{Fat digestion power (unit/g)} = 50 \times (a - b) \times 1/20 \times F \times D$$

50: Equivalent amount (μmol) of fatty acid in 1 mL of 0.05 mol/L hydrochloric acid

f: Factor of 0.05 mol/L hydrochloric acid

D: Dilution factor of the sample

1/ 20: Conversion factor

Definition of potency—When lipase acts with olive oil under the above conditions; the amount of enzymes

that bring about an increase in 1 μmol of fatty acid for the initial 1 minute of reaction is defined as 1 unit of fat digestion activity.

Packaging and storage Preserve in tight containers.

Compound Ursodeoxycholic Acid·Taurine·Ginseng 30% Ethanol Extract Capsules
복방우르소데옥시콜산·타우린·인삼30%에탄올엑스 캡슐

Compound Ursodeoxycholic Acid·Taurine·Ginseng 30% Ethanol Extract Capsules contain NLT 90.0% and NMT 110.0% of ursodeoxycholic acid ($C_{24}H_{40}O_4$: 392.58), NLT 90.0% and NMT 130.0% of taurine ($C_{12}H_7NO_3S$:125.14), NLT 90.0% and NMT 150.0% of inocitol ($C_6H_{12}O_6$: 180.16) and thiamine nitrate ($C_{12}H_{17}N_5O_4S$:327.36), NLT 90.0% of ginsenoside Rb_1 in ginseng 30% ethanol extract ($C_{54}H_{92}O_{23}$: 1,109.31), respectively, according to the labeled amount.

Method of preparation Prepare as directed under Capsules, with Ursodeoxycholic Acid, Taurine, Inocitol, Thiamine Nitrate and Ginseng 30% Ethanol Extract.

Identification (1) ***Ursodeoxycholic acid***—Weigh an amount of Compound Ursodeoxycholic Acid·Taurine·Ginseng 30% Ethanol Extract Capsules, equivalent to 10 mg of ursodeoxycholic acid, transfer into a Soxhlet extractor, add 70 mL of ethyl acetate, and extract for 1 hour. Then, remove ethyl acetate, dissolve this residue with 10 mL of acetic anhydride, and use this solution as the test solution. Separately, weigh 10 mg of ursodeoxycholic acid RS, dissolve with acetic anhydride to make 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of toluene, acetone and acetic acid (60 : 30 : 1) to a distance of about 15 cm, dry at 110 ºC for 20 minutes, and cool. Spray evenly sulfuric acid on the plate; the R_f values and the colors of the spots obtained from the test solution and the standard solution are the same.

(2) ***Taurine*—**Perform the test with Compound Ursodeoxycholic Acid·Taurine·Ginseng 30% Ethanol Extract Capsules as directed under the Identification for taurine in compound thioctic acid-orotic acid choline-taurine solution.

(3) ***Ginseng 30% ethanol extract***—**Method 1** Weigh an amount of Compound Ursodeoxycholic Acid·Taurine·Ginseng 30% Ethanol Extract Capsules, equivalent to about 1 g of ginseng, add 100 mL of 80% ethanol, and extract under a reflux condenser for 1 hour. After cooling, filter, evaporate the filtrate to concentrate about 20 mL, add 20 mL of 20% ethanolic sulfuric acid, and hydrolyze on a steam bath for 30 minutes. After cooling, extract 3 times each with 20 mL of ether, combine all ether layers, transfer into a separatory funnel, and wash 3 times each with 10 mL of sodium bicarbonate. Concentrate the ether layer in vacuum, dissolve the residue with 2 mL of ethanol, and use this solution as the test solution. Separately, weigh about 1.0 g of Ginseng, proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel G. Next, develop the plate with a mixture of chloroform and acetone (4 : 1) as the developing solvent to a distance of about 10 cm, and heat the plate at 105 ℃ for 10 minutes. Spray evenly vanillin-sulfuric acid TS on the plate; the R_f values and the colors of the spots obtained from the test solution and the standard solution are the same.

Method 2 Weigh an amount of Compound Ursodeoxycholic Acid·Taurine·Ginseng 30% Ethanol Extract Capsules, equivalent to about 1 g of ginseng, add 50 mL of methanol, and extract under a reflux condenser for 30 minutes. After cooling, concentrate the filtrate in vacuum, dissolve the residue with 2 mL of methanol, and use this solution as the test solution. Separately, weigh about 1.0 g of Ginseng, proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel G. Next, develop the plate with a mixture of chloroform, methanol and water (13 : 7 : 2) as the developing solvent to a distance of about 10 cm, and heat the plate at 105 ℃ for 10 minutes. Spray evenly sulfuric acid TS for spraying onto the plate; the R_f values and the colors of the spots obtained from the test solution and the standard solution are the same.

(4) ***Inocitol and thiamine nitrate*—**The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Disintegration Meets the requirements.

Uniformity of dosage units Meet requirements.

Assay (1) ***Ursodeoxycholic acid***—Weigh accurately the mass of NLT 20 capsules of Compound Ursodeoxycholic Acid·Taurine·Ginseng 30% Ethanol Extract Capsules. Weigh accurately an amount of Compound Ursodeoxycholic Acid·Taurine·Ginseng 30% Ethanol Extract Capsules, equivalent to about 50 mg of ursodeoxycholic acid ($C_{24}H_{40}O_4$), add 40 mL of methanol, shake for 30 minutes to dissolve, and then add 5.0 mL of the internal standard solution and methanol to make exactly 50 mL. Then, filter, and use the filtrate as the test solution. Separately,

weigh accurately about 50 mg of ursodeoxycholic acid RS, dissolve in 40 mL of methanol, add 5.0 mL of the internal standard solution and methanol to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 60 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area, A_T and A_S, of ursodeoxycholic acid in each solution.

Amount (mg) of ursodeoxycholic acid ($C_{24}H_{40}O_4$)
= Amount (mg) of ursodeoxycholic acid RS× $\frac{A_T}{A_S}$

Operating conditions

Detector: A differential refractometer

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: Take 500 mL of a mixture of methanol and water (70 : 30) and adjust the pH to 3.5 with 0.1 mol/L phosphoric acid.

Flow rate: 1.0 mL/min

Internal standard solution—Weigh 500 mg of cholic acid, and dissolve in methanol to make 50 mL.

(2) ***Taurine*—**Weigh accurately the mass of NLT 20 capsules of Compound Ursodeoxycholic Acid·Taurine·Ginseng 30% Ethanol Extract Capsules, weigh accurately an amount of these capsules, equivalent to about 50 mg of taurine ($C_{12}H_7NO_3S$), dissolve in water to make exactly 100 mL. After filtering, pipet 5 mL of the filtrate, add 10 mL of diluent, then add sodium carbonate solution (3 in 300) to make exactly 100 mL, and warm at 90 ℃ for 30 minutes. Then, cool at ordinary temperature, 15 ~ 25 ℃. Next, filter through a membrane filter with a pore size of 0.45 μm, and use this solution as the test solution. Separately, weigh accurately about 50 mg of taurine RS, proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with each 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of taurine in each solution.

Amount (mg) of taurine ($C_{12}H_7NO_3S$)
= Amount (mg) of taurine RS× $\frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of 1% acetic acid and acetonitrile (70 : 30).

Efflux rate: 1.0 mL/min

Diluent—Dissolve 0.6 g of dansyl chloride in acetone to make 100 mL.

(3) ***Inocitol and thymine nitrate*—**Weigh accurately the mass of NLT 20 capsules of Compound Ursodeoxycholic Acid·Taurine·Ginseng 30% Ethanol Extract Capsules, and perform the test as directed under the Assay for inocitol and thiamine nitrate under the Analysis for Vitamins.

(4) ***Ginsenoside Rb_1 in ginseng 30% ethanol extract*—**Weigh accurately the mass of NLT 20 capsules of Compound Ursodeoxycholic Acid·Taurine·Ginseng 30% Ethanol Extract Capsules. Weigh accurately an amount of these capsules, equivalent to about 1 mg of ginsenoside Rb_1 in ginseng 30% ethanol extract ($C_{54}H_{92}O_{23}$), transfer into a 25-mL volumetric flask, add methanol, and sonicate to dissolve. Then, add methanol exactly to the gauge line, and use this solution as the test solution. Separately, weigh accurately about 6 mg of ginsenoside Rb_1 RS, and dissolve in methanol to make exactly 50 mL. Pipet 5 mL of this solution, add methanol to make exactly 15 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of ginsenoside Rb_1 in each solution.

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 203 nm).

Column: A stainless steel column about 7 mm in internal diameter and about 33 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (1.5 μm in particle diameter).

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: Acetonitrile

Mobile phase B: Water

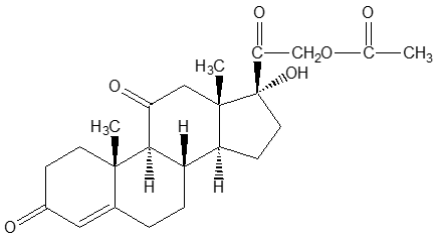
Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 10	20 → 25	80 → 75
10 - 25	25 → 37	75 → 63
25 - 35	37	63
35 - 36	37 → 20	63 → 80
36 - 40	20	80

Flow rate: 1.2 mL/min

Amount (mg) of ginsenoside Rb_1 ($C_{54}H_{92}O_{23}$)
= Amount (mg) of ginsenoside Rb_1 RS× $\frac{A_T}{A_S}$ × $\frac{1}{6}$

Packaging and storage Preserve in tight containers.

Cortisone Acetate
코르티손아세테이트



$C_{23}H_{30}O_6$: 402.48

[2-[(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-Hydroxy-10,13-dimethyl-3,11-dioxo-1,2,6,7,8,9,12,14,15,16-decahydrocyclopenta[a]phenanthren-17-yl]-2-oxoethyl] acetate [*50-04-4*]

Cortisone Acetate, when dried, contains NLT 97.0% and NMT 102.0% of cortisone acetate ($C_{23}H_{30}O_6$).

Description Cortisone Acetate occurs as white crystals or a crystalline powder.
It is sparingly soluble in methanol, slightly soluble in ethanol(99.5) and practically insoluble in water.

Melting point—About 240 °C (with decomposition).

Identification (1) Add 2 mL of sulfuric acid to 2 mg of Cortisone Acetate and allow to stand for a while; the solution exhibits a yellowish green and slowly changes to orange yellow. This solution has a light green fluorescence under ultraviolet light. Carefully add 10 mL of water to this solution; the solution loses its orange yellow color and becomes clear.

(2) Determine the absorption spectra of solutions of Cortisone Acetate and Cortisone Acetate RS in methanol (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Cortisone Acetate and Cortisone Acetate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears, dissolve each in acetone, then evaporate the acetone and repeat the test using the residue on evaporation.

Optical rotation $[\alpha]_D^{20}$: Between +207° and +216° (0.1 g, after drying, methanol, 10 mL, 100 mm).

Purity ***Related substances***—Dissolve 25 mg of Cortisone Acetate in a mixture of acetonitrile, water and acetic acid(100) (70 : 30 : 1), and use this solution as the test solution. Pipet 10 mL of this solution, add a mixture of acetonitrile, water and acetic acid(100) (70 : 30 : 1) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 15 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by automatic integration method; each peak area other than the peak of Cortisone Acetate from the test solution is not greater than 1/2 of the peak area of Cortisone Acetate from the standard solution. The total area of the peaks other than the peak of Cortisone Acetate from the test solution is not greater than 1.5 times the peak area of Cortisone Acetate from the standard solution.

Operating conditions

Detector: An ultraviolet photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: A mixture of water and acetonitrile (7 : 3).

Mobile phase B: A mixture of acetonitrile and water (7 : 3).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 5	90	10
5 - 25	90 → 10	10 → 90
25 - 30	10	90

Flow rate: 1 mL/min

System suitability

Test for required detectability: Pipet 1 mL of the standard solution and add a mixture of acetonitrile, water and acetic acid(100) (70 : 30 : 1) to make exactly 10 mL. Confirm that the peak area of cortisone acetate obtained from 15 μL of this solution is equivalent to between 8% and 12% of the peak area of cortisone acetate obtained from the standard solution.

System performance: Proceed with 15 μL of the standard solution under the above operating conditions; the number of theoretical plates and symmetry factor of the peak of cortisone acetate are NLT 10000 and NMT 1.3, respectively.

System repeatability: Repeat the test 3 times with 15 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area for cortisone acetate is NMT 5.0%.

Time span of measurement: About 3 times the retention time of cortisone acetate after the solvent peak.

Loss on drying NMT 1.0% (0.5 g, 105 °C, 3 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Dissolve about 10 mg each of Cortisone Acetate and cortisone acetate RS, previously dried and accurately weighed, in 50 mL of methanol, add exactly 5 mL each of the internal standard solution, and add methanol to make 100 mL. Use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak area, Q_T and Q_S of cortisone acetate to that of the internal standard.

$$\text{Amount (mg) of cortisone acetate } (C_{23}H_{30}O_6) = \text{Amount (mg) of cortisone acetate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of butyl parahydroxybenzoate in methanol (3 in 5000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of water and acetonitrile (13 : 7).

Flow rate: Adjust the flow rate so that the retention time of cortisone acetate is about 12 minutes.

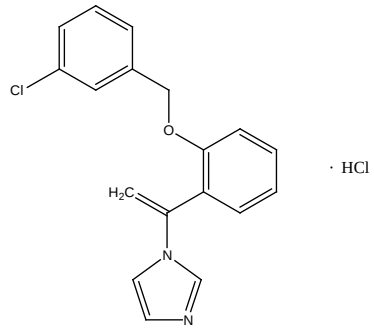
System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; cortisone acetate and the internal standard are eluted in this order with the resolution being NLT 4.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area of cortisone acetate to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Croconazole Hydrochloride
크로코나졸염산염



$C_{18}H_{15}ClN_2O \cdot HCl$: 347.24

1-[1-[2-[(3-Chlorophenyl)methoxy]phenyl] ethenyl]imidazole hydrochloride [*77174-66-4*]

Croconazole Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of croconazole hydrochloride ($C_{18}H_{15}ClN_2O \cdot HCl$).

Description Croconazole Hydrochloride occurs as white to pale yellow crystals or a crystalline powder.
It is very soluble in water, freely soluble in methanol, acetic acid(100) or acetone, and practically insoluble in ether.

Identification (1) Determine the absorption spectra of methanol solutions of Croconazole Hydrochloride and croconazole hydrochloride RS (1 in 20000) as directed under the Ultraviolet-visible spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectrum of Croconazole Hydrochloride and croconazole hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 50 mg of Croconazole Hydrochloride in 10 mL of water, add 2 mL of sodium hydroxide TS, add 20 mL of ether, and shake to mix. Separately collect the aqueous layer, wash 2 times with 10 mL of ether each time, and add 2 mL of dilute nitric acid to acidify; the solution responds to the Qualitative Analysis for chloride.

Melting point Between 148 and 153 ℃.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Croconazole Hydrochloride according to Method 4 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Weigh accurately 50 mg of Croconazole Hydrochloride, dissolve in 10 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. With

these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, hexane, methanol and ammonia water(28) (30 : 15 : 5 :1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (principal wavelength: 254 nm); the spots other than the principal spot and the spot of the starting point from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1.0 g, 60 ℃, 4 hours).

Residue on ignition NMT 0.1% (1.0 g).

Assay Weigh accurately about 0.6 g of Croconazole Hydrochloride, previously dried, dissolve in 10 mL of acetic acid(100), add 40 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS [indicator: 1 to 2 drops of a solution of malachite green oxalate in acetic acid(100) (1 in 100)]. However, the endpoint of titration is when the bluish green of the solution turns to green and then finally to yellowish green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 34.724 mg of $C_{18}H_{15}ClN_2O \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Crotamiton Ointment
크로타미톤 연고

Crotamiton Ointment contains NLT 90.0% and NMT 110.0% of the labeled amount of crotamiton ($C_{13}H_{17}NO$: 203.28).

Method of preparation Prepare as directed under Ointments, with Crotamiton.

Identification The retention times of the major peaks from the test solution and the standard solution obtained in the Assay are the same.

Assay Weigh accurately an amount of Crotamiton Ointment equivalent to about 50 mg of crotamiton ($C_{13}H_{17}NO$), dissolve in methanol to make 50.0 mL, take 20 mL of this solution, and filter. Take 10.0 mL of this solution, add 5.0 mL of the internal standard solution, add methanol to make 50 mL, and use this solution as the test solution. Separately, take an appropriate amount of crotamiton RS and dissolve in methanol to obtain a solution having a concentration of 1 mg per mL. Take 10.0 mL of this solution, add 5.0 mL of the internal standard solution, add methanol to make 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of crotamiton to that of the internal standard, respectively.

Amount (mg) of crotamiton ($C_{13}H_{17}NO$)
$= \text{Amount (mg) of crotamiton RS} \times \frac{Q_T}{Q_S} \times 50$

Internal standard solution—Take an appropriate amount of butyl benzoate and dissolve in methanol to make a solution having a concentration of 17.5 mg per mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 nm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and water (3 : 2).

System suitability

System performance: Proceed with the standard solution according to the above conditions; the resolution between crotamiton and butyl benzoate is NLT 2.0.

System repeatability: Repeat the test 6 times with the standard solution according to the above conditions; the relative standard deviation of the peak areas of crotamiton and butyl benzoate is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Cupric Oxide
산화제이구리

CuO : 79.55

Copper oxide, [*1317-38-0*]

Cupric Oxide contains NLT 97.5% and NMT 101.0% of cupric oxide (CuO).

Description Cupric Oxide occurs as a dark black powder or grain.
It is freely soluble in dilute nitric acid and slowly soluble in ammonia water.

Identification Add an excessive amount of ammonia water to a solution of Cupric Oxide in dilute nitric acid; the solution exhibits an intense blue color. Also, add potassium ferrocyanide solution to a solution of Cupric Oxide in acetic acid; a reddish brown precipitate is produced.

Purity (1) ***Water solubles*—**To 10 g of Cupric Oxide, add 100 mL of water, shake for 1 minute to mix, and filter. Take 50 mL of the filtrate, put in a porcelain crucible, previously measured in the mass, evaporate to dryness on a steam bath, ignite, and cool in a desiccator. Measure the mass; the mass difference before and after the measure is NMT 2 mg (NMT 0.04%).

(2) ***Hydrochloric acid insolubles*—**Weigh 5 g of Cupric Oxide, add 25 mL of hydrochloric acid and NMT 15 mL of water, heat on a steam bath to dissolve, and add water to make 100 mL. Filter this solution, wash the residue with water, dry to a constant mass at 105 ℃, and measure the mass; the mass is NMT 1 mg (NMT 0.02%) (Store this solution and use it for the test of ammonia precipitate.).

(3) ***Free alkali*—**Weigh 3 g of Cupric Oxide, add 30 mL of water, boil, and cool. Take 20 mL of the clear supernatant, add 2 drops of phenolphthalein TS; the solution does not exhibit a red color.

(4) ***Chloride*—**Weigh 1 g of Cupric Oxide and dissolve in 20 mL of water and 5 mL of nitric acid (filter if necessary). Add water to make 40 mL and perform the test; the solution is not more intense than the control solution. Prepare the control solution with 0.14 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.005%).

(5) ***Sulfate*—**Weigh 2 g of Cupric Oxide, add 10 mL of hydrochloric acid and 5 mL of water, and heat to dissolve. Add water to make 100 mL, and heat at about 70 ℃ to saturate the hydrogen sulfide and to completely sink the copper as a precipitate. After cooling, add hydrogen sulfide TS to make 200 mL, shake well to mix, and filter. Take 100 mL of the filtrate, add 5 drops of sulfuric acid, evaporate to dryness in a sand bath, and ignite. Measure the mass; the residue is NMT 2 mg (NMT 0.2%).

(6) ***Ammonia precipitate*—**To the filtrate obtained from the Hydrochloric acid insolubles in (2), add ammonia water until the first produced precipitate dissolves, and filter. Wash the residue with water containing a small amount of ammonia water, dry, ignite, and measure the mass; the residue is NMT 10 mg (NMT 0.2%).

(7) ***Total amount of carbon*—**Weigh 5 g of Cupric Oxide, put in the center of a porcelain combustion tube, and heat the porcelain combustion tube at 1000 to 1,100 ℃ for 10 minutes while passing oxygen at the speed of 100 mL per minute. Slowly, lower the temperature to 900 ℃ and keep the temperature for 30 minutes. While maintaining the temperature, pass the gas generated from heating through chromic acid saturated sulfuric acid solution through a mixture of 30 mL of carbon dioxide free water and 1 mL of ammonia water. To the mixture of carbon dioxide free water and ammonia water, add carbon dioxide free water to make the final volume of 50 mL. Place 25 mL of this solution into a stoppered test tube, add 5 mL of 10% barium chloride solution, and allow to stand for 10 minutes. The solution is not more intense than the control solution. Prepare the control solution by adding 5 mL of 10% barium chloride solution to 2.5 mL of standard carbonate solution (0.1 mg CO_3/mL) (NMT 0.002%).

(8) ***Total sulfur content*—**Dissolve 5 g of Cupric Oxide in 10 mL of hydrochloric acid and 5 mL of nitric acid, heat to dissolve, and evaporate to dryness on a steam bath. Dissolve the residue in 100 mL of water and 1 mL of hydrochloric acid, and if necessary, filter. Wash the residue with water, combine the filtrate with the washings, and boil. Add 10 mL of 10% barium chloride solution and allow to stand over night. Filter, wash the precipitate with water, dry, and ignite at 700 ℃. The residue is NMT 1.5 mg (NMT 0.03%).

(9) ***Cupric dioxide*—**To 1 g of Cupric Oxide, add 7 mL of hydrochloric acid and 50 mL of water, and titrate with 0.02 mol/L potassium permanganate VS; the consumed amount is NMT 0.1 mL. Use o-toluidine hydrochloride solution as the indicator.

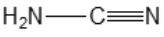
(10) ***Total nitrogen*—**Perform the test as directed under the Nitrogen Determination; the result is NMT 0.02%.

Assay Weigh accurately about 1 g of Cupric Oxide, add 15 mL of phosphoric acid, and heat on a steam bath to dissolve. After cooling, add water to make exactly 100 mL. Pipet 10 mL of this solution, add 50 mL of water, 3 mL of ammonia water (1 in 2), 6 mL of acetic acid (1 in 2) and 3 g of potassium iodide, and titrate with 0.1 mol/L sodium thiosulfate VS (indicator: starch TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium thiosulfate VS
= 7.955 mg of CuO

Packaging and storage Preserve in tight containers.

Cyanamide
시아나미드



CH_2N_2 : 42.04

Cyanamide [*420-04-2*]

Cyanamide contains NLT 97.0% and NMT 101.0% of cyanamide (CH2N2), calculated on the anhydrous basis.

Description Cyanamide occurs as white crystals or a crystalline powder and has a faint, characteristic odor.
It is very soluble in water, methanol or ethanol(95) and freely soluble in ether.
Dissolve about 1.0 g of Cyanamide in 100 mL of water; the pH of this solution is between 5.0 and 6.5.
It is hygroscopic.

Melting point—About 46 °C.

Identification (1) To 1 mL of a solution of Cyanamide

(1 in 100), add 1 mL of potassium 1,2-naphthoquinone-4-sulfonate TS and 0.2 mL of sodium hydroxide TS; the solution exhibits a deep red color.

(2) Spot one or two drops each of solutions of Cyanamide and cyanimide RS in acetone (1 in 100) onto potassium bromide disks prepared as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy, and air-dry the disks. Determine the infrared spectra of the disks as directed under the film method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Cyanamide in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 2.0 g of Cyanamide according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

Water NMT 1.0% (1 g, volumetric titration, direct titration).

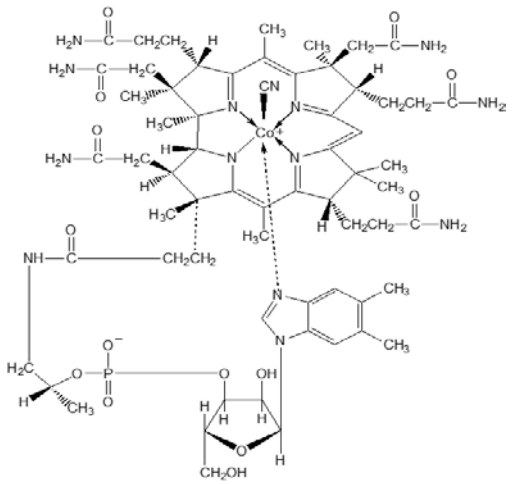
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 1 g of Cyanamide and add water to make exactly 250 mL. Pipet 15 mL of this solution, add 2 to 3 drops of dilute nitric acid, and then add 10 mL of ammonia TS. Next, add exactly 50 mL of 0.1 mol/L silver nitrate, allow to stand for 15 minutes with occasional shaking, add water to make exactly 100 mL, and filter. Discard the first 20 mL of the filtrate and pipet 50 mL of the subsequent filtrate. After neutralizing this solution with dilute nitric acid, add 3 mL of dilute nitric acid, and titrate the excess silver nitrate with 0.1 mol/L ammonium thiocyanate VS (indicator: 2 mL of ammonium iron(III) sulfate TS). Perform a blank test in the same manner.

Each mL of 0.1 mol/L silver nitrate VS
= 2.1020 mg of CH_2N_2

Packaging and storage Preserve in tight containers and store in a cold place.

Cyanocobalamin
시아노코발라민



Vitamin B_{12} $C_{63}H_{88}CoN_{14}O_{14}P$: 1355.37
Cobalt(3+);[5-(5,6-dimethylbenzimidazol-1-yl)-4-hydroxy-2-(hydroxymethyl)oxolan-3-yl][(2*S*)-1-[3-[(2*R*,3*R*,4*Z*,7*S*,9*Z*,12*S*,13*S*,14*Z*,17*S*,18*S*,19*R*)-2,13,18-tris(2-amino-2-oxoethyl)-7,12,17-tris(3-amino-3-oxopropyl)-3,5,8,8,13,15,18,19-octa-methyl-2,7,12,17-tetrahydro-1*H*-corrin-21-id-3-yl]propanoylamino]propan-2-yl]phosphate; cyanide [*68-19-9*]

Cynocobalamin contains NLT 96.0% and NMT 102.0% of Cynocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$), calculated on the dried basis.

Description Cynocobalamin occurs as dark red crystals or a crystalline powder.
It is sparingly soluble in water and slightly soluble in ethanol(95).
It is hygroscopic.

Identification (1) Determine the absorption spectra of the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Mix 1 mg of Cynocobalamin with 50 mg of potassium hydrogen sulfate, and fuse by igniting. After cooling, break up the fused mass with a glass rod, dissolve in 3 mL of water by boiling, and add 1 drop of phenolphthalein TS. Put sodium hydroxide TS dropwise until the solution shows pale light red, and add 0.5 g of sodium acetate trihydrate, 0.5 mL of dilute acetic acid and 0.5 mL of 1-nitroso-2-naphthol-3,6-disulfonic acid disodium (1 in 500); the resulting solution exhibits red to orange immediately. Then add 0.5 mL of hydrochloric acid and boil for 1 minute; the red color of the solution does not disappear.

(3) Put 5 mg of Cynocobalamin into a 50-mL distillation flask, dissolve in 5 mL of water, add 2.5 mL of hypophosphorous acid, connect the flask with a short

condenser, and dip the condenser's tip into 1 mL of sodium hydroxide solution (1 in 50) in a test tube. Next, boil at a low temperature for 10 minutes and distill 1 mL to a test tube To the solution in the test tube, add 4 drops of a saturated solution of ammonium iron(II) sulfate hexahydrate, shake gently to mix, add 30 mg of sodium fluoride, and heat to boiling. Add immediately diluted sulfuric acid (1 in 7) dropwise until the solution becomes clear, and then add again 3 to 5 drops of diluted sulfuric acid (1 in 7); the resulting solution exhibits blue to bluish green.

pH Dissolve 0.10 g of Cynocobalamin in 20 mL of freshly boiled and cooled water; the pH of the resulting solution is between 4.2 and 7.0.

Purity (1) ***Clarity and color of solution*—**Dissolve 20 mg of Cynocobalamin in 10 mL of water; the resulting solution is clear and exhibits a red color.

(2) **Related substances—**This test uses light-resistant containers. Weigh 10 mg of Cynocobalamin, dissolve accurately in 10 mL of the mobile phase, and use this solution as the test solution. Take exactly 3 mL of this solution, dissolve exactly in the mobile phase to make 100 mL, use this solution as the standard solution. With 20 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions. Determine peak area of each solution by the automatic integration method; the total area of the peaks other than Cyanocobalamin from the test solution is not larger than the peak area of Cyanocobalamin from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 361 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Weigh 10 g of anhydrous sodium dihydrogen phosphate, dissolve in 1000 mL of water, and adjust the pH to 3.5 with phosphoric acid. To 147 mL of this solution, add 53 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of Cyanocobalamin is about 7 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the test solution, dissolve in the mobile phase to make 100 mL, use this solution as the system suitability solution. Pipet 1 mL of this solution and dissolve in the mobile phase to make exactly 10 mL. Confirm that the peak area of cyanocobalamin obtained from 20 μL of this solution is 7% to 13% of the peak area of cyanocobalamin from the system suitability solution.

System performance: Perform the test quickly after preparing the solution. Dissolve 25 mg of Cyanocobalamin in 10 mL of water by warming if necessary, cool, add 0.5 mL of sodium toluenesulfonchloramide TS and 0.5 mL of 0.05 mol/L hydrochloric acid TS, add water to make 25 mL, shake to mix, and allow to stand for 5 minutes. To 1 mL of this solution, add the mobile phase to make 10 mL. With 20 μL of the resulting solution, proceed according to the above conditions; two major peaks appear, and their peak resolution is NLT 2.5.

System repeatability: Repeat the test 6 times with 20 μL each of the system suitability solution according to the above conditions; the relative standard deviation of the cyanocobalamin peaks is not more 3.0%.

Time span of measurement: About 4 times of the retention time of cyanocobalamin after the solvent peak.

Loss on drying NMT 12% (50 mg, NMT 0.67 kPa, phosphorus oxide, 100 °C, 4 hours).

Assay Weigh accurately about 20 mg each of Cyanocobalamin and cyanocobalamin RS (previously measure the loss on drying in the same manner as Cyanocobalamin), dissolve in water to make exactly 1000 mL, and use them as the test solution and the standard solution. Perform the test with these solutions as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbances AT and AS at a wavelength of 361 nm.

Amount (mg) of cynocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$) = Amount (mg) of cyanocobalamin RS, calculated on the dried basis $\times \frac{A_T}{A_S}$

Packaging and storage Preserve in light-resistant, tight containers.

0.1% Cyanocobalamin Powder
시아노코발라민 1000배산

0.1% Cyanocobalamin Powder contains NLT 1 mg of cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$) per g.

Method of preparation Prepare by finely dispersing cyanocobalamin in an excipient such as citric acid. 0.1% Cyanocobalamin Powder is a drug substance.

Description 0.1% Cyanocobalamin Powder occurs as a pink, odorless powder.

Identification Determine the absorption spectra as directed under the Assay; the standard solution and the test solution exhibit absorption maxima at the same wavelengths.

Purity ***Clarity and color of solution*—**The test solution from the Assay does not contain insoluble substances.

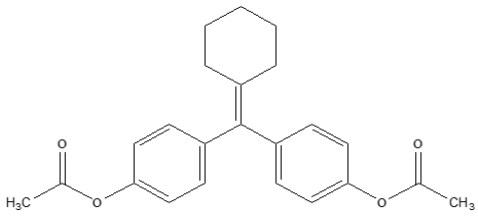
Loss on drying NMT 5.0% (1 g, 105 °C, 4 hours).

Assay Weigh accurately an amount of 0.1% Cyanocobalamin Powder, equivalent to about 1 mg of cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$), dissolve in water to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of cyanocobalamin RS and dissolve in water to make 100 mL. Pipet 5 mL of this solution, add water to make exactly 50 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution at the wavelength of 361 nm as directed under the Ultraviolet-visible Spectroscopy, using water as a control solution.

$$\text{Amount (mg) of cyanocobalamin } (C_{63}H_{88}CoN_{14}O_{14}P) = \text{Amount (mg) of cyanocobalamin RS} \times \frac{A_T}{A_S} \times \frac{1}{20}$$

Packaging and storage Preserve in light-resistant, tight containers.

Cyclofenil
시클로페닐



$C_{23}H_{24}O_4$: 364.43

4,4'-(Cyclohexylidenemethylene)bis-phenol-1,1'-diacetate, [*2624-43-3*]

Cyclofenil, when dried, contains NLT 98.0% and NMT 101.0% of cyclofenil ($C_{23}H_{24}O_4$).

Description Cyclofenil occurs as white crystals and is odorless. It is freely soluble in chloroform or dimethylformamide, soluble in acetic acid(100), sparingly soluble in ether, slightly soluble in methanol or ethanol(95), and practically insoluble in water.

Identification (1) To 1 mL of an ethanol(95) solution (1 in 1000) of cyclofenil, add 0.5 mL each of an ethanol saturated solution of hydroxyammonium hydrochloride and an ethanol saturated solution of sodium hydroxide, and dissolve by heating on a steam bath for 1 minute. After cooling, add 0.1 mL of iron(III) chloride solution (1 in 100) diluted with 1 mL of 1 mol/L hydrochloric acid TS to make it acidic; the solution exhibits a reddish purple color.

(2) Add 1 drop of potassium permanganate TS to 5 mL of acetic acid(100) solution (1 in 500) of Cyclofenil, a red color of the solution disappears soon.

(3) Determine the absorption spectra of the test solution according to the Assay as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 243 and 247 nm.

Melting point Between 137 and 141 °C.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Cyclofenil in 5 mL of chloroform; the solution is colorless and clear.

(2) ***Chloride***—Dissolve 0.5 g of Cyclofenil in 40 mL of dimethylformamide, add 6 mL of dilute nitric acid and dimethylformamide to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 6 mL of dilute nitric acid and dimethylformamide to 0.25 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.018%).

(3) ***Sulfate***—Dissolve 40 mL of dimethylformamide in 1.0 g of Cyclofenil, add 1 mL of dilute hydrochloric acid and dimethylformamide to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 1 mL of dilute hydrochloric acid and dimethylformamide to 0.40 mL of 0.01 mol/L sulfuric acid to make 50 mL (NMT 0.019%).

(4) ***Heavy metals***—Proceed with 1.0 g of Cyclofenil as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(5) ***Arsenic***—Proceed with 1.0 g of Cyclofenil according to Method 3 and perform the test (NMT 2 ppm).

(6) ***Related substances***—Dissolve 0.10 g of Cyclofenil in 10 mL of chloroform, and use this solution as the test solution. Separately, pipet 1.0 mL of this solution, add chloroform to make exactly 100 mL, and use this solution as the standard solution. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography (fluorescent indicator added). Next, develop the plate with a mixture of hexane, acetone and methanol (20 : 10 : 3) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (10 g, 105 °C, 3 hours).

Residue on ignition NMT 0.10% (1 g).

Assay Weigh accurately about 10 mg of Cyclofenil, previously dried, and dissolve in methanol to make exactly 100 mL. Pipet 5.0 mL of this solution, add methanol to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of cyclofenil RS, previously dried, proceed in the same manner as in the test solution, and use this solution as the standard solution. With methanol as the control solution, perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, and

determine the absorbance, A_T and A_S at a wavelength of 245 nm.

$$\text{Amount (mg) of cyclofenil } (C_{23}H_{24}O_4) = \text{Amount (mg) of cyclofenil RS} \times (A_T / A_S)$$

Packaging and storage Preserve in tight containers.

Cyclofenil Tablets
시클로페닐 정

Cyclofenil Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of cyclofenil ($C_{23}H_{24}O_4$: 364.43).

Method of preparation Prepare as directed under Tablets, with Cyclofenil.

Identification (1) To 1 mL of a solution of Cyclofenil Tablets in ethanol(95) (1 in 100), add 0.5 mL each of ethanol saturated solution of hydroxyammonium hydrochloride and ethanol saturated solution of sodium hydroxide, and dissolve by warming on a steam bath for 1 minute. Add 1 mL of 1 mol/L hydrochloric acid to make it acidic, then add 0.1 mL of dilute iron(III) chloride solution (1 in 100); the solution exhibits a reddish purple color.

(2) Determine the absorption spectra of the test solution according to the Assay as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelength of between 243 and 247 nm.

Disintegration Meets the requirements.

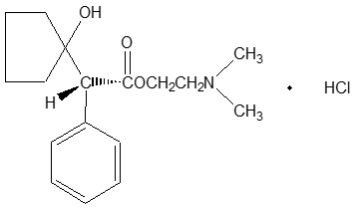
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Cimetidine Tablets and powder. Weigh accurately a portion of powder, equivalent to about 0.1 mg of cyclofenil ($C_{23}H_{24}O_4$), dissolve in about 60 mL of methanol, and shake to mix by warming on a steam bath. After colling, add methanol to make exactly 100 mL, and filter. Pipet 5 mL of this solution, add methanol to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of cyclofenil RS, previously dried at 105 °C for 3 hours, and proceed in the same manner as the test solution. Use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at 245 nm as directed under the Ultraviolet-visible Spectroscopy, using methanol as a control solution.

$$\text{Amount (mg) of cyclofenil } (C_{23}H_{24}O_4) = \text{Amount(mg) of cyclofenil RS} \times (A_T / A_S)$$

Packaging and storage Preserve in well-closed containers.

Cyclopentolate Hydrochloride
시클로펜톨레이트염산염



and enantiomer

$C_{17}H_{25}NO_3 \cdot HCl$: 327.85

2-(Dimethylamino)ethyl (1-hydroxycyclopentyl) phenylacetate hydrochloride [*5870-29-1*]

Cyclopentolate Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of cyclopentolate hydrochloride ($C_{17}H_{25}NO_3 \cdot HCl$).

Description Cyclopentolate Hydrochloride occurs as a white crystalline powder and is odorless or has a characteristic odor.
It is very soluble in water, freely soluble in ethanol(95) or acetic acid(100), slightly soluble in acetic anhydride, and practically insoluble in ether.

Identification (1) Add 1 mL of Reinecke salt TS to 1 mL of an aqueous solution of Cyclopentolate Hydrochloride (1 in 100); a pale red precipitate develops.

(2) Dissolve 0.2 g of Cyclopentolate Hydrochloride in 2 mL of water, add 2 mL of sodium hydroxide TS, and boil for 5 minutes. After cooling, add two drops of nitric acid; an odor like phenylacetic acid is perceptible.

(3) Determine the infrared spectra of Cyclopentolate Hydrochloride and cyclopentolate hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) An aqueous solution of Cyclopentolate Hydrochloride (1 in 50) responds to the Qualitative Analysis for chloride.

pH Dissolve 0.20 g of Cyclopentolate Hydrochloride in 20 mL of water; the pH is between 4.5 and 5.5.

Melting point Between 135 and 138 ºC.

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Cyclopentolate Hydrochloride in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals*—**Proceed with 1.0 g of Cyclopentolate Hydrochloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances*—**Dissolve 0.20 g of Cyclo-

pentolate Hydrochloride in 10 mL of chloroform and use this solution as the test solution. Pipet 1 mL of this solution and add chloroform to make exactly 20 mL. Pipet 1 mL of this solution, add chloroform to make exactly 10 mL, and use this solution as the standard solution. Perform the test directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of 2-propanol, acetic acid, n-butyl acetate, water and ammonia water(28) (100 : 60 : 23 : 17) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly sulfuric acid in ethanol(99.5) solution (1 in 10) on the plate, heat the plate at 120 ℃ for 30 minutes, and examine the plate under ultraviolet light (wavelength 254 nm); spots other than the principal spot obtained from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

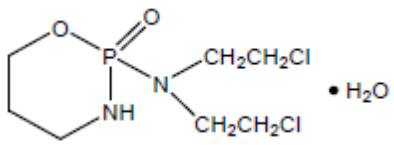
Residue on Ignition NMT 0.05% (1 g).

Assay Weigh accurately about 0.5 g of Cyclopentolate Hydrochloride, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (4 : 1), and titrate with 0.1 mol/L perchloric acid VS (indicator: two drops of Methylrosaniline chloride TS). The endpoint of the titration is when the purple color of this solution turns bluish green to yellowish green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 32.79 mg of $C_{17}H_{25}NO_3 \cdot HCl$

Packaging and storage Preserve in tight containers.

Cyclophosphamide Hydrate
시클로포스파미드수화물



Cyclophosphamide $C_7H_{15}Cl_2N_2O_2P \cdot H_2O$: 279.10
2-[*N*,*N*-Bis(2-chloroethyl)]amino-2-oxo-1,3,
$2\lambda^5$-oxazaphosphinane hydrate [*6055-19-2*]

Cyclophosphamide Hydrate, when dried, contains NLT 97.0% and NMT 101.0% of cyclophosphamide hydrate ($C_7H_{15}Cl_2N_2O_2P \cdot H_2O$).

Description Cyclophosphamide Hydrate occurs as white crystals or a crystalline powder and is odorless. It is very soluble in acetic acid(100), freely soluble in acetic anhydride, ethanol(95) or chloroform and soluble in water or ether.

Melting point—Between 45 and 53 ℃.

Identification (1) Dissolve 0.1 g of Cyclophosphamide Hydrate in 10 mL of water, and add 5 mL of silver nitrate TS; precipitates are not formed. Boil this solution; precipitates are formed. Separately, take a portion of the precipitates and add dilute nitric acid; it still does not dissolve. Add excess ammonia TS to the remaining portion; the precipitates dissolve.

(2) Add 1 mL of diluted sulfuric acid (1 in 25) to 20 mg of Cyclophosphamide Hydrate and heat until white fumes are produced. After cooling, add 5 mL of water, shake to mix, neutralize with ammonia TS, and acidify it with dilute nitric acid. This solution responds to the Qualitative Analysis (2) for phosphate.

(3) Determine the infrared spectra of Cyclophosphamide Hydrate and cyclophosphamide hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Clarity and color of solution***—Dissolve 0.20 g of Cyclophosphamide Hydrate in 10 mL of water; the solution is clear and colorless.

(2) ***Chloride***—Proceed with 0.40 g of Cyclophosphamide Hydrate at below 20℃ and perform the test. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid (NMT 0.036%).

(3) ***Heavy metals*—**Proceed with 1.0 g of Cyclophosphamide Hydrate according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Water Between 5.5% and 7.0% (0.5 g, volumetric titration, direct titration).

Assay Weigh accurately about 0.1 g of Cyclophosphamide Hydrate, previously dried, put in a 300-mL Erlenmeyer flask, and add 50 mL of sodium hydroxide solution (1 in 100) of ethylene glycol. Install a reflux condenser and heat at a low heat for 30 minutes. After cooling, wash the lower end of the reflux condenser and the upper end of the Erlenmeyer flask with 30 mL of water, transfer the washings to the Erlenmeyer flask, add 75 mL of 2-propanol, 15 mL of dilute nitric acid and exactly 10 mL of 0.1 mol/L silver nitrate, and titrate the excess silver nitrate with 0.1 mol/L ammonium thiocyanate VS (Indicator: 2 mL of ammonium iron(III) sulfate TS).

Each mL of 0.1 mol/L silver nitrate VS
= 13.955 mg of $C_7H_{15}Cl_2N_2O_2P \cdot H_2O$

Packaging and storage Preserve in tight containers and store at below 30 ℃.

Cyclophosphamide for Injection
주사용 시클로포스파미드

Cyclophosphamide for Injection is a preparation for injection which is dissolved before use and Cyclophosphamide for Injection contains NLT 90.0% and NMT 110.0% of the labeled amount of anhydrous cyclophosphamide ($C_7H_{15}Cl_2N_2O_2P$: 261.09).

Method of preparation Prepare as directed under Injections, by mixing Cyclophosphamide Hydrate and Sodium Chloride.

Description Cyclophosphamide for Injection occurs as a white powder.

Identification (1) Determine the infrared spectra of Cyclophosphamide for Injection and cyclophosphamide hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention times of the major peaks obtained from the test solution and the standard solution prepared as directed under the Assay are the same.

pH Weigh accurately an amount of Cyclophosphamide for Injection, equivalent to 0.2 g of anhydrous cyclophosphamide, dissolve in 10 mL of water, and measure the pH after 30 minutes; the pH of the solution is between 3.0 and 9.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.20 EU per mg of cyclophosphamide.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately an amount of Cyclophosphamide for Injection, equivalent to 0.1 g of anhydrous cyclophosphamide ($C_7H_{15}Cl_2N_2O_2P$) and perform the test as directed under the Assay Cyclophosphamide Tablets.

Packaging and storage Preserve in hermetic containers below 30 ℃.

Not exceeding 25℃ is recommended.

Cyclophosphamide Tablets
시클로포스파미드 정

Cyclophosphamide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of anhydrous cyclophosphamide ($C_7H_{15}Cl_2N_2O_2P$: 261.09).

Method of preparation Cyclophosphamide Tablets are prepared as directed under Tablets, with Cyclophosphamide Hydrate.

Identification (1) Powder Cyclophosphamide Tablets, weigh a portion of powder, equivalent to 50 mg of cyclophosphamide, extract with 25 mL of chloroform, filter, mix 2 mL of filtrate with 0.5 g of potassium bromide, and evaporate chloroform to dryness. Remove carefully the solvent completely in a small vacuum flask. Determine the residue and cyclophosphamide hydrate RS (previously dried) as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy at the wavenumber in a range between 700 and 1600 cm^{-1}; both exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention times of the major peaks obtained from the test solution and the standard solution in the Assay are the same.

Dissolution Perform the test with 1 tablet of Cychlphosphamide Tablets using 900 mL of deaerated water as the test solution, according to Method 1 under the Dissolution. Take NLT 20 mL of the dissolved solution 45 minutes after starting the Dissolution and filter using a 0.8-μm membrane filter. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately an appropriate amount of cyclophosphamide RS, dissolve in water to make it the same concentration as the test solution, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution according to the following operating conditions as directed under the Liquid Chromatography, and determine the peak areas, A_T and A_S, of cyclophosphamide. It meets the requirements when the dissolution rate in 45 minutes is NLT 75% (Q).

Dissolution rate (%) with respect to the labeled amount of cyclophosphamide ($C_7H_{15}Cl_2N_2O_2P$)

$$= C_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 90000$$

C_S: Concentration of the standard solution (mg/mL)

C: Labeled amount (mg) of cyclophosphamide ($C_7H_{15}Cl_2N_2O_2P$) in 1 tablet

Operating conditions

Proceed as directed under the operating conditions under the Assay.

System suitability

System performance: Proceed with 50 μL of the standard solution according to the above conditions; the symmetry factor is NMT 2.0.

System repeatability: Repeat the test 5 times with 50 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of cyclophosphamide is NMT 2.0%.

Uniformity of dosage units It meets the requirements

when the Content uniformity test is performed according to the following procedure.

Take 1 tablet of Cyclophosphamide Tablets, put in an appropriately sized volumetric flask with a final concentration of about 500 μg/mL, add water to 2/3 of the volume, shake well to mix until the tablet is completely disintegrated, and add water to the gauge line. Filter this solution, discard the first 10 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, dissolve an appropriate amount of cyclophosphamide hydrate RS in water to make about 500 mL, and use this solution as the standard solution. Take 2.0 mL each of the test solution, the standard solution and water (blank test solution), add 0.7 mL of perchloric acid solution to each solution, shake to mix, heat for 10 minutes at 95 °C and then cool. Mix with 1.6 mL of sodium acetate TS and 1.6 mL of 4-(*p*-nitrobenzile)pyridine solution, heat for 10 minutes at 95 °C and then cool. Mix with 8.0 mL of sodium hydroxide solution and shake, and perform the test as directed under the Ultraviolet-visible Spectroscopy within 4 minutes. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength (λmax) of around 560 nm with the blank test solution as a control.

$$C\text{: Amount (mg) of cyclophosphamide } (C_7H_{15}Cl_2N_2O_2P\text{: } 261.09) \text{ in 1 tablet} = \frac{T}{500} \times C \times \frac{A_T}{A_S}$$

T: Labeled amount (mg) of anhydrous cyclophosphamide in 1 tablet

C: Concentration of cyclophosphamide in the cyclophosphamide standard solution (μg/mL), calculated on the anhydrous basis

Assay Weigh accurately the mass of NLT 20 tablets of Cyclophosphamide Tablets and powder. Weigh accurately a portion of the powder, equivalent to about 0.1 g of anhydrous cyclophosphamide ($C_7H_{15}Cl_2N_2O_2P$), add about 50 mL of methanol, mix by shaking for about 30 minutes, and add water to make exactly 100 mL. Filter with a filter paper immediately, discard the first 40 to 50 mL of the filtrate. Pipet 25 mL of the subsequent filtrate, add 5.0 mL of the internal standard solution and water to make exactly 50 mL. Use this solution as the test solution. Separately, weigh accurately about 25 mg of cyclophosphamide hydrate RS (determined for water), dissolve in 25 mL of water, add 5.0 mL of the internal standard solution and water to make exactly 50 mL. Use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and calculate the ratios, Q_T and Q_S, of the peak area of cyclophosphamide to that of the internal standard.

$$\text{Amount (mg) of cyclophosphamide } (C_7H_{15}Cl_2N_2O_2P) = \text{Amount (mg) of cyclophosphamide hydrate RS, calculated on the anhydrous basis} \times \frac{Q_T}{Q_S} \times 4$$

Internal standard solution—Dissolve ethylparaben TS in 250 mL of ethanol(95) and add water to make 1000 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 195 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of water and acetonitrile (70 : 30).

Flow rate: 1.5 mL/minute

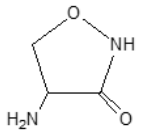
System suitability

System performance: Proceed with 25 μL of the standard solution according to the above operating conditions; cyclophosphamide and the internal standard are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 25 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak area ratios is NMT 2.0%.

Packaging and storage Preserve in tight containers and store at below 30 °C.

Cycloserine
시클로세린



$C_3H_6N_2O_2$: 102.09

(4*R*)-4-Amino-1,2-oxazolidin-3-one [*68-41-7*]

Cycloserine, when dried, contains NLT 950 μg and NMT 1020 μg (potency) of Cycloserine ($C_3H_6N_2O_2$: 102.09) per mg.

Description Cycloserine occurs as white to pale yellowish white crystals or a crystalline powder.

It is soluble in water and sparingly soluble in ethanol(95).

Identification Determine the infrared spectra of Cycloserine and cycloserine RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between +108° and +114° (2.5

g, calculated on the dried basis, 2mol/L sodium hydroxide TS, 50 mL, 100 mm).

pH Dissolve 0.5 g (potency) of Cycloserine in 10 mL of water; the pH of the solution is between 5.0 and 7.4.

Purity (1) ***Heavy metals*—**Proceed with 1.0 g of Cycloserine according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Condensation*—**Weigh 20 mg of Cycloserine and dissolve in sodium hydroxide TS to make exactly 50 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at a wavelength of 285 nm is NMT 0.8.

Loss on drying NMT 1.5% (0.5 g, in vacuum, 60 ℃, 3 hours).

Residue on ignition 0.5% (1g).

Assay ***Cylinder plate method*** (1) Medium Agar media for seed and base layer Use the medium in (A) (2) (a) ① ⓐ under the Microbial Assays for Antibiotics. However, adjust the pH to 6.0 to 6.1.

(2) ***Test organism*—**Use *Bacillus subtilis* ATCC 6633 as the test organism.

(3) Weigh accurately about 40 mg (potency) of Cycloserine, and dissolve it in sterile purified water to make a solution containing 400 μg (potency) per mL. Pipet an appropriate amount of this solution, dilute with 1% phosphate buffer solution, pH 6.0 to contain 100.0 and 50.0 μg (potency) per mL, and use them as the high-concentration test solution and the low-concentration test solution, respectively. Separately, weigh about 40 mg (potency) of the cycloserine RS and dissolve in sterile purified water to prepare a standard stock solution containing 400 μg (potency) per mL. Store this standard stock solution at below 5 ℃ and use it within 24 hours. Pipet an appropriate amount of this standard stock solution and dilute with 1% phosphate buffer solution (pH 6.0) to contain 100.0 and 50.0 μg (potency) per mL, and use them as the high-concentration standard solution and the low-concentration standard solution, respectively. Perform the test with these solutions according to the Microbial Assays for Antibiotics (A)(8).

Packaging and storage Preserve in tight containers.

Cycloserine Capsules
시클로세린 캡슐

Cycloserine Capsules contain NLT 90.0% and NMT 120.0% of the labeled amount of cycloserine ($C_3H_6N_2O_2$: 102.09).

Method of preparation Prepare as directed under Capsules, with Cycloserine.

Identification (1) Weigh an amount of Cycloserine Capsules, equivalent to about 10 mg (potency), add 2 mL of water, shake to mix, and filter. To the filtrate, add 1 to 2 drops of iron(III) chloride TS; the resulting solution exhibits a dark red color.

(2) Weigh an amount of Cycloserine Capsules, equivalent to 5 mg (potency) of cycloserine, and dissolve in 10 mL of sodium hydroxide solution (1 in 250). To 1 mL of this solution, add 3 mL of dilute acetic acid, shake to mix, and add 1 mL of cycloserine reaction TS; the resulting solution exhibits a blue color.

Loss on drying NMT 1.0% (0.1 g, 0.7 kPa, 60 ℃, 3 hours).

Dissolution Perform the test with 1 capsule of Cycloserine Capsules at 100 revolutions per minute according to Method 1 under the Dissolution, using 900 mL of pH 6.8 phosphate buffer solution as the dissolution medium. Take the dissolved solution 30 minutes after starting the test, and filter. Discard the first 10 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately an appropriate amount of cycloserine RS, dissolve in pH 6.8 phosphate buffer solution to make a solution containing about 0.25 mg (potency) of cycloserine per mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of cycloserine, respectively. The acceptable dissolution criterion of Cycloserine Capsules is NLT 80% (Q) dissolved in 30 minutes.

$$\text{Dissolution rate (\%) of the labeled amount of cycloserine } (C_3H_6N_2O_2) = C_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 90000$$

Cs: Concentration [mg (potency)/mL] of the standard solution

C: Labeled amount [mg (potency)] of cycloserine ($C_3H_6N_2O_2$) in 1 tablet

pH 6.8 phosphate buffer solution—Mix 50 mL of 0.2 mol/L potassium dihydrogen phosphate TS and 22.4 mL of 0.2 mol/L sodium hydroxide solution, and add water to make 200 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 219 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5

μm in particle diameter).

Mobile phase: Dissolve 0.5 g of sodium 1-decanesulfonate in 800 mL of water, add 50 mL of acetonitrile and 5 mL of acetic acid(100), mix well, and adjust the pH to 4.4 with 1 mol/L sodium hydroxide. Filter and degas the solution.

Flow rate: 1 mL/min

Column temperature: A constant temperature of about 30 °C.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the symmetry factor is NMT 1.8.

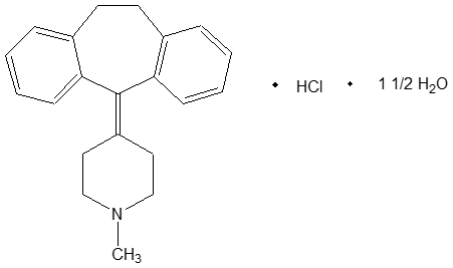
System repeatability: Repeat the test 5 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of cycloserine is NMT 2.0%.

Uniformity of dosage units Meets the requirements.

Assay ***Cylinder plate method—***Perform the test as directed under the Assay of Cycloserine. However, weigh accurately the mass of NLT 20 Cycloserine Capsules, weigh accurately an amount equivalent to about 40 mg (potency) of the labeled potency, add sterile purified water to make exactly 100 mL, shake vigorously to mix, and filter, if necessary. Pipet an appropriate amount of this solution, dilute it with 1% phosphate buffer solution (pH 6.0) to make the concentration of (3), and use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Cyproheptadine Hydrochloride Hydrate
시프로헵타딘염산염수화물



Cyproheptadine Hydrochloride

$C_{21}H_{21}N \cdot HCl \cdot 1½H_2O$: 350.88

4-(5*H*-Dibenzo[a,d]cyclohepten-5-ylidene)-1-methylpiperidine hydrochloride sesquihydrate [*41354-29-4*]

Cyproheptadine Hydrochloride Hydrate, when dried, contains NLT 98.5% and NMT 101.0% of cyproheptadine hydrochloride ($C_{21}H_{21}N \cdot HCl$: 323.86).

Description Cyproheptadine Hydrochloride Hydrate occurs as a white to pale yellow crystalline powder. It is odorless and has a slightly bitter taste.
It is freely soluble in methanol or acetic acid(100), soluble in chloroform, sparingly soluble in ethanol(95), slightly soluble in water, and practically insoluble in ether.

Identification (1) Dissolve about 0.1 g of Cyproheptadine Hydrochloride Hydrate in 10 mL of methanol, apply 1 drop of this solution to a filter paper and dry with air. Examine the solution under ultraviolet light (main wavelength: 254 nm); the resulting solution exhibits a pale blue fluorescent.

(2) Put 0.1 g of Cyproheptadine Hydrochloride Hydrate into the separatory funnel, dissolve in 5 mL of chloroform, add 4 mL of water and 1 mL of sodium carbonate TS, and shake to mix well. Separate the chloroform layer into the separatory funnel, wash with 4 mL water, and shake to mix and wash. Filter the chloroform layer first with the absorbent cotton, previously moistened with chloroform, and evaporate the filtrate to dryness. Add 8 mL of dilute ethanol to the residue and dissolve it by warming at 65 °C; then rub the inside wall with a glass rod while cooling. Allow it to stand for 30 minutes when crystals begin to be produced. Filter and take crystals and dry them at 80 °C for 2 hours; the crystals melt between 111 and 115 °C.

(3) Determine the absorption spectra of ethanol(95) solutions of Cyproheptadine Hydrochloride Hydrate and cyproheptadine hydrochloride hydrate RS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) The saturated solution of Cyproheptadine Hydrochloride Hydrate responds to the Qualitative Analysis (2) for chloride.

Purity (1) ***Acid***—Dissolve about 2.0 g of Cyproheptadine Hydrochloride Hydrate in 25 mL of methanol, and add 1 drop of methyl red TS and 0.30 mL of 0.1 mol/L sodium hydroxide solution; the resulting solution exhibits yellow.

(2) ***Heavy metals—***Weigh and proceed with 1.0 g of Cyproheptadine Hydrochloride Hydrate according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Loss on drying Between 7.0% and 9.0% (1 g, NMT 0.67 kPa, 100 °C, 5 hours).

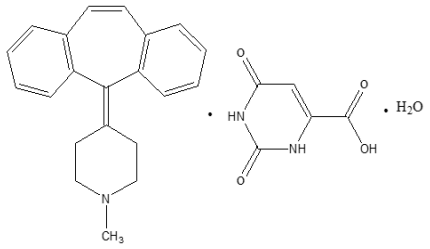
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Cyproheptadine Hydrochloride Hydrate, previously dried, add 20 mL of acetic acid(100), and dissolve by warming at 50 °C. After cooling, add 40 mL of acetic anhydride and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 32.386 mg of $C_{21}H_{21}N \cdot HCl$

Packaging and storage Preserve in well-closed containers.

Cyproheptadine Orotate Hydrate
시프로헵타딘오로트산염수화물



$C_{26}H_{25}N_3O_4 \cdot H_2O$: 461.51
4-(5*H*-Dibenzo[a,d]cyclohepten-5-ylidene)-1-methylpiperidine with orotic acid hydrate, [*129-03-3* cyproheptadine, *65-86-1* orotic acid]

Cyproheptadine Orotate Hydrate contains NLT 63.5% and NMT 66.1% of cyproheptadine ($C_{21}H_{21}N$: 287.40), and NLT 34.5% and NMT 35.9% of orotic acid ($C_5H_4N_2O_4$: 156.10), calculated on the anhydrous basis.

Description Cyproheptadine Orotate Hydrate occurs as a white crystalline powder.
It is freely soluble in chloroform and slightly soluble in acid.

Identification (1) Weigh 10 mg of Cyproheptadine Orotate Hydrate, dissolve in 10 mL of methanol, and use this solution as the test solution. Separately, use 0.1% methanol solution of cyproheptadine orotate hydrate RS as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of methanol and ammonia water(28) (100 : 1.5), and dry the plate with hot-air. Examine the plate under ultraviolet light; the R_f values and colors of the spots from the test solution and the standard solution are the same.

(2) Determine the absorption spectrum of the methanol solution (5 in 100000) of Cyproheptadine Orotate Hydrate as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelength of about 284 nm.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Cyproheptadine Orotate Hydrate according to Method 3 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Cyproheptadine Orotate Hydrate according to Method 3 under the Arsenic and perform the test (NMT 2 ppm).

Water NMT 5.0% (0.2 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay (1) ***Cyproheptadine—***Weigh accurately about 0.5 g of Cyproheptadine Orotate Hydrate, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: two drops of methylrosaniline chloride TS). However, the endpoint of titration is when the color of the solution changes to green. Perform a blank test in the same manner and make any necessary correction.

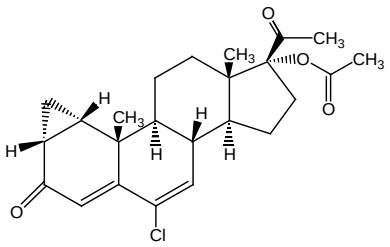
Each mL of 0.1 mol/L perchloric acid VS
= 28.74 mg of $C_{21}H_{21}N$

(2) ***Orotic acid—***Weigh accurately about 0.5 g of Cyproheptadine Orotate Hydrate, dissolve in 100 mL of acetone, and titrate with 0.1 mol/L tetrabutylammonium hydroxide VS (indicator: three drops of thymol blue TS). However, the endpoint of titration is when the color of the solution changes to blue. Perform a blank test in the same manner and make any necessary correction.

Each of 0.1 mol/L of Tetrabutylammonium hydroxide TS
= 15.61 mg of C5H4N2O4

Packaging and storage Preserve in tight containers.

Cyproterone Acetate
시프로테론아세테이트



$C_{24}H_{29}ClO_4$: 416.94
17-Acetyloxy-6-chloro-1α,2α-methylenepregna-4,6-diene-3,20-dione [*427-51-0*]

Cyproterone Acetate, contains NLT 97.0% and NMT 103.0% of cyproterone acetate ($C_{24}H_{29}ClO_4$), calculated on the dried basis.

Description Cyproterone Acetate occurs as white crystals or a crystalline powder.
It is very soluble in dichloromethane, freely soluble in acetone, soluble in methanol, sparingly soluble in ethanol(95) and practically insoluble in water.

Identification (1) Take 1 mg of Cyproterone Acetate, add 2 mL of sulfuric acid, heat on a steam bath for 2 minutes, and cool. Add carefully the resulting solution to 4 mL of water and shake well to mix; it exhibits a violet color.

(2) Determine the infrared spectra of Cyproterone Acetate and cyproterone acetate RS according to the potassium bromide disk method as directed under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 20 mg of Cyproterone Acetate in water to make 10 mL, and use this solution as the test solution. Separately, weigh 10 mg of cyproterone acetate RS, dissolve in dichloromethane to make 5 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of cyclohexane and ethyl acetate (50 : 50) as a developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254nm); the R_f values of the principal spots obtained from the test solution and the standard solution are the same.

(4) Mix 30 mg of Cyproterone Acetate with 0.3 g of anhydrous sodium carbonate, heat it for about 10 minutes over a flame. After cooling, dissolve the residue in 5 mL of dilute nitric acid, and filter it. Add 1 mL of water to 1 mL of the filtrate and mix; the resulting solution responds to the Chemical identification reaction (2) for chloride.

(5) Put 15 mg of Cyproterone Acetate and 0.15 mL of phosphoric acid into a test tube (about 180 mm × 18 mm) and close it with a stopper equipped with a small test tube (about 100 mm × 10 mm) containing water to which 1 drop of 5 w/v% lanthanum nitrate solution is added. Allow this device to stand for 5 minutes on a steam bath and take out the small tube. Transfer the liquid drop from the outside of the test tube onto the porcelain plate and mix with 0.05 mL of 0.01 mol/L iodine solution. Spot 0.05 mL of 2 mol/L ammonia TS on the edge; after 1 or 2 minutes, a blue color persisting for a while develops at the interface of the two solutions.

Optical rotation $[\alpha]_D^{20}$: Between -152° and +157° (After drying, 0.25 g, acetone, 20 mL, 100 mm).

Purity ***Related substances*—**Dissolve 10.0 mg of Cyproterone Acetate in acetonitrile to make exactly 10 mL, and use this solution as the test solution. Add acetonitrile to 1.0 mL of the test solution to make exactly 100 mL, and use this solution as the standard solution (1). Separately, dissolve 5.0 mg of medroxyprogesterone acetate RS in acetonitrile to make exactly 50 mL. Add the standard solution (1) to 1.0 mL of this solution to make exactly 10 mL, and use this solution as the standard solution (2). Perform the test with 20 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. The total area of peaks other than the major peak from the test solution is not greater than 0.5 times the area of the major peak from the standard solution (1) (0.5%). However, exclude any peak having an area smaller than 0.05 times the area of the major peak from the standard solution (1).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 125 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Mobile phase: A mixture of water and acetonitrile (60 : 40).

Flow rate: 1.5 mL/min

System suitability

Perform the test with the standard solution (1) and the standard solution (2) according to the operation conditions defined above. Adjust the detection sensitivity so that the height of the major peak from the standard solution (1) is NLT 50% of the full scale. The resolution between cyproterone acetate peak and medroxyprogesterone acetate peak obtained from the standard solution (2) is NLT 3.0.

Loss on drying NMT 0.5% (1 g, 80 °C, NMT 0.67 kPa, constant mass).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh exactly about 50.0 mg of Cyproterone Acetate and dissolve in methanol to make exactly 50 mL. Add methanol to 1.0 mL of this solution to make exactly 100 mL, and use this solution as the test solution. With the test solution and methanol with a control solution, measure the absorbance A at 282 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of cyproterone acetate } (C_{24}H_{29}ClO_4) = \frac{A}{414} \times 50000$$

Packaging and storage Preserve in light-resistant, well-closed containers.

L-Cysteine, Ascorbic Acid and Calcium Pantothenate Tablets
L-시스테인·아스코르브산·판토텐산칼슘 정

L-Cysteine, Ascorbic Acid and Calcium Pantothenate Tablets contains NLT 90.0% and NMT 130.0% of the labeled amounts of L-cysteine ($C_3H_7NO_2S$: 121.16), and NLT 90.0% and NMT 150.0% of the labeled amount of ascorbic acid ($C_6H_8O_6$: 176.12) and calcium pantothe-

nate ($C_{18}H_{32}CaN_2O_{10}$: 476.53).

Method of preparation Prepare as directed under Tablets, with L-Cysteine, Ascorbic Acid, and Calcium Pantothenate.

Identification (1) ***L-cysteine***—Perform the test with L-Cysteine, Ascorbic Acid and Calcium Pantothenate Tablets as directed under the Identification and Assay for Amino Acids.

(2) ***Ascorbic acid and calcium pantothenate***—Perform the test with L-Cysteine, Ascorbic Acid and Calcium Pantothenate Tablets as directed under the Analysis for Vitamins.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of 20 tablets of L-Cysteine, Ascorbic Acid and Calcium Pantothenate Tablets and powder. Weigh accurately a portion of powder, equivalent to about 100 mg of L-cysteine ($C_3H_7NO_2S$) [about 125 mg of ascorbic acid ($C_6H_8O_6$) and about 10 mg of calcium pantothenate ($C_{18}H_{32}CaN_2O_{10}$)], add water to make exactly 100 mL, sonicate for 30 minutes, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Use the filtrate as the test solution. Separately, weigh accurately about 100 mg of L-cysteine RS, about 125 mg of ascorbic acid RS, and about 10 mg of calcium pantothenate RS, add water to make exactly 100 mL, and use this solution as the standard solution. Take exactly 10 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas of L-cysteine, ascorbic acid and calcium pantothenate, A_{T1}, A_{S1}, A_{T2}, A_{S2}, A_{T3} and A_{S3}, for each solution.

Amount (mg) of L-cysteine ($C_3H_7NO_2S$)
= Amount (mg) of L-cysteine RS × (A_{T1} / A_{S1})

Amount (mg) of ascorbic acid ($C_6H_8O_6$)
= Amount (mg) of ascorbic acid RS × (A_{T2} / A_{S2})

Amount (mg) of calcium pantothenate ($C_{18}H_{32}CaN_2O_{10}$)
= Amount (mg) of calcium pantothenate RS × (A_{T3} / A_{S3})

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Use mobile phases A and B to control a stepwise or gradient elution-wise as follows.

Mobile phase A: Dissolve 1.36 g of potassium dihydrogen phosphate in 1000 mL and adjust the pH to 2.0 with a saturated solution of potassium phosphate or hydroxide.

Mobile phase B: Methanol

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0-5	100	0
5-10	100 → 50	0 → 50
10-20	50	50

Flow rate: 1.0 mL/min

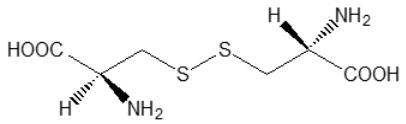
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; L-cysteine, ascorbic acid and calcium pantothenate peaks are eluted in this order with the resolution being NLT 3.1.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of L-cysteine, ascorbic acid and calcium pantothenate is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

L-Cystine
L-시스틴



$C_6H_{12}N_2O_4S_2$: 240.30

Cystine [*56-89-3*]

L-Cystine, when dried, contains NLT 98.5% and NMT 101.0% of L-cystine ($C_6H_{12}N_2O_4S_2$).

Description L-Cystine occurs as a white crystalline powder.
It is practically insoluble in water or ethanol(95).
It dissolves in dilute sodium hydroxide TS.

Identification (1) Determine the infrared spectra of L-Cystine and L-cystine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The principal spot from the test solution (2) is the same in color and R_f value as the spot from the standard solution (1) in the thin-layer chromatograms obtained from ninhydrin-positive substances under the Purity (2).

(3) To 0.1 g of L-Cystine, add carefully 1 mL of

strong hydrogen peroxide TS and 0.1 mL of iron(III) chloride TS, and allow to cool. Add 1 mL of dilute hydrochloric acid, 5 mL of water and 1 mL of barium chloride TS; the solution becomes turbid or produces a white precipitate within 3 minutes.

Optical Rotation $[\alpha]_D^{20}$: Between -218° and -224° (after drying 0.5 g, 1 mol/L hydrochloric acid, 25 mL, 100 mm).

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of L-Cystine in 10 mL of dilute hydrochloric acid TS; the solution is clear and is not more intense than the matching fluid F.

(2) ***Ninhydrin-positive substances*—**Dissolve 0.1 g of L-Cystine in 10 mL of 1 mol/L hydrochloric acid TS, and use this solution as the test solution (1). Pipet 1 mL of the test solution, add water to make 50 mL, and use this solution as the test solution (2). Separately, dissolve 10 mg of L-cystine RS in 1 mL of 1 mol/L hydrochloric acid TS, add water to make 50 mL, and use this solution as the standard solution (1). To 2 mL of the test solution (2) add water to make 20 mL, and use this solution as the standard solution (2). Dissolve 10 mg of L-cystine RS and 10 mg of arginine hydrochloride in 1 mL of 1 mol/L hydrochloric acid TS, add water to make 25 mL and use this solution as the standard solution (3) With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution (1), the test solution (2), the standard solution (1), the standard solution (2) and the standard solution (3) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ammonia water(28) and 2-propanol (30 : 70) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray evenly with ninhydrin TS on the plate and heat the plate at 100 to 150 °C for 15 minutes; the spots other than the principal spot from the test solution (1) are not more intense than the spot from the standard solution (2) and the chromatogram obtained from the standard solution (3) shows two clearly separated spots.

(3) ***Chloride*—**Perform the test with 0.50 g of L-Cystine. Prepare the control solution with 0.29 mL of 0.01 mol/L hydrochloric acid (NMT 0.020%).

(4) ***Sulfate*—**Weigh 0.50 g of L-Cystine, add 5 mL of dilute hydrochloric acid and water to make 15 mL, and use this solution as the test solution. Prepare the control solution with 0.32 mL of 0.005 mol/L sulfuric acid VS, 5 mL of dilute hydrochloric acid and add water to make 15 mL (NMT 0.030%).

(5) ***Ammonium*—**Perform the test with 0.25 g of L-Cystine. Prepare the control solution with 5.0 mL of ammonium standard solution (NMT 0.020%).

(6) ***Heavy metals*—**Proceed with 2.0 g of L-Cystine according to Method 1 under Heavy Metals Limit Test and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(7) ***Iron*—**Weigh 1.0 g of L-Cystine, put into a separatory funnel, dissolve in 10 mL of dilute hydrochloric acid, and extract three times with each 10 mL of 4-methyl-2-pentanone for 3 minutes. To the 4-methyl-2-pentanone layer, add 10 mL of water and shake to mix for 3 minutes. Take the water layer, add 30 mL of acetic acid-sodium acetate buffer solution, pH 4.5, and use this solution as the test solution. Perform the test according to Method B. Prepare the control solution with 1.0 mL of iron standard solution (NMT 10 ppm).

Loss on drying NMT 0.5% (1 g, 105 °C, constant mass).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.1 g of L-Cystine, previously dried, transfer to a capped flask, and dissolve in 2 mL of dilute sodium hydroxide TS and 10 mL of water. Add 10 mL of potassium bromide solution (2 in 10), 50.0 mL of 1/60 mol/L potassium bromate and 15 mL of dilute hydrochloric acid, place a stopper on top of the flask, cool in iced water, and allow to stand in the dark for 10 minutes. Next, add 1.5 g of potassium iodide and after 1 minute, titrate with 0.1 mol/L sodium thiosulfate VS (indicator: 2 mL of starch TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1/60 mol/L potassium bromate VS
= 2.4030 mg of $C_6H_{12}N_2O_4S_2$

Packaging and storage Preserve in light-resistant, well-closed containers.

L-Cystine Capsules
L-시스틴 캡슐

L-Cystine Capsules contain NLT 90.0% and NMT 130.0% of the labeled amount of L-cystine ($C_6H_{12}N_2O_4S_2$: 240.30).

Method of preparation Prepared as directed under Capsules, with L-Cystine.

Identification Perform the test with L-Cystine Capsules as directed under the Identification and Assay for Amino Acids.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 capsules of L-Cystine Capsules, and powder. Weigh accurately an amount equivalent to about 0.5 g of L-cystine ($C_6H_{12}N_2O_4S_2$), add 10 mL of 1 mol/L hydrochloric acid and water, sonicate, and add water to make exactly 100 mL. Then, filter. Pipet 10 mL of the filtrate, add 0.1 mol/L hydrochloric acid to make exactly 100 mL, and use

this solution as the test solution. Separately, weigh accurately about 0.5 g of L-cystine RS, proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of L-cysteine in each solution.

$$\text{Amount (mg) of L-cystine } (C_6H_{12}N_2O_4S_2) = \text{Amount (mg) of L-cystine RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A solution of 0.005 mol/L hexanesulfonate in a mixture of 0.1% phosphoric acid solution and acetonitrile (95 : 5).

Flow rate: 0.8 mL/min

Packaging and storage Preserve in tight containers.

L-Cystine and Choline Tartrate Capsules
L-시스틴·콜린타르타르산염 캡슐

L-Cystine and Choline Tartrate Capsules contain NLT 90.0% and NMT 130.0% of the labeled amount of L-cystine ($C_6H_{12}N_2O_4S_2$: 240.30) and NLT 90.0% and NMT 150.0% of choline tartrate ($C_9H_{19}NO_7$: 253.30).

Method of preparation Prepared as directed under Capsules, with L-Cystine and Choline Tartrate.

Identification (1) ***L-Cystine*—**Weigh an amount of L-Cystine and Choline Tartrate Capsules, equivalent to about 10 mg of L-cystine, dissolve in 10 mL of 0.1 mol/L hydrochloric acid, centrifuge, and use the clear supernatant as the test solution. Separately, weigh 10 mg of L-cystine RS, dissolve in 10 mL of 0.1 mol/L of hydrochloric acid, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethanol(95), water, and ammonia water(28) (7 : 2 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray evenly a ninhydrin TS on the plate; the R_f value and color of the spots obtained from the test solution and the standard solution are the same.

(2) ***Choline tartrate*—**Weigh an amount of L-Cystine and Choline Tartrate Capsules, equivalent to about 0.1 g of choline tartrate, powder, and perform the test as directed under the Analysis for Vitamins.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***L-Cystine*—**Weigh accurately the mass of NLT 20 capsules of L-Cystine and Choline Tartrate Capsules. Weigh accurately an amount equivalent to about 0.2 g of L-Cystine ($C_6H_{12}N_2O_4S_2$), and perform the test as directed under the Identification and Assay for Amino Acids.

(2) ***Choline tartrate*—**Weigh accurately the mass of NLT about 20 capsules of L-Cystine and Choline Tartrate Capsules. Weigh accurately an amount equivalent to about 50 mg of choline tartrate ($C_9H_{19}NO_7$), and perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in well-closed containers.

L-Cystine and Pyridoxine Hydrochloride Tablets
L-시스틴·피리독신염산염 정

L-Cystine and Pyridoxine Hydrochloride Tablets contain NLT 90.0% and NMT 130.0% of the labeled amount of L-cystine ($C_6H_{12}N_2O_4$: 240.30) and NLT 90.0% and NMT 150.0% of the labeled amount of pyridoxine hydrochloride($C_8O_11NO_3$·HCl: 205.64).

Method of preparation Prepare as directed under Tablets, with L-Cystine and Pyridoxine Hydrochloride.

Identification (1) ***L-cystine***—Perform the test with L-Cystine and Pyridoxine Hydrochloride Tablets as directed under the Identification and Assay for Amino Acids.

(2) ***Pyridoxine hydrochloride***—Perform the test with L-Cystine and Pyridoxine Hydrochloride Tablets as directed under the Analysis for Vitamins.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***L-cystine and pyridoxine hydrochloride*—**Weigh accurately the mass of NLT 20 tablets of L-Cystine and Pyridoxine Hydrochloride Tablets, and powder. Weigh accurately a portion of powder, equivalent to about 0.5 g of L-cystine ($C_6H_{12}N_2O_4S_2$) [about 0.1 g of pyridoxine hydrochloride ($C_8O_{11}NO_3$·HCl)], dissolve in about 10 mL of 1 mol/L hydrochloric acid TS and water, sonicate, add water to make 100 mL, and filter. Pipet 10 mL of the filtrate, add 0.1 mol/L hydrochloric acid TS to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 500 mg of

L-cystine and about 100 mg of pyridoxine hydrochloride RS, proceed in the same manner as the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of L-cystine } (C_6H_{12}N_2O_4S_2) = \text{Amount (mg) of L-cystine RS} \times \frac{A_{T1}}{A_{S1}}$$

$$\text{Amount (mg) of pyridoxine hydrochloride } (C8H11NO3{\cdot}HC1) = \text{Amount (mg) of pyridoxine hydrochloride RS} \times \frac{A_{T2}}{A_{S2}}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 238 nm).

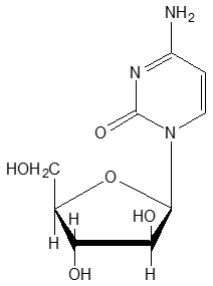
Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of 0.1% phosphate solution of 0.005 mol/L of sodium octanesulfonate acetonitrile (85 : 15).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in well-closed containers.

Cytarabine
시타라빈



$C_9H_{13}N_3O_5$: 243.22

4-Amino-1-[(2*R*,3*S*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]pyrimidin-2-one [*147-94-4*]

Cytarabine contains NLT 98.5% and NMT 101.0% of cytarabine ($C_9H_{13}N_3O_5$), calculated on the dried basis.

Description Cytarabine occurs as white crystals or a crystalline powder.

It is freely soluble in water, soluble in acetic acid(100), very slightly soluble in ethanol(95) and practically insoluble in ether.

Melting point—About 214 °C (with decomposition).

Identification (1) Determine the absorption spectra of Cytarabine and cytarabine RS in 0.1 mol/L hydrochloric acid (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Cytarabine and cytarabine RS according to the potassium bromide disk method as directed under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +154° and +160° (after drying, 0.1 g, water, 10 mL, 100 mm).

pH Dissolve 0.20 g of Cytarabine in 20 mL of water; the pH of this solution is between 6.5 and 8.0.

Absorbance $E_{1cm}^{1\%}$ (282 nm): Between 530 nm and 570 nm (after drying, 2 mg, 0.1 mol/L hydrochloric acid TS, 200 mL).

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Cytarabine in 10 mL of water: the solution is clear and colorless.

(2) ***Chloride*—**Perform the test with 1.0 g of Cytarabine. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid (NMT 0.009%).

(3**)** ***Heavy metals*—**Proceed with 1.0 g of Cytarabine according to Method 1 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic*—**Prepare the test solution with 1.0 g of Cytarabine according to Method 3 and perform the test (NMT 2 ppm).

(5) ***Related substances*—**Dissolve 0.10 g of Cytarabine in 10 mL of water, and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 200 mL, and use this solution as the standard solution. Perform the test directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Then, develop the plate with water-saturated 1-butanol as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution. Spray evenly acidic potassium permanganate TS on the plate; no spots other than the principal spot are observed in the test solution.

Loss on drying NMT 1.0% (1 g, in vacuum, silica gel, 4 hours).

Residue on ignition NMT 0.5% (1 g).

Assay Weigh accurately about 0.2 g of Cytarabine, pre-

viously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.05 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L perchloric acid VS
= 12.161 mg of $C_9H_{13}N_3O_5$

Packaging and storage Preserve in tight containers.

Cytarabine for Injection
주사용 시타라빈

Cytarabine for Injection is a preparation for injection which is dissolved before use. Cytarabine for Injection contains NLT 90.0% and NMT 110.0% of the labeled amount of cytarabine ($C_9H_{13}N_3O_5$: 243.22).

Method of preparation Prepare as directed under Injections, with Cytarabine.

Description Cytarabine for Injection occurs as a white powder.

Identification (1) The retention times of the major peaks obtained from the test solution and the standard solution prepared as directed under the Assay are the same.

pH Weigh accurately an amount of Cytarabine for Injection, equivalent to 0.2 g (potency) of cytarabine, and dissolve in 20 mL of water; the pH of the solution is between 4.0 and 6.0.

Water NMT 3.0% (1 g, volume titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.07 EU per mg of cytarabine.

Uniformity of dosage units Meets the requirements.

Assay Take 10 units of Cytarabine for Injection, dissolve in water to prepare solution A having known concentration of about 10 mg of cytarabine ($C_9H_{13}N_3O_5$) per mL, according to the labeled amount. Pipet 5 mL of this solution and add water to make exactly 50 mL. Pipet 3.0 mL of this solution, add 5.0 mL of the internal standard solution and mobile phase to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of cytarabine RS, previously dried at 60 °C and at a pressure not higher than 0.67 kPa, for 3 hours and dissolve in water to make exactly 50 mL. Pipet 3 mL of this solution, add 5.0 mL of the internal standard solution and the mobile phase to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under Liquid Chromatography according to the following conditions and calculate the ratios, QT and QS, of the peak area of Cytarabine to that of the internal standard for the test solution and the standard solution, respectively.

Amount (mg) of cytarabine ($C_9H_{13}N_3O_5$) in 1 mL of solution A
= Amount (mg) of cytarabine RS$\times \frac{Q_T}{Q_S} \times \frac{1}{5}$

Internal standard solution—0.14% *p*-toluic acid in methanol.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column, about 4 to 4.6 mm in internal diameter and 25 to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Mobile phase: Dissolve 0.69 g of potassium dihydrogen phosphate and 1.34 g of dibasic sodium phosphate in about 950 mL of water. To this solution, add 50 mL of methanol and mix.

Flow rate: 1 mL/min

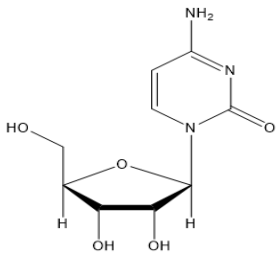
System suitability

System performance: Weigh a sufficient portion of Uracylarabinoside RS and Cytarabine RS, dissolve in water to make a solution containing 10 μg and 600 μg per mL, respectively, dilute with same volume of internal standard solution, mix with about four times volume of mobile phase. When the procedure is run with 10 mL of this solution under the above operating condition, cytarabine, uracylarabinoside and p-toluenic acid are eluted in this order with a resolution between cytarabine and uracylarabinoside peaks being NLT 2.5.

System repeatability: Repeat the test 6 times with each 10 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area ratio is NMT 2.0%.

Packaging and storage Preserve in hermetic containers.

Cytidine
시티딘



$C_9H_{13}N_3O_5$: 243.22

4-Amino-1-β-*D*-ribofuranosyl-2-(1*H*)-pyrimidinone, [*65-46-3*]

Cytidine contains NLT 99.0% of cytidine ($C_9H_{13}N_3O_5$), calculated on the anhydrous basis.

Description Cytidine occurs as a white, crystalline powder and is odorless.
It is very soluble in water, and slightly soluble in ethanol(95).

Identification (1) Dissolve 0.2 g of Cytidine in 2 mL of hydrochloric acid with stirring, add 10 mL of saturated trinitrophenol solution, recrystallize, and dry; the melting point is about 180 °C.

(2) To 5 mL of a solution containing 0.1% Cytidine, add 0.1% iron(III) chloride TS and 5 mL of hydrochloric acid containing 0.1% orcin, warm on a steam bath; it turns green after 45 minutes.

(3) With a solution of Cytidine in 0.001% 0.1 mol/L hydrochloric acid, determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at a wavelength of 280 nm. Furthermore, the ratios of the absorbances at wavelengths of 250 nm, 260 nm and 280 nm are as follows.

$$A_{250}/A_{260} = 0.45 \pm 0.04$$
$$A_{280}/A_{260} = 2.10 \pm 0.07$$

(4) A solution of Cytidine in 0.001% 0.05 mol/L phosphate buffer solution, pH 7.0, exhibits a maximum at a wavelength of 271 nm.

Melting point Between 210 and 220 ℃.

Optical rotation $[\alpha]_D^{20}$: Between +30° and +35° (0.5 g, water, 25 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Cytidine according to Method 1 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Nitrogen content***—Perform the test with Cytidine as directed under the Nitrogen Determination; the content of nitrogen (N) is 17.3 ± 2%.

Water NMT 0.5% (1 g).

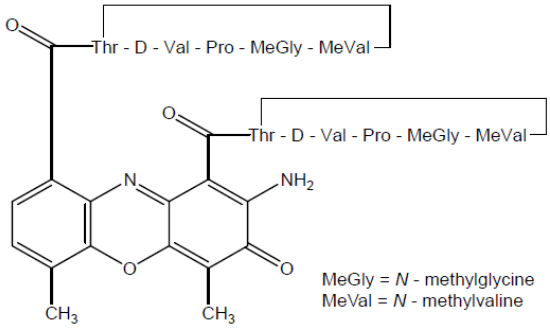
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.35 g of Cytidine, dissolve in 30 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: methylrosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 24.32 mg of $C_9H_{13}N_3O_5$

Packaging and storage Preserve in tight containers.

Dactinomycin
닥티노마이신



$C_{62}H_{86}N_{12}O_{16}$: 1255.42

2-Amino-*N*,*N*'-*bis*[(6*S*,9*R*,10*S*,13*R*,18a*S*)-6,13-diisopropyl-2,5,9-trimethyl-1,4,7,11,14-pentaoxohexadecahydro-1*H*-pyrrolo[2,1-i][1,4,7,10,13]oxatetraazacyclohexadecin-10-yl]-4,6-dimethyl-3-oxo-3*H*-phenoxazine-1,9-dicarboxamide [*50-76-0*]

Dactinomycin is a peptide compound with antitumor activity obtained from the incubation of *Streptomyces parvulus*. Daptomycin, when dried, contains NLT 950 μg and NMT 1030 μg (potency) per mg of dactinomycin ($C_{62}H_{86}N_{12}O_6$: 1255.42).

Description Dactinomycin occurs as an orange to red crystalline powder. It is freely soluble in acetone, sparingly soluble in acetonitrile or methanol, slightly soluble in ethanol(95), and practically insoluble in water.

Identification (1) Determine the absorption spectra of Dactinomycin and dactinomycin RS in methanol (3 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Dissolve 0.1 g of Dactinomycin and dactinomycin RS in 10 mL of acetone and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Then, develop the plate with a mixture of 1-butanol, water and methanol (4 : 2 : 1) to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the R_f value of the principal spot obtained from the test and the spots from standard solutions are identical.

Optical rotation $[\alpha]_D^{20}$: Between -292° and -317° (10 mg after drying, methanol, 10 mL, 100 mm).

Loss on drying NMT 5.0% (1 g, in vacuum, 60 ºC, 3

hours).

Sterility It meets the requirements when Daptomycin Hydrochloride is used in a sterile preparation.

Bacterial endotoxins Less than 100 per mg (potency) of dactinomycin when used in a sterile preparation.

Assay Weigh accurately about 60 mg each of Dactinomycin and dactinomycin RS, previously dried, dissolve in the mobile phase to make exactly 50 mL, and use each solution as the test solution and the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the area of the peak of dactinomycin in the test solution, A_T, and in the standard solution, A_S.

$$\text{Potency (μg) of dactinomycin } (C_{62}H_{86}N_{12}O_{16}) = \text{Potency (μg) of dactinomycin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 3.9 mm in internal diameter and 30 cm in length, packed with octylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of 0.02 mol/L acetic acid, sodium acetate TS and acetonitrile (25 : 23).

Flow rate: Adjust the flow rate so that the retention time of dactinomycin is about 23 minutes.

System suitability

System performance: Proceed with 25 μL of the standard solution under the above operating conditions; the number of theoretical plates for the dactinomycin peak is NLT 2000 and the symmetry factor is NMT 1.5.

System repeatability: Repeat the test 5 times with 25 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of dactinomycin is NMT 2.0%

Packaging and storage Preserve in light-resistant, tight containers.

Dactinomycin for Injection
주사용 닥티노마이신

Dactinomycin for Injection contains NLT 90.0% and NMT 120.0% of dactinomycin ($C_{62}H_{86}N_{12}O_{16}$: 1255.42), calculated as dissolved injections.

Method of preparation Prepare Dactinomycin for Injection as directed under Injections, with Dactinomycin.

Description Dactinomycin for Injection occurs as a yellow to bright red powder.

Identification (1) Dilute Dactinomycin for Injection with methanol, and perform the test according to the Identification test (1) of Dactinomycin where 1 mL contains 25 μg (potency).

(2) Perform the test according to the Identification test (2) of Dactinomycin.

pH Dissolve 5.0 mg (potency) of dactinomycin in Dactinomycin for Injection in 11 mL of water; the pH of this solution is between 5.5 and 7.5.

Loss on drying NMT 4.0% (0.1 g, 0.7 kPa, 60 ºC, 3 hours).

Sterility Meets the requirements

Bacterial endotoxins NMT 100 EU per mg (potency) of dactinomycin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately about 250 μg (potency) of Dactinomycin for Injection, add exactly 10 mL of mobile phase, make it the concentration of 25 μg (potency) per mL, and use this solution as the test solution. Separately, weigh accurately about 250 μg (potency) of dactinomycin RS, add exactly 10 mL of mobile phase, make it the concentration of 25 μg (potency) per mL, and use this solution as the standard solution. Prepare the test solution and the standard solution in the dark. Perform the test with exactly 10 μL each of the test solution and standard solution as directed under the Assay of dactinomycin according to the following operating conditions.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 mm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and water (6 : 4).

Flow rate: 2.5 mL/min

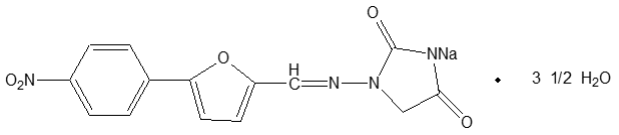
System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; the number of theoretical plates for the dactinomycin peak is NLT 1200 and the symmetry factor is NMT 2.

System repeatability: Repeat the test 6 times with 10 µL each of the standard solutions according to the above operating conditions; the relative standard deviation of the peak area of dactinomycin is NMT 3.0%

Packaging and storage Preserve in light-resistant, hermetic containers.

Dantrolene Sodium Hydrate
단트롤렌나트륨수화물



$C_{14}H_9N_4NaO_5 \cdot 3½H_2O$: 399.29

Sodium(*E*)-1-(((5-(4-nitrophenyl)furan-2-yl)methylene)amino)imidazolidine-2,4-dionehemiheptahydrate

[*24868-20-0*]

Dantrolene Sodium contains NLT 98.0% and NMT 101.0% of dantrolene sodium ($C_{14}H_9N_4NaO_5$: 336.24), calculated on the anhydrous basis.

Description Dantrolene Sodium Hydrate occurs as a yellowish orange to deep orange, crystalline powder.
It is soluble in propylene glycol, sparingly soluble in methanol, slightly soluble in ethanol(95), very slightly soluble in water or acetic acid(100) and practically insoluble in acetone, tetrahydrofuran or ether.

Identification (1) Determine the absorption spectra of Dantrolene Sodium Hydrate and dantrolene sodium hydrate RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Dantrolene Sodium Hydrate and dantrolene sodium hydrate RS as directed in the potassium bromide disk method under Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

(3) To about 0.1 g of Dantrolene Sodium Hydrate, add 20 mL of water and 2 drops of acetic acid(100), shake well to mix, and filter. The filtrate responds to the Qualitative Analysis (1) for sodium salt.

Purity (1) ***Alkali***—To about 0.7 g of Dantrolene Sodium Hydrate, add 10 mL of water, mix well by shaking, and centrifuge or pass through a membrane filter. Take 5 mL of the clear supernatant or the filtrate, add 45 mL of water and 3 drops of phenophthalein TS and 0.10 mL of 0.1 mol/L hydrochloric acid VS; the resulting solution does not exhibit a red color.

(2) ***Heavy metals***—Proceed with 1.0 g of Dantrolene Sodium Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve 50.0 mg of Dantrolene Sodium Hydrate in 20 mL of tetrahydrofuran and 2 mL of acetic acid(100), add ethanol(99.5) to make exactly 100 mL. and use this solution as the test solution. Pipet 1 mL of this solution, add ethanol(99.5) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 10 µL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution as directed in the automatic integration method; the total area of all peaks other than the peak of dantrolene from the test solution is not greater than the peak area of dantrolene from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 300 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with silica gel for liquid chromatography (5 µm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of hexane, acetic acid(100), and ethanol(99.5) (90 : 10 : 9).

Flow rate: Adjust the flow rate so that the retention time of dantrolene is about 8 minutes.

System suitability

Detection sensitivity: Adjust the sensitivity so that the peak height of dantrolene from 10 µL of the standard solution is between 10% and 40% of the full scale.

System performance: Dissolve about 5 mg of Dantrolene Sodium Hydrate and 0.1 g of theophylline in 20 mL of tetrahydrofuran and 2 mL of acetic acid(100) and add ethanol(99.5) to make 100 mL. Pipet 10 mL of this solution and add in ethanol(99.5) to make 100 mL. Proceed with 10 µL of this solution under the above operating conditions; theophylline and dantrolene are eluted in this order with a resolution being 6.

Time span of measurement: About 2 times the retention time of dantrolene after the solvent peak.

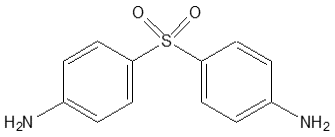
Water Between 14.5% and 17.0% (0.2 g, volumetric titration, direct titration).

Assay Weigh accurately about 0.7 g of Dantrolene Sodium Hydrate, dissolve in 180 mL of a mixture of propylene glycol and acetone (1 : 1) and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 33.624 mg of $C_{14}H_9N_4O_5$

Packaging and storage Preserve in tight containers.

Dapsone
답손



D.D.S $C_{12}H_{12}N_2O_2S$: 248.30
4-(4-Aminophenyl)sulfonylaniline [*80-08-0*]

Dapsone contains NLT 98.0% and NMT 102.0% of dapsone ($C_{12}H_{12}N_2O_2$), calculated on the dried basis.

Description Dapsone occurs as a white or pale yellow crystalline powder.
It is freely soluble in acetone, sparingly soluble in ethanol(95) and very slightly soluble in water.
It is soluble in dilute hydrochloric acid.

Identification (1) Determine the absorption spectra of Dapsone and dapsone RS in methanol (1 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Dapsone and dapsone RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 175 and 181 ℃.

Purity (1) ***Selenium***—Add 0.5 mL of a mixture of perchloric acid and sulfuric acid (1 : 1), 2 mL of nitric acid to about 0.10 g of Dapsone and heat on a steam bath. Cool the solution until a brown gas is not produced and the solution becomes clear with a light yellow color. Then, add 4 mL of nitric acid and water to make exactly 50 mL and use this solution as the test solution. Separately, pipet 3 mL of selenium standard solution, add 0.5 mL of a mixture of perchloric acid and sulfuric acid (1 : 1), 6 mL of nitric acid, and add water to make exactly 50 mL. Use this solution as the standard solution. Perform the test on the test and the standard solution as directed under the Atomic Absorption Spectroscopy. Measure the absorbance A_T for the test solution and A_S for the standard solution when the reading of the display rapidly rises and then reaches a plateau; A_T is less than A_S (NMT 30 ppm). This test is performed using a hydride generator and a heating absorption cell.

Lamp: Selenium hollow cathode lamp
Wavelength: 196.0 nm
Atomizing temperature: About 1000 ℃ when an electric furnace is used.
Carrier gas: Nitrogen or argon

(2) ***Related substances***—Dissolve about 0.5 g of Dapsone in 5 mL methanol to make 50 mL and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make 100 mL, and use this solution as the standard solution (1). Pipet 10 mL of the standard solution (1), add methanol to make 50 mL, and use this solution as the standard solution (2). With these solutions, perform the test according to the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solutions (1) and (2) on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, *n*-heptane, methanol and 13.5 mol/L ammonia water (20 : 20 : 6 : 1) as a developing solvent, and air-dry the plate. Spray evenly 0.1% 4-dimethylaminocinnamaldehyde solution of a mixture of ethanol(95) and hydrochloric acid (99 : 1); the spot that showed a strong intensity second to the principal spot from the test solution is not more intense than that from the standard solution (1). Also, the spots other than the above two spots from the test solution are not more intense than that from the standard solution (2).

Loss on drying NMT 1.5% (1 g, 100 - 105 °C, constant mass).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg of Dapsone and dissolve in methanol to make exactly 200 mL. Pipet 5 mL of this solution, add methanol to make exactly 50 mL, and use this solution as the test solution. Separately, proceed in the same manner as in the preparation of the test solution with about 50 mg of dapsone RS and use this solution as the standard solution. Perform the test with 10 mL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the area of the peak of dapsone, A_T and A_S in the test and standard solutions.

$$\text{Amount (mg) of dapsone } (C_{12}H_{12}N_2O_2S) = \text{Amount (mg) of dapsone RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

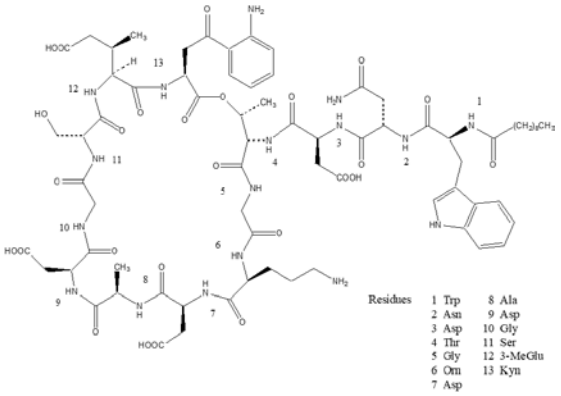
Mobile phase: Mix 100 mL of 2-propanol, 100 mL of ethylacetate and 100 mL of acetonitrile, add pentane to make 1000 mL, and cool at room temperature.

System suitability

System repeatability: Repeat the test 6 times with 10 μL of the standard solution each according to the above operating conditions; the relative standard deviation of the peak area of dapsone is NMT 2.0%.

Packaging and storage Preserve in light-resistant, well-closed containers.

Daptomycin
답토마이신



$C_{72}H_{101}N_{17}O_{26}$: 1620.67

Daptomycin contains NLT 870 μg and NMT 1050 μg (potency) per mg of daptomycin ($C_{72}H_{101}N_{17}O_{26}$: 1620.67), calculated on the anhydrous basis.

Description Daptomycin occurs as a light yellow to light brown crystalline powder.

Identification Weigh 10 mg (potency) each of Daptomycin and daptomycin RS, add a suitable amount of methanol, shake, and make exactly 200 mL with methanol. Use these solutions as the test solution and the standard solution. Determine the absorption spectra of the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy; both exhibit an absorption maximum and minimum at the same wavelengths.

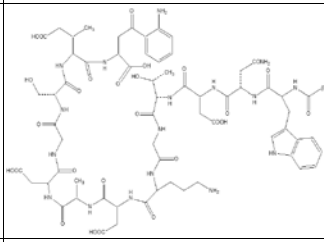
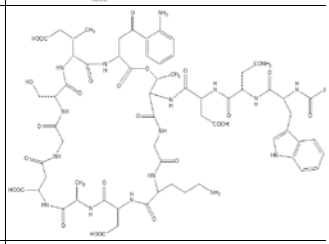
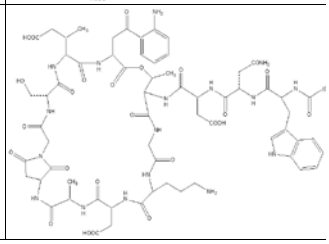
Optical rotation $[\alpha]_D^{25}$: Between + 8° and +13° (100 mg, calculated on the anhydrous basis, methanol, 10 mL, 100 mm).

pH Dissolve Daptomycin in water to make 130 mg (potency)/mL; the pH of the solution is between 2.6 and 3.6.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Daptomycin according to Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(2) ***Related substances***—Weigh accurately about 0.23 g (potency) of Daptomycin, dissolve in the mobile phase B to make exactly 200 mL and use this solution as the test solution. Perform the test according to the following conditions with 20 μL of the test solution as directed under the Liquid Chromatography and determine the peak area in the test solution. However, store the test solution in a refrigerator before the test and calculate only the peak NLT 0.05% (anhydrodaptomycin NMT 4.0%. β-isomer NMT 2.0% lactone hydrolysate NMT 1.5% any other individual related substances NMT 1.0%, total related substances NMT 8.0%).

Relative retention time and structure of each of the related substances

Component	Relative Retention time	Structure
Lactone Hydrolysate	0.68	
β-isomer	0.85	
anhydrodaptomycin	1.32	

Content of each related substance (%)

$$= \frac{A_S}{A_T} \times 100$$

A_T: Total sum of all peak areas excluding the solvent peak in the test solution

A_S: Peak area of individual related substance in the test solution

Total content (%) of related substances
= Sum of concentration (%) for any other individual related substances

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 250 mm in length, packed with octylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Adjust the mobile phase A and the mobile phase B in a suitable rate so the peak retention time of daptomycin is about 36 minutes.

Mobile phase A: Weigh 9 g of ammonium dihydrogen phosphate, dissolve in 1500 mL of water, adjust the pH to 3.25 with 0.1 mol/L phosphoric acid, and add water to make 2000 mL. Add 1000 mL of acetonitrile to 1000 mL of this solution and mix.

Mobile B: Weigh 9 g of ammonium dihydrogen phosphate, dissolve in 1500 mL of water, adjust the pH to 3.25 with 0.1 mol/L phosphoric acid, and add water to make 2000 mL. Add 400 mL of acetonitrile to 1600 mL of this solution and mix.

Flow rate: About 1.5 mL/min

Temperature of automatic injector: Between 3 and 7 °C.

Time span of measurement: 75 min

System suitability

System performance: Dissolve the mobile phase B in daptomycin RS to make 20 μL of 1 mg (potency)/mL solution and perform the test according to the above operating conditions; the peak retention time is about 24 minutes for lactone hydrolysate, about 30 minutes for β-isomer, 36 minutes for daptomycin, and about 48 minutes for anhydrodaptomycin. The tailing factor of the daptomycin peak is NMT 2.0, the resolution between β-isomer and daptomycin peak is NLT 2.0, and the resolution between daptomycin and anhydrodaptomycin peak is NLT 3.0.

Microbiological examination of non-sterile products The total aerobic microbial count is NMT 10 in 100 mL and *Escherichia coli*, *Salmonella*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* are not detected when the test is performed as directed under the Microbiological Examination of Non-sterile Products. However, do not perform the test when the Sterility is performed.

Sterility It meets the requirements when Daptomycin is used in a sterile preparation. However, it is excluded in cases where there is a final sterilization process in the manufacturing of a sterile preparation.

Bacterial endotoxins It meets the requirements when Daptomycin is used in a sterile preparation. However, Daptomycin is less than 0.30 EU per mg (potency) of daptomycin.

Water NMT 5.0% (0.2 g, volumetric titration, direct titration).

Residue on ignition NMT 0.5% (1 g).

Assay Weigh accurately about 30 mg (potency) each of Daptomycin and daptomycin RS and dissolve in water to make exactly 10 mL. Pipet 2 mL of this solution, add the internal standard solution to make exactly 100 mL, and use each solution as the test solution and the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Calculate the ratios, Q_T and Q_S, of the peak area of daptomycin to that of the internal standard, for the test solution and the standard solution. However, store the test solution and the standard solution in a refrigerator before the test.

$$\text{Potency (μg) of daptomycin } (C_{72}H_{101}N_{17}O_{26}) = \text{Potency (μg) of daptomycin RS} \times \frac{Q_T}{Q_S}$$

Weigh about 25 mg of the internal standard solution ethylparaben and dissolve the mobile phase A to make 1000 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 250 mm in length, packed with octylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Adjust the mobile phase A and the mobile phase B in a suitable rate so the peak retention time of daptomycin is about 15 minutes.

Mobile phase A: Weigh 9 g of ammonium dihydrogen phosphate, dissolve in 1500 mL of water, adjust the pH to 3.25 with 0.1 mol/L phosphoric acid, and add water to make 2000 mL. Mix 1000 mL of acetonitrile to 1000 mL of this solution.

Mobile B: Weigh 9 g of ammonium dihydrogen phosphate, dissolve in 1500 mL of water, adjust the pH to 3.25 with 0.1 mol/L phosphoric acid, and add water to make 2000 mL. Mix 400 mL of acetonitrile to 1600 mL of this solution.

Flow rate: Adjust the flow rate so that the retention time of daptomycin is about 15 minutes.

Temperature of automatic injector: Between 3 and 7 °C.

System suitability

System performance: Perform the test according to the above operating conditions with 20 μL of the standard solution; the peak retention time of daptomycin is about 15 minutes, the peak retention time of ethylparaben is about 5.5 minutes, the tailing factor of daptomycin peak is NMT 1.6, and the resolution of the peak between daptomycin and ethylparaben is NLT 5.0.

System repeatability: Repeat the injection 5 times with 20 μL of the standard solution according to the above operating conditions; the relative standard deviation (RSD) of daptomycin and ethylparaben is NMT 2.0%.

Packaging and storage Preserve in hermetic containers.

Daptomycin for Injection
주사용 답토마이신

Daptomycin for Injection is an injection used by

dissolving and contains NLT 90.0% and NMT 120.0% of daptomycin ($C_{72}H_{101}N_{17}O_{26}$: 1620.67).

Method of preparation Prepare Daptomycin for Injection as directed under Injections, with Daptomycin.

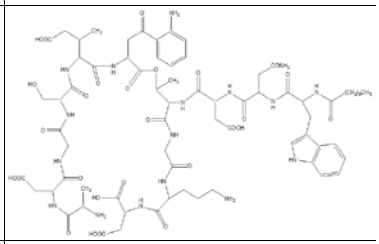
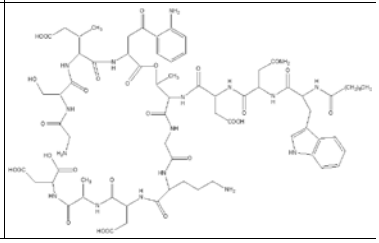
Identification (1) Perform the test according to the Identification test of Daptomycin.

(2) Determine the infrared spectra of Daptomycin for Injection and daptomycin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

pH Dissolve Daptomycin for Injection according to the labeled amount; the pH of this solution is between 4.5 and 5.5.

Purity Perform the test according to the purity test (2) of the related substances Daptomycin. Weigh accurately 0.5 g (potency) of Daptomycin for Injection and dissolve in water to make 200 mL. Take exactly 2 mL of this solution, add water to make 10 mL, and use this solution as the test solution. (NMT 3.5% of anhydrodaptomycin, NMT 2.0% of β-isomer, NMT 1.5% of lactone hydrolysate, NMT 0.5% of RS-2, NMT 0.4% of RS-3, NMT 0.15% of any other individual related substances, and NMT 8.0% of the total related substances)

Relative retention time and structure of RS-2 and RS-3

Component	Relative Retention time	Structure
RS-2	0.54	
RS-3	0.60	

Sterility Meets the requirements.

Bacterial endotoxins Daptomycin for Injection is NMT 0.30 EU per mg (potency) of daptomycin.

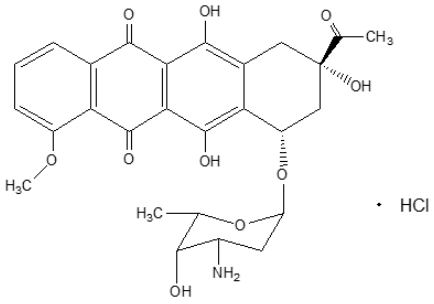
Uniformity of dosage units It meets the requirements when tested according to the Content uniformity test.

Water NMT 2.0% (0.2 g, volumetric titration, direct titration).

Assay Perform the test as directed under the Assay of Daptomycin under the Liquid Chromatography. But weigh accurately 0.5 g (potency) of Daptomycin for Injection and dissolve in water to make 200 mL. Pipet 2 mL of this solution, add the internal standard solution to make exactly 100 mL, and use this solution as the test solution.

Packaging and storage Preserve in hermetic containers.

Daunorubicin Hydrochloride
다우노루비신염산염



$C_{27}H_{29}NO_{10}\cdot HCl$: 563.98

(7*S*,9*S*)-9-Acetyl-7-[(2*R*,4*S*,5*S*,6*S*)-4-amino-5-hydroxy-6-methyloxan-2-yl]oxy-6,9,11-trihydroxy-4-methoxy-8,10-dihydro-7*H*-tetracene-5,12-dione hydrochloride [*23541-50-6*]

Daunorubicin Hydrochloride is the hydrochloride of an anthracycline compound with antitumor property obtained by growing *Streptomyces peucetius*.

Daunorubicin Hydrochloride contains NLT 940 μg (potency) and NMT 1050 μg (potency) per mg of daunorubicin hydrochloride ($C_{27}H_{29}NO_{10}\cdot HCl$), calculated on the dried basis.

Description Daunorubicin Hydrochloride occurs as a red powder.
It is soluble in water or methanol and slightly soluble in ethanol(99.5).

Identification (1) Determine the absorption spectra of solutions of Daunorubicin Hydrochloride and daunorubicin hydrochloride RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) The aqueous solution of Daunorubicin Hydrochloride (1 in 50) responds to the Qualitative Analysis (2) for chloride.

Optical rotation $[\alpha]_D^{20}$: Between +250° and +275° (15

mg, calculated on the dried basis, methanol, 10 mL, 100 mm).

pH Dissolve 0.15 g of Daunorubicin Hydrochloride in 30 mL of water; the pH is between 4.5 and 6.0.

Absorbance $E_{1cm}^{1\%}$ (495 nm): Between 210 and 250 (10 mg, calculated on the dried basis, methanol, 500 mL).

Purity (1) ***Clarity and color of solution***—Dissolve about 20 mg of Daunorubicin Hydrochloride in 10 mL of water; the resulting solution is clear and exhibits a red color.

(2) ***Heavy metals***—Proceed with 1.0 g of Daunorubicin Hydrochloride as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve 10 mg of Daunorubicin Hydrochloride in 5 mL of methanol and use this solution as the test solution. Pipet 3 mL of the test solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solutions and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, methanol, water and acetic acid (15 : 5 : 1 : 1) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Observe the plate with the naked eyes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 7.5% (0.1 g, NMT 0.67 kPa, 60 °C, 3 hours).

Sterility It meets the requirements when used in sterile preparations.

Bacterial endotoxins Less than 4.3 EU per mg (potency) of daunorubicin hydrochloride when used in sterile preparations.

Histamine It meets the requirements when used in sterile preparations. Weigh an appropriate amount of Daunorubicin Hydrochloride, make a solution containing 5.0 mg (potency) per mL, and use this solution as the test solution.

Assay Weigh accurately Daunorubicin Hydrochloride and about 20 mg (potency) of daunorubicin hydrochloride RS, add exactly 4 mL of the internal standard solution, and make exactly 20 mL with the mobile phase. Use these solutions as the test solution and the standard solution, respectively. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and calculate the ratios, Q_T and Q_S, of the peak area of Daunorubicin Hydrochloride to that of the internal standard.

$$\text{Potency (μg) of daunorubicin hydrochloride } (C_{27}H_{29}NO_{10}\cdot HCl) = \text{Potency (μg) of daunorubicin hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh 1 g of 2-naphthalenesulfonic acid hydrate and dissolve in the mobile phase to make 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 30 cm in length, packed with octylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of water and acetonitrile (31 : 19), adjusted pH to 2.2 with phosphoric acid.

Flow rate: Adjust the flow rate so that the retention time of daunorubicin is about 9 minutes.

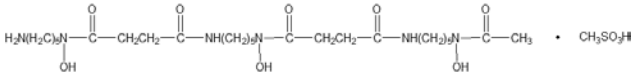
System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; 2-naphthalenesulfonic acid hydrate and daunorubicin are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solutions according to the above conditions; the relative standard deviation of the ratios of the peak area of daunorubicin to that of the internal standard is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Deferoxamine Mesilate
데페록사민메실산염



$C_{25}H_{46}N_6O_8\cdot CH_4O_3S$: 656.79

N-[5-[[4-[5-[Acetyl(hydroxy)amino]pentylamino]-4-oxobutanoyl]-hydroxyamino]pentyl]-*N'*-(5-aminopentyl)-*N*'-hydroxybutanediamide;methanesulfonic acid [*138-14-7*]

Deferoxamine Mesilate contains NLT 98.0% and NMT 102.0% of deferoxamine mesilate ($C_{25}H_{46}N_6O_8\cdot CH_4O_3S$), calculated on the anhydrous basis.

Method of preparation If there is a possibility that alkyl methanesulfonate esters (such as methyl, ethyl, and isopropyl) of methanesulfonic acid are introduced as poten-

tial impurities during the manufacturing process of Deferoxamine Mesilate, cautions should be taken with the starting materials, manufacturing process and intermediate product control to minimize residual impurities in consideration of the risk assessment result. If necessary, the manufacturing process can be validated with study data demonstrating that there's no quality risk to the final drug substance.

Description Deferoxamine Mesilate occurs as a white to pale yellow, crystalline powder.
It is freely soluble in water and practically insoluble in ethanol(99.5), 2-propanol or ether.

Melting point—About 147 °C (with decomposition).

Identification (1) To 5 mL of Deferoxamine Mesilate aqueous solution (1 in 500), add 1 drop of iron(III) chloride TS; the solution appears deep red.

(2) Deferoxamine Mesilate responds to the Qualitative Analysis (1) for mesilate.

(3) Determine the infrared spectra of Deferoxamine Mesilate and deferoxamine mesilate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

pH Dissolve 1.0 g of Deferoxamine Mesilate in 10 mL of water; the pH of this solution is between 3.5 and 5.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Deferoxamine Mesilate in 10 mL of water; the solution is clear, and colorless to pale yellow.

(2) ***Chloride***—Perform the test with 1.0 g of Deferoxamine Mesilate. Prepare the control solution with 0.90 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.032%).

(3) ***Sulfate***—Perform the test with 0.6 g of Deferoxamine Mesilate. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid VS (NMT 0.040%).

(4) ***Heavy metal***—Proceed with 2.0 g of Deferoxamine Mesilate according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Arsenic***—Prepare the test solution with 1.0 g of Deferoxamine Mesilate according to Method 3 and perform the test. Use a solution of magnesium nitrate in ethanol(95) (1 in 10) (NMT 2 ppm).

(6) ***Related substances***—Dissolve 50 mg of Deferoxamine Mesilate in 50 mL of the mobile phase and use this solution as the test solution. Pipet 3 mL of the test solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area obtained from each solution according to the automatic integration method; the sum of peak areas other than deferoxamine for the test solution is not larger than the peak area of deferoxamine for the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 20 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 1.32 g of ammonium dihydrogen phosphate, 0.37 g of ethylenediaminetetraacetic acid disodium salt dihydrate and 1.08 g of sodium 1-heptanesulfonate in 950 mL of water. Adjust the pH of this solution with phosphoric acid to 2.8, take 800 mL of this solution, and add 100 mL of 2-propanol.

Flow rate: Adjust the flow rate so that the retention time of deferoxamine is about 15 minutes.

System suitability

Detection sensitivity: Adjust the sensitivity so that the peak height of deferoxamine obtained from 20 μL of the standard solution is between 5 mm and 20 mm.

System performance: Dissolve 16 mg of Deferoxamine Mesilate and 4 mg of methylparahydroxybenzoate in 50 mL of the mobile phase. Proceed with 20 μL of this solution under the above conditions; deferoxamine and methyl *p*-hydroxybenzoate are eluted in the order with the resolution being NLT 4.

Time span of measurement: About 2 times the retention time of deferoxamine after the solvent peak.

Water NMT 2.0% (0.2 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

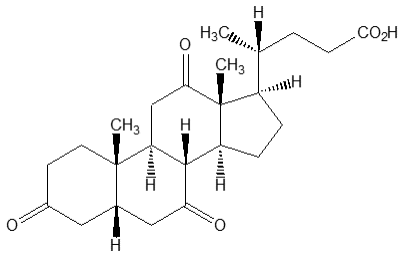
Assay Weigh accurately about 60 mg each of Deferoxamine Mesilate and deferoxamine mesilate RS (determine the content of water before use, in the same manner as Deferoxamine Mesilate), dissolve each in 20 mL of water, add exactly 10 mL of 0.05 mol/L sulfuric acid TS and add water to make exactly 50 mL. Pipet 5 mL of each solution, add exactly 5 mL of 0.05 mol/L sulfuric acid TS and 0.2 mL of iron(III) chloride TS, and add water to make exactly 50 mL. Use each solution as the test solution and the standard solution, respectively. Perform the test with the solutions as directed under the Ultraviolet-visible Spectroscopy, using a solution prepared by adding 0.05 mol/L sulfuric acid TS to 0.2 mL of iron(III) chloride TS to make exactly 50 mL as a control solution, and determine the absorbances, A_T and A_S, for the test solution and the standard solution, respectively, at 430 nm.

Amount (mg) of deferoxamine mesylate ($C_{25}H_{46}N_6O_8 \cdot CH_4O_3S$)
= Amount (mg) of deferoxamine mesylate RS,

as calculated on the anhydrous basis$\times \frac{A_T}{A_S}$

Packaging and storage Preserve in tight containers.

Dehydrocholic Acid
데히드로콜산



$C_{24}H_{34}O_5$: 402.52

(4*R*)-4-[(5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-Di-methyl-3,7,12-trioxo-1,2,4,5,6,8,9,11,14,15,16,17-dodecahydro-cyclopenta[a]phenanthren-17-yl]pentanoic acid [*81-23-2*]

Dehydrocholic Acid, when dried, contains NLT 98.5% and NMT 101.0% of dehydrocholic acid ($C_{24}H_{34}O_5$).

Description Dehydrocholic Acid occurs as a white, crystalline, odorless powder, with a bitter taste.
It is sparingly soluble in 1,4-dioxane, slightly soluble in ethanol(95) and practically insoluble in water or ether.
It is soluble in sodium hydroxide TS.

Identification (1) Dissolve 5 mg of Dehydrocholic Acid by adding 1 mL of sulfuric acid and 1 drop of formaldehyde solution and allow the solution to stand for 5 minutes. Add 5 mL of water to the resulting solution; the solution exhibits a yellow color with bluish green fluorescence.

(2) To 20 mg of Dehydrocholic Acid, add 1 mL of ethanol(95) and shake to mix. To this, add 5 drops of *m*-dinitrobenzene TS and 0.5 mL of sodium hydroxide solution (1 in 8) and allow it to stand; the solution exhibits a purple to reddish purple color, which gradually changes to brown.

Optical rotation $[\alpha]_D^{20}$: Between +27° and +30° (after drying, 0.2 g, sodium hydroxide TS, 10 mL, 100 mm).

Melting point Between 233 and 242 °C.

Purity (1) ***Odor***—To 2.0 g of Dehydrocholic Acid, add 100 mL of water and boil for 2 minutes; the solution is odorless.

(2) ***Clarity and color of solution***—Weigh 0.10 g of Dehydrocholic Acid, previously powdered, add 30 mL of ethanol(95) and dissolve by shaking for 10 minutes; the solution is clear and colorless.

(3) ***Chloride***—To 2.0 g of Dehydrocholic Acid, add 100 mL of water, shake to mix for 5 minutes and filter. Take 25 mL of the filtrate, add 6 mL of dilute nitric acid, and heat on a steam bath for 6 minutes. After cooling, filter it and take a clear filtrate. Wash the residue with 10 mL of water, combine the washings with the filtrate, and add water to make 50 mL. Use the resulting solution as the test solution and perform the test. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.021%).

(4) ***Sulfate***—Add 1 mL of dilute hydrochloric acid to 25 mL of the test solution obtained from (3), and heat on a steam bath for 6 minutes. After cooling, filter and take a clear filtrate. Wash the residue with 10 mL of water, combine the washings with the filtrate, and add water to make 50 mL. Use the resulting solution as the test solution and perform the test. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid VS (NMT 0.048%).

(5) ***Heavy metal***—Proceed with 1.0 g of Dehydrocholic Acid according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(6) ***Barium***—To the solution obtained from (1), add 2 mL of hydrochloric acid and boil for 2 minutes. After cooling, filter and wash with water until 100 mL of the filtrate is obtained. To 10 mL of this solution, add 1 mL of dilute sulfuric acid; no turbidity is produced.

Loss on drying NMT 1.0% (1 g, 105 °C, 2 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.5 g of Dehydrocholic Acid, previously dried, add 40 mL of neutralized ethanol and 20 mL of water and heat to dissolve. Add 2 drops of phenolphthalein TS, titrate with 0.1 mol/L sodium hydroxide VS, add 100 mL of freshly boiled and then cooled water near the endpoint, and titrate again.

Each mL of 0.1 mol/L sodium hydroxide VS
= 40.25 mg of $C_{24}H_{34}O_5$

Packaging and storage Preserve in well-closed containers.

Deoxyribonuclease
데옥시리보뉴클레아제

Deoxyribonuclease is an enzyme extracted from bovine pancreases, with the molecular weight of 62000 and isoelectric point (pl) between pH 4.7 and 5.0.

Each mg of Deoxyribonuclease contains NLT 3000 Kunitz units.

Description Deoxyribonuclease occurs as a white or pale yellow, amorphous, odorless powder.
It is soluble in water and insoluble in organic solvent.

Identification Dissolve 0.2 g of Sodium Deoxyribonucleate in water in a mortar, transfer it to a 100-mL volumetric flask, and use it as the substrate solution. Separately, weigh equivalent to about 0.1 g of Deoxyribonuclease and perform extraction with 100 mL of 0.02 mol/L magnesium chloride solution. Pipet 1 mL of this solution, transfer it to a 100-mL volumetric flask, add 0.02 mol/L magnesium chloride solution up to the gauge line, and use the solution as the test solution.
Put 2 mL of the substrate solution and 2 mL of pH 7.0 phosphate buffer solution into a test tube, and mix well. After heating it in a 35 ℃ water bath for 1 hour, add 2 mL of 50% trichloroacetic acid, and put the test tube in iced water for 15 minutes. Filter the solution with a filter paper. To 20 mL of the filtrate, add 4 mL of Dische reagent, and warm for 10 minutes on a steam bath; the solution exhibit a dark blue color.

Loss on drying NMT 0.3% (1 g, 60 ℃, 4 hours).

Residue on ignition NMT 1.0% (1 g).

Assay The amount of enzyme required for decreasing the relative viscosity by 1° when 0.1 mL of the test solution and 2.4 mL of the substrate solution are put for reaction at 30 ℃ for 10 minutes is expressed in 1 Kunitz unit.

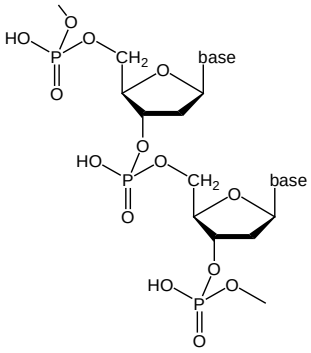
Weigh accurately about 0.15 g of Sodium Deoxyribonucleate, put it in a mortar, add barbital buffer solution, (pH 7.5), and grind well for mixing. To this, add buffer solution to make 100 mL. To this solution, add magnesium sulfate to make the final concentration 0.03 mol/L, and use it as the substrate solution (This solution has a viscosity between 4.1 and 5.7 at 30 ℃). Separately, weigh accurately about 0.1 g of Deoxyribonuclease, transfer it into a volumetric flask, dilute with water to 100 mL, and use this solution as the test solution.

Pipet 2.4 mL of the substrate solution into the Ostwald viscometer that is scale marked at the top to have a flow rate of bubble and distilled water of 1.5 mL volume per between 18 and 20 seconds, put this viscometer in a constant temperature water bath adjusted to 30 ± 0.2 ℃ for 10 minutes, and add 0.1 mL of water (control solution). Put this viscosimeter again into the constant temperature water bath under the above conditions, and measure the flow rate at 1, 3, 5, 7 and 10 minutes. Perform the same procedure with 0.1 mL of the test solution instead of 0.1 mL of water and measure the flow rate. As seen in the table below, the viscosity decrease of the substrate solution is constant during the test (decreased by between 0.2 and 1° within 10 minutes).

If 0.1 mL of the test solution decreased the relative viscosity of 2.4 mL of the substrate solution by 0.9 at 30 ℃ for 10 minutes, 0.1 mL of the test solution contains 0.9 units of Deoxyribonuclease.

	Flow rate relative viscosity				
Time (min)	1	3	5	7	10
Temperature (30 ℃) Control solution (2.4 mL of sodium deoxyribonucleate + 0.1 mL of water)	108″ 5.4	108″ 5.3	108″ 5.4	108″ 5.3	108″ 5.4
Test solution (DNaSedor) (2.4 mL of sodium deoxyribonucleate + 0.1 mL of the test solution)	107″ 5.35	104″ 5.2	98″ 4.9	94″ 4.7	89″ 4.45

Deoxyribonucleic Acid
데옥시리보핵산



[9007-49-2]

Deoxyribonucleic Acid, when dried, contains NLT 14.5% of nitrogen (N : 14.00) and NLT 9.0% of phosphorus (P : 30.97).

Description Deoxyribonucleic Acid occurs as a white to yellow powder.
It is insoluble in most organic solvents.
It is insoluble in the acid of about pH 2, soluble in alkaline solution and alkali-activated salt solution (acetate, phosphate, and glycerol phosphate), and stable under alkalinity.

Identification (1) Dissolve 10 mg of Deoxyribonucleic Acid in 5 mL of 10% trichloroacetic acid solution, put 1 mL of this solution into a test tube, add 2 mL of diphenylamine-acetic acid(100) TS, and heat on a steam bath for 10 minutes; the solution exhibits a dark blue color.

(2) Dissolve 10 mg of Deoxyribonucleic Acid in 5 mL of 10% trichloroacetic acid solution, put 1 mL of this solution into a test tube, add 5 mL of xanthydrol TS, and heat on a steam bath for 3 minutes; the solution exhibits a red color.

Purity (1) ***Protein impurities***—Put 1 g of Deoxyribonucleic Acid in a test tube, add 1 mL of 95% ethanol, add 10 mL of 10% sodium acetate solution, while stirring; the

solution is clear, and colorless or pale yellow.

(2) ***Simple protein***—To 4 mL of the solution obtained as above, add 2 mL of sodium hydroxide TS, boil, and add 2 to 3 drops of copper-alkali TS; the solution does not turn to purple.

(3) ***RNA***—Dissolve 10 mg of Deoxyribonucleic Acid in 0.2 mL of sodium hydroxide TS (1 in 4) by shaking. To this solution, dissolve 2 mL of orcinol-hydrochloric acid solution by shaking, add 2 mL of orcinol-hydrochloric acid solution, and heat on a steam bath with shaking. After cooling, add 10 mL of water and perform extraction with isoamyl alcohol; the solution exhibits a greenish yellow color.

Loss on drying NMT 7.0% (1 g, 105 °C, 4 hours).

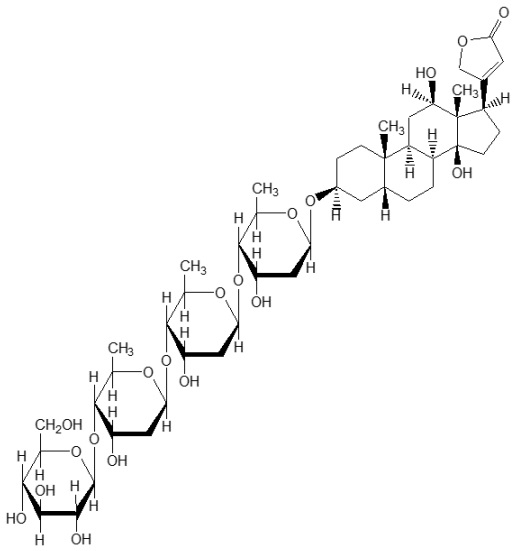
Residue on ignition NMT 0.5% (1 g, 450 °C - 500 °C).

Assay (1) ***Nitrogen***—Weigh accurately about 0.25 g of Deoxyribonucleic Acid, previously dried, and perform the test according to the Nitrogen Determination method (semi-micro Kjeldahl method).

(2) ***Phosphorus***—Perform the test with a suitable amount of Deoxyribonucleic Acid, previously dried, according to the Analysis for Minerals.

Packaging and storage Preserve in well-closed containers.

Deslanoside
데슬라노시드



$C_{47}H_{74}O_{19}$: 943.08

3-[(3*S*,5*R*,8*R*,9*S*,10*S*,12*R*,13*S*,14*S*,17*R*)-12,14-Dihydroxy-3-[(2*R*,4*S*,5*S*,6*R*)-4-hydroxy-5-[(2*S*,4*S*,5*S*,6*R*)-4-hydroxy-5-[(2*S*,4*S*,5*S*,6*R*)-4-hydroxy-6-methyl-5-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyoxan-2-yl]oxy-6-methyloxan-2-yl]oxy-10,13-dimethyl-1,2,3,4,5,6,7,8,9,11,12,15,16,17-tetradecahydrocyclopenta[a]phenanthren-17-yl]-2*H*-furan-5-one [*17598-65-1*]

Deslanoside, when dried, contains NLT 90.0% and NMT 102.0% of deslanoside ($C_{47}H_{74}O_{19}$).

Description Deslanoside occurs as colorless to white crystals or a crystalline powder.
It is freely soluble in pyridine anhydrous, sparingly soluble in methanol, slightly soluble in ethanol(95) and practically insoluble in water or ether.
It is hygroscopic.

Identification Take about 1 mg of Deslanoside in a small test tube about 10 mm in internal diameter, dissolve 1 mL of acetic acid(100) of iron(III) chloride hexahydrate solution (1 in 10000), and add 1 mL of sulfuric acid to make two layers; at the boundary layer of two liquids, a brown ring is shown and the color of the upper layer near to the contact zone changes gradually to blue through purple and the entire acetic acid(100) layer changes to a bluish green color through a deep blue color.

Optical rotation $[\alpha]_D^{20}$: Between + 6.5° and + 8.5° (0.5 g after drying, pyridine anhydrous, 25 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 20 mg of Deslanoside in 10 mL of ethanol(95) and 3 mL of water by warming, cool and add water to make 100 mL; the solution is clear and colorless.

(2) ***Related substances***—Dissolve 10 mg of Deslanoside in exactly 5 mL of methanol and use this solution as the test solution. Separately, weigh about 1.0 mg of deslanoside RS, add exactly 5 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on a plate of silica gel for thin-layer chromatography. Then, develop the plate with a mixture of dichloromethane, methanol and water (84 : 15 : 1) as a developing solvent to a distance of about 13 cm, and air-dry the plate. Spray evenly dilute sulfuric acid on the plate and heat the plate at 110 ℃ for 10 minutes; the spots other than the principal spot from the test solution are not larger than and not more intense than the spot from the standard solution.

Loss on drying NMT 8.0% (0.5 g, in vacuum, phosphorus oxide (V), 60 ℃, 4 hours).

Residue on ignition NMT 0.5% (0.1 g).

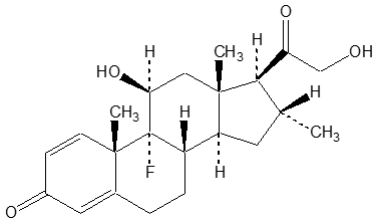
Assay Weigh accurately about 12 mg of Deslanoside and deslanoside RS, previously dried, dissolve in 20 mL each of methanol, add water to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Pipet 5.0 mL each of the test solution

and the standard solution, transfer to a 25 mL light-resistant volumetric flasks, add and shake well to mix with 5 mL each of 2,4,6-trinitrophenol TS and 0.5 mL each of sodium hydroxide solution (1 in 10), and add diluted methanol (1 in 4) to make exactly 25 mL. Allow the solution to stand at a temperature between 18 and 22 ℃ for 25 minutes. With these solutions, perform the test as directed under the Ultraviolet-visible Spectroscopy, using a solution prepared with 5 mL of methanol (1 in 5) in the same manner as a control solution. Determine the absorbances, A_T and A_S, of each solution, obtained from the test solution and the standard solution, at 485 nm.

$$\text{Amount (mg) of deslanoside } (C_{47}H_{74}O_{19}) = \text{Amount (mg) of deslanoside RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers.

Desoximetasone
데속시메타손



$C_{22}H_{29}FO_4$: 376.46

(8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*R*,17*R*)-9-Fluoro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-3-one [*382-67-2*]

Desoximetasone contains NLT 97.0% and NMT 103.0% of desoximetasone ($C_{22}H_{29}FO_4$), calculated on the dried basis.

Description Desoximetasone occurs as a white or almost white, crystalline powder.
It is very soluble in ethanol(95), acetone or chloroform and practically insoluble in water.

Identification (1) Determine the infrared spectra of Desoximetasone and desoximetasone RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve about 0.1 g of Desoximetasone in a mixture of chloroform and ethanol(95) (3 : 1) to make 10 mL, and use this solution as the test solution. Separately, dissolve about 0.1 g of desoximetasone RS in a mixture of chloroform and ethanol(95) (3 : 1) to make 10 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography (with fluorescence agent). Then, develop the plate with a mixture containing chloroform and ethyl acetate (1 : 1) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Expose the plate with ultraviolet light (main wavelength: 254 nm) and spray evenly the plate with p-toluenesulfonic acid monohydrate in ethanol(95) (1 in 5); the R_f value of the principal spot obtained from the test solution corresponds to that from the standard solution.

Optical rotation $[\alpha]_D^{25}$: Between + 107° and -112° (0.1 g after drying, chloroform, 20 mL, 100 mm).

Melting point Between 206 and 218 ℃. However, the range of temperature from the initiation of solubility and the end of fusion is NMT 4 ℃.

Purity ***Heavy metals***—Proceed with 1.0 g of Desoximetasone according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Loss on drying NMT 1.0% (1 g, 105 °C, constant mass).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 40 mg of Desoximetasone, dissolve methanol to make exactly 100 mL, pipet 10.0 mL of this solution, and add a mixture of methanol and acetonitrile (1 : 1) to make exactly 100 mL. Use this solution as the test solution. Separately, weigh accurately about 40 mg of desoximetasone RS, dissolve methanol to make exactly 100 mL, pipet 10.0 mL of this solution, and add a mixture of methanol and acetonitrile (1 : 1) to make exactly 100 mL. Use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and determine the peak height of desoximetasone, H_T, and H_S in the test and standard solutions.

$$\text{Amount (mg) of desoximetasone } (C_{22}H_{29}FO_4) = \text{Amount (mg) of desoximetasone RS} \times \frac{H_T}{H_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 to 10 μm in particle diameter).

Mobile phase: A mixture of methanol, water, and acetic acid(100) (65 : 35 : 1). However, adjust so the retention time of desoximetasone is NMT 6 minutes.

Flow rate: 1 mL/min

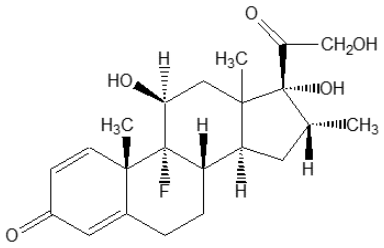
System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; the symmetry factor for desoximetasone peak is NMT 1.5.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solution under the above operating conditions; the relative standard deviation (RSD) of the peak height of desoximetasone is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Dexamethasone
덱사메타손



$C_{22}H_{29}FO_5$: 392.46

(8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*R*,17*R*)-9-Fluoro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-3-one [*50-02-2*]

Dexamethasone, when dried, contains NLT 97.0% and NMT 102.0% of dexamethasone ($C_{22}H_{29}FO_5$).

Description Dexamethasone occurs as white to pale yellow crystals or a crystalline powder.
It is sparingly soluble in methanol, ethanol(95) or acetone and practically insoluble in water.

Melting point—About 245 °C (with decomposition).

Identification (1) Proceed with 10 mg of Dexamethasone as directed under the Oxygen Flask Combustion, using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as an absorbent; the solution responds to the Qualitative Analysis for fluoride.

(2) Dissolve 1.0 mg each of Dexamethasone and dexamethasone RS in 10 mL of ethanol(95). To 2.0 mL of this solution, add 10 mL of phenylhydrazinium hydrochloride TS, mix by shaking, and heat on a steam bath at 60 ℃ for 20 minutes. After cooling, determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy, using a solution prepared with 2.0 mL of ethanol(95) in the same manner, as a control solution; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Dexamethasone and dexamethasone RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears, dissolve Dexamethasone and dexamethasone RS in acetone, respectively, evaporate to dryness and repeat the test using the residue on evaporation.

Optical rotation $[\alpha]_D^{20}$: Between +86° and +94° (after drying, 0.1 g, methanol, 10 mL, 100 mm).

Purity (1) ***Heavy metal***—Proceed with 1.0 g of Dexamethasone according to Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(2) ***Related substances***—Dissolve 0.18 g of Dexamethasone in 100 mL of acetonitrile. Pipet 33 mL of this solution, add ammonium formate buffer solution (pH 3.6) to make 100 mL, and use this solution as the test solution. Pipet 1 mL of the test solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area from each solution according to the automatic integration method; the peak area other than dexamethasone from the test solution is not larger than the peak area of dexamethasone from the standard solution, and the sum of peak areas other than dexamethasone from the test solution is not larger than 2 times the peak area of dexamethasone from the standard solution.

Ammonium formate buffer solution—Add water to 1.32 g of ammonium formate, pH 3.6 to make 1000 mL and adjust the pH to 3.6 with formic acid.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column, 4.6 mm in internal diameter and 25 cm in length, packed with phenylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 1.32 g of ammonium formate in 1000 mL of water and adjust the pH to 3.6 with formic acid. To 670 mL of this solution, add 330 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of dexamethasone is about 13 minutes.

System suitability

Detection sensitivity: Pipet 1 mL of the standard solution and add the mobile phase to make exactly 10 mL. Confirm that the peak area of dexamethasone obtained from 10 μL of this solution is equivalent to 8 - 12% of the peak area of dexamethasone obtained from the standard solution.

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; the number of theoretical plates of dexamethasone peak is

NLT 5000 with the symmetry factor being NMT 1.5.

System repeatability: Repeat the test 6 times according to the above conditions with 10 μL of the standard solution each time; the relative standard deviation of the peak areas of dexamethasone is NMT 1.0%.

Time span of measurement: About 4 times the retention time of dexamethasone after the solvent peak.

Loss on drying NMT 0.5% (0.2 g, 105 °C, 3 hours).

Residue on ignition NMT 0.1% (0.2 g, platinum crucible).

Assay Weigh accurately about 10 mg each of Dexamethasone and dexamethasone RS, previously dried, dissolve by adding diluted methanol (1 in 2) to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of dexamethasone, A_T and A_S, in each solution.

Amount (mg) of dexamethasone ($C_{22}H_{29}FO_5$)
= Amount (mg) of dexamethasone RS × A_T / A_S

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column, 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of water and acetonitrile (2 : 1).

Flow rate: Adjust the flow rate so that the retention time of dexamethasone is about 6 minutes.

System suitability

System repeatability: Repeat the test 6 times according to the above conditions with 10 μL of the standard solution each time; the relative standard deviation of the peak areas of dexamethasone is NMT 2.0%.

Packaging and storage Preserve in light-resistant tight containers.

Dexamethasone Tablets
덱사메타손 정

Dexamethasone Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of dexamethasone ($C_{22}H_{29}FO_5$: 392.46).

Method of preparation Prepare Dexamethasone Tablets as directed under Tablets, with Dexamethasone.

Identification Take 10 mL of the methanol extract obtained by the preparation of the test solution under the Assay, evaporate to dryness on a steam bath, dissolve by putting 1 mL of chloroform, and use this solution as the test solution. Separately, weigh an appropriate amount of dexamethasone RS and dissolve in chloroform to make a solution containing 500 μg per mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL of the test solution and 20 μL of the standard solution on a plate of made silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methylene chloride and methanol (45 : 4) to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254nm); the R_f values of the principal spots obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 tablet of Dexamethasone Tablets and 500 mL of hydrochloric acid diluted with the test solution (1 in 100) at 100 revolutions per minutes according to Method 1. Take the dissolved solution 45 minutes after starting the test, filter, discard the first 10 mL of filtrate and take exactly V mL of the subsequent filtrate. Add methanol diluted to contain 0.75 μg of dexamethasone per mL according to the labeled amount (1 in 10), make exactly V' mL, and use this solution as the test solution. Separately, weigh accurately about 15 mg of dexamethasone RS, previously dried at 105 °C for 3 hours, and dissolve in 10 mL of methanol, and put water to make exactly 100 mL. Pipet 1 mL of this solution, add diluted methanol (1 in 10) to obtain the same concentration as the test solution, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of dexamethasone, A_T and A_S, in each solution. It meets the requirements when the dissolution rate of Dexamethasone Tablets in 45 minutes is NLT 70%.

Dissolution rate (%) for the labeled amount of dexamethasone ($C_{22}H_{29}FO_5$)
= C_S × A_T / A_S × V' / V × 1 / C × 50000

C_S: Concentration of the standard solution (mg/mL)

C: Labeled amount (mg) of dexamethasone ($C_{22}H_{29}FO_5$) in 1 tablet

Operating conditions

For the column, column temperature and mobile phase, proceed as directed in the operating conditions under the Assay of Dexamethasone.

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Flow rate: 1.5 mL/min

System suitability

System repeatability: Repeat the test 6 times according to the above conditions with 50 μL of the standard solution; the relative standard deviation of the peak areas of dexamethasone is NMT 2.0%.

Uniformity of dosage units Perform the procedure for content uniformity with Dexamethasone Tablets as directed under the Assay; it meets requirements.

Assay Weigh accurately the mass of NLT 20 Dexamethasone Tablets and powder. Weigh accurately an amount of Dexamethasone Tablets, equivalent to about 10 mg of dexamethasone ($C_{22}H_{29}FO_5$), transfer to a 100-mL volumetric flask, add 30 mL of diluted methanol (1 in 2), and shake to mix for 30 minutes. To this, add diluted methanol (1 in 2) up to the gauge line, and mix. Filter and use the filtrate as the test solution. Separately, weigh accurately about 10 mg of dexamethasone RS, transfer to a 100-mL volumetric flask and dissolve in 30 mL of diluted methanol (1 in 2). To this, add diluted methanol (1 in 2) up to the gauge line, mix, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of dexamethasone, A_T and A_S, in each solution.

Amount (mg) of dexamethasone ($C_{22}H_{29}FO_5$)
= Amount (mg) of dexamethasone RS × A_T / A_S

Operating conditions

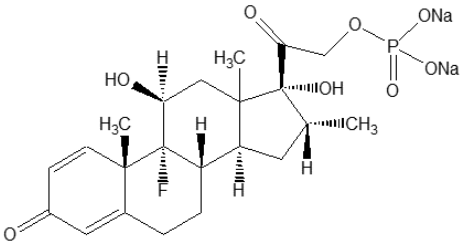
Use the operating conditions as directed under the Assay of Dexamethasone.

System suitability

System repeatability: Repeat the test 6 times according to the above conditions with 10 μL of the standard solution each time; the relative standard deviation of the peak areas of dexamethasone is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Dexamethasone Phosphate Disodium
덱사메타손포스페이트이나트륨



Dexamethasone Sodium Phosphate

$C_{22}H_{28}FNa_2O_8P$: 516.41

Sodium 2-[(8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*R*,17*R*)-9-fluoro-11,17-dihydroxy-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-17-yl]-2-oxoethyl] phosphate [*2392-39-4*]

Dexamethasone Phosphate Disodium contains NLT 97.0% and NMT 102.0% of dexamethasone phosphate disodium ($C_{22}H_{28}FNa_2O_8P$), calculated on the anhydrous and ethanol-free basis.

Description Dexamethasone Phosphate Disodium occurs as a white or pale yellow, crystalline powder, with no odor or a slight odor of ethanol.
It is freely soluble in water, slightly soluble in ethanol(95), very slightly soluble in 1,4-dioxane, and practically insoluble in chloroform and in ether.
It is very hygroscopic.

Identification (1) Put 20 mg of Dexamethasone Phosphate Disodium in a 15-mL centrifuge tube, add 5.0 mL of alkaline phosphatase TS, shake hard to mix, and allow it to stand for 30 minutes. Add 5.0 mL of ethyl acetate, shake hard to mix, centrifuge, and use the ethyl acetate layer as the test solution. Separately, put 15 mg of dexamethasone RS in a 5 mL volumetric flask, dissolve in ethyl acetate, add ethyl acetate again up to the gauge line for mixing, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of chloroform, methanol and water (180 : 15 : 1) to a distance of about 15 cm, take out the plate, and air-dry the plate. Observe the plate under ultraviolet light (main wavelength: 254nm); the R_f values of the principal spots obtained from the test solution and the standard solution are the same.

(2) Residue on ignition of Dexamethasone Phosphate Disodium responds to the Qualitative Analysis for sodium salt and phosphate.

pH The pH of a solution of Dexamethasone Phosphate Disodium (1 in 100) is between 7.5 and 10.5.

Optical rotation $[\alpha]_D^{20}$: Between +74° and +82° (on the anhydrous and ethanol-free basis, 0.1 g, water, 10 mL, 100 mm).

Purity (1) ***Ethanol***—Weigh accurately about 50 mg of Dexamethasone Phosphate Disodium, add exactly 5 mL of the internal standard solution, add water to make exactly 25 mL, and use it as the test solution. Separately, add exactly water to exactly 2 mL of ethanol(99.5) to make 100 mL and use it as the standard stock solution. With this solution, measure the specific gravity at 25 ℃ to obtain the content of ethanol. Pipet 0.25 mL of the standard stock solution, add exactly 5 mL of the internal standard solution, add water to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 1 μL each of the test solution and the standard solu-

tion as directed under the Gas Chromatography according to the following conditions, and determine the ratio of peak area of ethanol from the test solution and the standard solution versus peak area of the internal standard, Q_T and Q_S, respectively; the amount of ethanol (C_2H_5OH) in Dexamethasone Phosphate Disodium is NMT 8.0%.

$$\text{Content (\%) of ethanol } (C_2H_5OH) = 0.25 \times S / W \times Q_T / Q_S$$

S: Content (%) of ethanol in the standard stock solution

W: Amount (g) of Dexamethasone Phosphate Disodium in the test solution

Internal standard solution—1-propanol solution (1 in 1000).

Operating conditions

Detector: A hydrogen flame-ionization detector

Column: A fused silica column 0.53 mm in internal diameter and 30 m in length, coated inside with 6% cyanopropylphenyl and 94% dimethylpolysiloxane for gas chromatography to a thickness of 3.0 μm.

Column temperature: Maintain at 50 °C for 5 minutes, then raise to 200 °C by 50 °C per minute, and keep at 200 °C for 5 minutes.

Sample injection port temperature: 210 °C

Detector temperature: 280 °C

Split ratio: 1 : 5

Carrier gas: Nitrogen

Flow rate: 5 mL/min

System suitability

System performance: Proceed with 1 μL of the standard solution under the above operating conditions; ethanol and the internal standard are eluted in this order.

System repeatability: Repeat the test 6 times under the above conditions with 1 μL each of the standard solution; the relative standard for the ratio of peak area is NMT 4.0%.

(2) ***Phosphate ion***—Weigh accurately about 50 mg of Dexamethasone Phosphate Disodium, transfer it to a 25 mL volumetric flask, add 10 mL of water, and shake to mix. To this, add 5 mL of 1 mol/L sulfuric acid and dissolve by heating, if necessary. After cooling, add 1 mL each of the phosphate TS A and phosphate TS B, add water up to the gauge line, and mix. Allow this solution to stand for 30 minutes at room temperature, and use the resulting solution as the test solution. Separately, pipet 5 mL of phosphate standard solution, proceed with it n the same manner as the test solution, and use it as the standard solution. Perform the test with the test solution and standard solution as directed under the Ultraviolet-visible Spectroscopy and determine the absorbance of each solution at the wavelength of 730 nm, using water as a control solution; the absorbance of the test solution is not greater than that of the standard solution (PO_4 NMT 1.0%).

Phosphate standard solution—Add water to 143.3 mg of potassium dihydrogen phosphate, previously dried, and dissolve to make 1000 mL (0.10 mg PO_4/mL).

Phosphate TS A—Weigh 5 g of ammonium heptamolybdate tetrahydrate, dissolve in 0.5 mol/L sulfuric acid to make 100 mL.

Phosphate B—Weigh 0.35 g of *p*-methylaminophenol sulfate, dissolve in 50 mL of water, add 20 g of sodium sulfite heptahydrate, mix by dissolving, and add water to make 100 mL.

(3) ***Free dexamethasone***—Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the conditions under the Assay, and determine the peak area of dexamethasone, A_T and A_S, in each solution, respectively (NMT 1.0%).

$$\text{Amount (μg) of dexamethasone } (C_{22}H_{29}FO_5) = 1000 \times C \times \frac{A_T}{A_S}$$

C: Concentration of the standard solution (μg/mL)

(4) ***Related substances***—Dissolve exactly 25 mg of Dexamethasone Phosphate Disodium in the mobile phase A to make 25 mL, and use this solution as the test solution. Perform the test with 15 μL of the test solution by the percentage peak area method under the Liquid Chromatography according to the following conditions; each of the related substances is NMT 1.0% and the total amount of related substances is NMT 2.0%.

$$\text{Content (\%) of each related substance} = 100 \times \frac{A_i}{A_S}$$

A_i: Peak area of each related substance obtained from the test solution.

A_S: Sum of all peak areas obtained from the test solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Use the mobile phases A and B to control stepwise or based on the gradient elution as follows.

Mobile phase A: A mixture of water, methanol and buffer (7 : 7 : 6).

Mobile phase B: A mixture of methanol and buff-

er (7 : 3).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0	90	10
0 - 3.5	90	10
3.5 - 23.5	90 → 60	10 → 40
23.5 - 34.5	60 → 5	40 → 95
34.5 - 59.5	5	95
59.5 - 60	5 → 90	95 → 10

Flow rate: 1 mL/min

System suitability

System performance: Proceed with 15 μL of the test solution according to the above operation conditions; the resolution between the major peak and the peak of the closest related substance is NLT 1.0.

System repeatability: Repeat the test 6 times according to the above conditions with 15 μL each of the test solution; the relative standard deviation of the peak area is NMT 4.0%.

Buffer solution—Dissolve 7.0 g of ammonium acetate in 1000 mL of water and add acetic acid(100) to adjust the pH to 4.0.

Water NMT 16.0% (including the content of ethanol, 0.4 g, volumetric titration, direct titration).

Assay Weigh accurately about 50 mg of Dexamethasone Phosphate Disodium, and dissolve in the mobile phase to make exactly 100 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of dexamethasone phosphate RS, previously dried at 40 ℃ and 0.67 kPa to a constant weight, and dissolve in the mobile phase to make a solution containing 0.5 mg per mL (Solution 1). Separately, weigh accurately a suitable amount of dexamethasone RS, previously dried at 105 ℃ for 3 hours, and dissolve in a mixture of water and methanol (1 : 1) to make a solution containing 50 μg per mL (Solution 2). Pipet 10.0 mL of Solution 1 and 1.0 mL of Solution 2, respectively, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of dexamethasone phosphate for each of the solutions, A_T and A_S, respectively.

Amount (mg) of dexamethasone phosphate disodium ($C_{22}H_{28}FNa_2O_8P$)

$$= \frac{516.41}{472.45} \times C \times \frac{A_T}{A_S}$$

C: Concentration (μg/mL) of the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.5 mm in internal diameter and about 25 cm in length, packed with phenylated silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Add water to 7.5 mL of triethylamine to make 1000 mL, and adjust the pH to 5.4 with phosphoric acid. Mix this solution with methanol in the ratio of 74 : 26.

Flow rate: 1.2 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; dexamethasone and dexamethasone phosphate are eluted in this order with the resolution between their peaks being NLT 1.8.

System repeatability: Repeat the test 6 times according to the above conditions with 10 μL of the standard solution each time; the relative standard deviation of the peak area is NMT 1.0%.

Packaging and storage Preserve in hermetic containers.

Dexamethasone Phosphate Disodium Injection
덱사메타손포스페이트이나트륨 주사액

Dexamethasone Phosphate Disodium Injection, as an aqueous injection, contains Dexamethasone Phosphate Disodium in the amount equivalent to NLT 90.0% and NMT 115.0% of the labeled amount of dexamethasone phosphate ($C_{22}H_{30}FO_8P$: 472.45).

Method of preparation Prepare Dexamethasone Phosphate Disodium Injection with as directed under Injections, with Dexamethasone Phosphate Disodium.

Description Dexamethasone Phosphate Disodium Injection occurs as a clear, colorless liquid.

Identification Take Dexamethasone Phosphate Disodium Injection in the amount equivalent to 10 mg of dexamethasone phosphate disodium, transfer to a 100-mL volumetric flask, add water to make 100 mL and shake to mix. Take 5 mL of this solution, put in a 125 mL separatory funnel, and perform washing twice with 10 mL of methylene chloride, previously washed with water. After discarding the washings, transfer the solution into a 50-mL glass stoppered test tube, add 5 mL of alkaline phosphatase solution prepared by dissolving 50 mg of alkaline phosphatase in 50 mL of magnesium buffer solution, pH 9.0, allow it to stand at 37 ℃ for 45 minutes, and perform extraction with 25 mL of dichloromethane. Evaporate 15 mL of dichloromethane extract to dryness

on a steam bath, and dissolve the residue in 1 mL of dichloromethane. Dissolve an appropriate amount each of this solution and dexamethasone RS in dichloromethane to obtain the standard solution containing 300 μg per mL. Spot 5 μL each of the standard solution on a plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of acetone, chloroform and water (50 : 50 : 1) to a distance of 15 cm, take out the plate, and air-dry it. Spray dilute sulfuric acid (1 in 2) onto this plate, and heat at 105 ℃ until a brown or black spot appears. The principal spots obtained from the test solution and standard solution are the same in the R_f value.

pH Between 7.0 and 8.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 31.3 EU per mg of dexamethasone phosphate.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Take Dexamethasone Phosphate Disodium Injection exactly in the amount equivalent to about 8 mg of dexamethasone phosphate ($C_{22}H_{30}FO_8P$), add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of dexamethasone phosphate RS, previously dried at 40 ℃ and 0.67 kPa to a constant weight, dissolve in the mobile phase to make a solution containing 80 μg per mL, and use this solution as the standard solution. Prepare the standard solution before use. Perform the test with 20 μL each of the test and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of dexamethasone for each of the solutions, A_T and A_S, respectively.

$$\text{Amount (mg/mL) of dexamethasone phosphate } (C_{22}H_{30}FO_8P) = \frac{0.1 \times C}{V} \times \frac{A_T}{A_S}$$

C: Concentration (μg/mL) of the standard solution
V: Amount (mL) of sample

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Mobile phase: 0.01 mol/L potassium dihydrogen phosphate solution using a mixture of water and methanol (1 : 1) as a solvent.

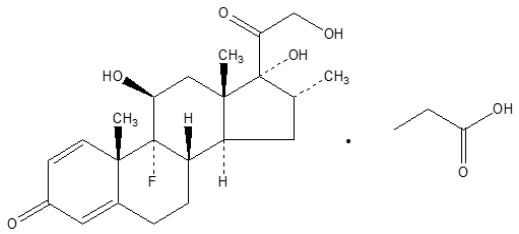
Flow rate: 1.6 mL/min

System suitability

System repeatability: Repeat the test 5 times according to the above conditions with 20 μL of the standard solution each time; the relative standard deviation of the peak area is NMT 1.5%.

Packaging and storage Preserve in light-resistant, hermetic containers.

Dexamethasone Propionate
덱사메타손프로피오네이트



$C_{22}H_{29}FO_5 \cdot C_3H_6O_2$: 466.55

(11β,16α)-9-Fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione propionic acid, [*15423-89-9*]

Dexamethasone Propionate, when dried, contains NLT 96.0% and NMT 104.0% of dexamethasone propionate ($C_{22}H_{29}FO_5 \cdot C_3H_6O_2$) as well as NLT 3.4% and NMT 4.1% of fluorine (F : 18.998).

Description Dexamethasone Propionate occurs as a white, crystalline, odorless powder.
It is freely soluble in dichloromethane, chloroform or acetone, soluble in ethyl acetate or methanol, sparingly soluble in ethanol, and slightly soluble in ether.
It is practically insoluble in water.

Melting point— Between 200 and 206 °C.

Identification (1) Dissolve 0.01 g of Dexamethasone Propionate in methanol to make 100 mL. To 2 mL of this solution, add 5 mL of isoniazid TS, and heat; the solution exhibits a yellow color.

(2) Dissolve 0.01 g of Dexamethasone Propionate in 0.5 mL of methanol, add 1 mL of Fehling's TS, and heat; a reddish brown precipitate is produced.

(3) Decompose 0.01 g of Dexamethasone Propionate according to the Oxygen Flask Combustion by using a mixture of 0.5 mL of 0.1 mol/L sodium hydroxide TS and 20 mL of water as the absorbent, and shake well to mix, and absorb; the resulting solution responds to the Qualitative Analysis 2) for fluoride.

(4) Add 2 mL of potassium hydroxide-ethanol TS to

0.05 g of Dexamethasone Propionate, and heat on a steam bath for 5 minutes. After cooling, add 2 mL of diluted sulfuric acid (2 in 7), and boil still for 1 minute; the odor of ethyl propionate is perceptible.

(5) Determine the absorption spectrum as directed under Ultraviolet-visible spectroscopy using a solution of Dexamethasone Propionate in methanol (3 in 200000); it exhibits a maximum between 236 nm and 240 nm.

Optical rotation $[\alpha]_D^{20}$: Between + 31° and + 37° (after drying, 0.1 g, dioxane, 10 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g of Dexamethasone Propionate in 10 mL of chloroform; the resulting solution is colorless and clear.

(2) ***Heavy metal***—Proceed with 0.7 g of Dexamethasone Propionate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 28 ppm).

(3) ***Arsenic***—Proceed with 0.5 g of Dexamethasone Propionate according to Method 3 and perform the test (NMT 4 ppm).

(4) ***Other steroids***—Weigh accurately 50 mg of Dexamethasone Propionate, dissolve in 25 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. The sum of peak area other than the peak area of Dexamethasone Propionate in the test solution is not larger than the peak area of Dexamethasone Propionate in the standard solution.

Operating conditions

Detector: An ultraviolet -visible spectrometer (wavelength: 254 nm).

Column: A stainless steel column, about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: A mixture of methanol and 0.1% potassium dihydrogen phosphate (13 : 7).

Flow rate: Adjust the flow rate so that the retention time of Dexamethasone Propionate is about 5.5 minutes.

Time span of measurement: About 2 times the retention time of Dexamethasone Propionate after the solvent peak.

Selection of column: Dissolve 0.05 g of Dexamethasone Propionate and 0.01 g of butyl *p*-hydroxybenzoate in 25 mL of methanol, take exactly 2 mL of this solution, and add methanol to make exactly 50 mL. Proceed with 20 μL of this solution under the above operating conditions; butyl *p*-hydroxybenzoate and Dexamethasone Propionate are eluted in this order with the resolution being NLT 3.5.

Detection sensitivity: Adjust the sensitivity so that the peak height of Dexamethasone Propionate obtained from 20 μL of the standard solution is between 20 and 60 mm.

Loss on drying NMT 0.5% (0.5 g, 105 °C, 3 hours).

Residue on ignition NMT 0.2% (0.5 g).

Assay (1) ***Dexamethasone Propionate***—Weigh accurately 25 mg each of Dexamethasone Propionate and previously dried dexamethasone propionate RS, dissolve in 30 mL of methanol, add exactly 10 mL of the internal standard solution, and add methanol to make exactly 50 mL. Use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of peak area of Dexamethasone Propionate, Q_T and Q_S, to that of the internal standard in each solution.

$$\text{Amount (mg) of dexamethasone propionate } (C_{22}H_{29}FO_5 \cdot C_3H_6O_2) = \text{Amount (mg) of dexamethasone propionate RS} \times (Q_T / Q_S)$$

Internal standard solution—A solution of fluorene in methanol (3 in 5000).

Operating conditions

Detector: An ultraviolet-visible spectrometer (wavelength: 254 nm).

Column: A stainless-steel column, about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: A mixture of methanol and 0.1% potassium dihydrogen phosphate (13 : 7).

Flow rate: Adjust the flow rate so that the peak retention time of Dexamethasone Propionate is about 5.5 minutes.

System suitability

System performance: Dissolve 50 mg of Dexamethasone Propionate and 10 mg of butyl *p*-hydroxybenzoate in methanol to make 100 mL. Proceed with 10 μL of this solution under the above operating conditions; butyl *p*-hydroxybenzoate and Dexamethasone Propionate are eluted in this order with the resolution being NLT 3.5.

(2) ***Fluorine***—Weigh accurately about 10 mg of Dexamethasone Propionate, previously dried, proceed according to the Oxygen Flask Combustion by using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as the absorbent to prepare the test solution. Separately, prepare the blank test solution by proceeding in the same manner without using Dexamethasone Propionate. Put the test solution and the blank test solution in a 100-mL volumetric flask, respectively, wash the combustion flask with water, and add washings and water to make 100 mL. Use each resulting solution as

the test solution and the calibration solution, respectively. Perform the test with 8 mL each of the test solution and the calibration solution and 5.0 mL of standard fluorine solution as directed under the 3) fluorine quantification method under the Oxygen Flask Combustion.

Packaging and storage Preserve in tight containers.

Dexamethasone Propionate Cream
덱사메타손프로피오네이트 크림

Dexamethasone Propionate Cream contains NLT 90.0% and NMT 110.0% of equivalent to the labeled amount of dexamethasone propionate ($C_{22}H_{29}FO_5 \cdot C_3H_6O_2$: 466.55).

Method of preparation Prepare as directed under Creams, with Dexamethasone Propionate.

Identification (1) Weigh an amount equivalent to 1 mg of Dexamethasone Propionate according to the labeled amount, add 10 mL of methanol and 25 mL of hexane, shake to mix, and take the methanol layer. To 2 mL of this solution, add 5 mL of isoniazid TS, and heat; the solution exhibits a yellow color.

(2) The retention time of major peak of the test solution and the standard solution for Assay is the same.

Assay Weigh accurately equivalent to about 2 mg of dexamethasone propionate ($C_{22}H_{29}FO_5 \cdot C_3H_6O_2$) according to the labeled amount, add 15 mL of a mixture of methanol and water (3 : 2) and 25 mL of hexane, shake to mix for 10 minutes, and take the separated lower layer. Add 15 mL of the mixture of methanol and water (3 : 2) again to the upper layer, mix by shaking, and take the separated lower layer. Repeat the process twice, add 2 mL of the internal standard solution, add the mixture of methanol and water (3 : 2) to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of dexamethasone propionate RS, add methanol to make 50 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio, Q_T and Q_S, of the peak area of Dexamethasone Propionate to that of the internal standard for the test solution and the standard solution.

$$\text{Amount (mg) of dexamethasone propionate } (C_{22}H_{29}FO_5 \cdot C_3H_6O_2) = \text{Amount (mg) of dexamethasone propionate RS} \times (Q_T / Q_S) \times (1 / 25)$$

Internal standard solution—A solution of diphenyl in methanol (1 in 2500).

Operating conditions

Detector: An ultraviolet-visible spectrometer (wavelength: 254 nm).

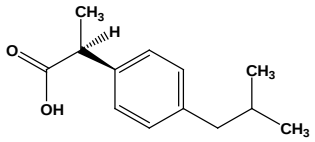
Column: A stainless steel column, about 4.6 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: To 350 mL of 0.01 mol/L potassium dihydrogen phosphate solution, add methanol to make 1.0 L.

Flow rate: Adjust the flow rate so that the retention time of Dexamethasone Propionate is about 5.5 minutes.

Packaging and storage Preserve in tight containers.

Dexibuprofen
덱시부프로펜



(S)-Ibuprofen $C_{13}H_{18}O_2$: 206.28
(+)-α-Methyl-4-(2-methylpropyl)benzeneacetic acid,
[*51146-56-6*]

Dexibuprofen contains NLT 98.5% and NMT 101.0% of dexibuprofen ($C_{13}H_{18}O_2$), calculated on the dried basis.

Description Dexibuprofen occurs as a white crystalline powder.
It is freely soluble in acetone, ether, methanol, or dichloromethane and practically insoluble in water.

Identification (1) Determine the infrared spectra of Dexibuprofen and dexibuprofen RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of major peak of the test solution and the standard solution for Section (i) and (ii) of Purity (3) is same.

Melting point Between 50 and 54 ℃.

Optical rotation $[\alpha]_D^{20}$: Between +55.0° and +60.0° (2.5 g, methanol, 50 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 1.5 g of Dexibuprofen in 15 mL of water. The solution is clear and colorless.

(2) ***Heavy metals***—Proceed with about 1.5 g of Dexibuprofen, add methanol, and dissolve to make 15.0 mL. Pipet 12.0 mL of this solution and perform the test according to the Method 2 under the Heavy Metals. Prepare the control solution with 1.2 mL of lead standard

solution (NMT 10 ppm).

(3) ***Related substances*—**(i) 2-(4-butylphenyl)-propionic acid and other related substances: Weigh accurately about 50 mg, dissolve in 5 mL of methanol, add the mobile phase to make 25 mL, and use this solution as the test solution. Pipet 2.0 mL of the test solution, add the mobile phase to make 200 mL, and use this solution as the standard solution (1). Separately, weigh accurately about 20 mg of dexibuprofen RS, add 2 mL of acetonitrile and dissolve, add 1.0 mL of 0.006% 2-(4-butylphenyl)-propionic acid-acetonitrile and the mobile phase to make 10 mL, and use this solution as the standard solution (2). Perform the test with 20 μL each of the test solution, the standard solution (1) and the standard solution (2) as directed under the Liquid Chromatography according to the following conditions, determine the peak areas from the these solutions, and calculate the content of each related substance according to the following equation; 2-(4-butylphenyl)-propionic acid is NMT 0.3%, other each related substance is NMT 0.3%, and the sum of other related substances is NMT 0.7%. However, ignore the peaks attributed to the solvent on chromatogram from the test solution and the peaks less than 0.1-fold of peak area from the standard solution (1).

$$\text{Content (\%) of 2-(4-butylphenyl)-propionic acid} = \frac{\text{Peak area of 2-(4-butylphenyl)-propionic acid in test solution}}{\text{Peak area of 2-(4-butylphenyl)-propionic acid in standard solution (2)}} \times \frac{\text{Concentration of 2-(4-butylphenyl)-propionic acid in standard solution (2)}}{\text{Concentration of test solution}} \times 100$$

$$\text{Content (\%) of each related substance} = \frac{\text{Peak area of each related substance in test solution}}{\text{Peak area of dexibuprofen in standard solution (1)}} \times \frac{\text{Concentration of standard solution (1)}}{\text{Concentration of test solution}} \times 100$$

Operating conditions

Detector: An ultraviolet-visible spectrometer (wavelength: 214 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and about 20 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Mix 0.5 mL of phosphoric acid, 340 mL of acetonitrile, and 600 mL of water, and add water to make 1000 mL.

Flow rate: 2 mL/minute

(ii) (R)-ibuprofen and (S)-ibuprofen: Weigh accurately about 50 mg of Dexibuprofen, add methanol, dissolve to make 100 mL, filter, and use the filtrate as the test solution. Weigh accurately about 48.5 mg of dexibuprofen RS, add 1 mL of a solution of 0.15% (R,S)-ibuprofen RS in methanol and methanol, dissolve to make 100 mL, filter, and use the filtrate as the standard solution. Perform the test with 20 μL each of the test and standard solutions as directed under the Liquid Chromatography, determine each peak area, and calculate the content of each related substance; (R)-ibuprofen is NMT 1.5% and (S)-ibuprofen is NLT 98.5% for the total peak area from the test solution.

Operating conditions

Detector: An ultraviolet-visible spectrometer (wavelength: 225 nm).

Column: A stainless steel column, about 4 mm in internal diameter and about 10 cm in length, packed with silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Mix 2.9 g of potassium dihydrogen phosphate, 1.6 g of *N*,*N*-dimethyloctylamine, 4 mL of 2-propanol, and 750 mL of water by shaking, and add water to make 1000 mL.

Flow rate: 0.9 mL/minute

$$\text{Content (\%) of (}R\text{)-ibuprofen} = \frac{\text{Peak area of } (R)\text{-ibuprofen in test solution}}{\text{Peak area of } (R)\text{-ibuprofen in test solution} + \text{Peak area of } (S)\text{-ibuprofen}} \times 100$$

$$\text{Content (\%) of (}S\text{)-ibuprofen} = \frac{\text{Peak area of } (S)\text{-ibuprofen in test solution}}{\text{Peak area of } (R)\text{-ibuprofen in test solution} + \text{Peak area of } (S)\text{-ibuprofen}} \times 100$$

(iii) α-Methyl benzenemethanamine and *N*-(1-Phenylethyl)-ibuprofenamide: Weigh accurately about 5 g of Dexibuprofen, dissolve in the diluent to make 2 mL, and use this solution as the test solution. Separately, weigh accurately about 0.15 g each of α-methyl benzenemethanamine RS and *N*-(1-phenylethyl)-Ibuprofenamide RS, add methanol, dissolve to make 250 mL, and use these solutions as the standard solution (1) and the standard solution (2), respectively. Pipet 2.0 mL each of the standard solutions (1) and (2), add the diluent to make 250 mL, and use this solution as the standard solution (3). Pipet 5.0 mL each of the standard solutions (1) and (2), add the diluent make 100 mL, and use this solution as the standard solution (4). Perform the test with 20 μL each of the test solution and the standard solutions (3) and (4) as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of these solutions. Calculate with the standard solutions (3) and (4) based on the calibration curve; the amount of α-benzenemethanamine and *N*-(1-phenylethyl)-ibuprofenamide in the test solution is NMT 100 ppm.

Diluent—Weigh 2.5 g of sodium 1-hexanesulfonate, dissolve in 100 mL of water, and add methanol to make 500 mL.

Operating conditions

Detector: An ultraviolet-visible spectrometer (wavelength: 214 nm).

Column: A stainless steel column, about 4.0 mm in internal diameter and about 25 cm in length, packed with octylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: Adjust the concentration of Solvent A in Solvent B from 10% to 64% for the initial 12 minutes, retain it for 33 minutes, and adjust the concentration of Solvent A in Solvent B from 64% to 10% for the next 15 minutes.

Solvent A: Methanol

Solvent B: Weigh 0.941 g of sodium 1-hexanesulfonate, 7.8 g of sodium dihydrogen phosphate hydrate and 0.3 g of potassium hydrogen sulfate, and add water to make 1000 mL.

Flow rate: 1.5 mL/minute

Loss on drying NMT 0.6% (1 g, in vacuum, phosphorus pentoxide, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.45 g of Dexibuprofen, dissolve in 50 mL of methanol and 0.4 mL of 1% phenolphthalein ethanol, and titrate with 0.1 mol/L sodium hydroxide VS until the color of solution becomes red. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 20.628 mg of $C_{13}H_{18}O_2$

Packaging and storage Preserve in well-closed containers.

Dextran 40
덱스트란 40

[*9004-54-0*]

Dextran 40 is a product of partial decomposition of polysaccharide, which is produced by sucrose fermentation by *Leuconostoc mesenteroides* van Tieghem (*Lactobacillaceae*), and has the average molecular weight of about 40000.

Dextran 40, when dried, contains NLT 98.0% and NMT 102.0% of dextran 70.

Description Dextran 40 occurs as a white, amorphous, odorless and tasteless powder.
It is practically insoluble in ethanol(95) or ether.
It dissolves gradually in water.
It is hygroscopic.

Identification Take 1 mL of the aqueous solution (1 in 3000) of Dextran 40 and add 2 mL of anthrone TS; the solution exhibits a bluish green color, which slowly changes to dark bluish green. Add 1 mL of diluted sulfuric acid (1 in 2) or 1 mL of acetic acid(100); the solution does not change in color.

Optical rotation $[\alpha]_D^{20}$: Between +195° and +203° (0.2 g, water, 10 mL, 100 mm), dissolve by warming on a steam bath, if necessary.

pH Dissolve 1.0 of Dextran 40 in 10 mL of water; the pH of this solution is between 5.0 and 7.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Dextran 40 in 10 mL of water by warming: the solution is clear and colorless.

(2) ***Chloride***—Perform the test with 2.0 g of Dextran 40. Prepare the control solution with 1.0 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.018%).

(3) ***Heavy metal***—Proceed with 2.0 of Dextran 40 according to Method 1 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 5 ppm).

(4) ***Arsenic***—Prepare the test solution with 1.5 g of Dextran 40 according to Method 1 and perform the test (NMT 1.3 ppm).

(5) ***Nitrogen***—Weigh accurately 2 g of Dextran 40, previously dried, and perform the test according to the Nitrogen Determination; the amount of nitrogen (N : 14.007) is NMT 0.010%. The amount of sulfuric acid used for decomposition should be 10 mL and the amount of added sodium hydroxide solution (2 in 5) should be 45 mL.

(6) ***Reducing substances***—Weigh exactly 3.00 g of Dextran 40, previously dried, dissolve in water to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately 0.450 g of glucose, dissolve in water to make exactly 500 mL, and use this solution as the control solution. Pipet 5 mL each of the test solution and control solution, and add water to make exactly 50 mL. Pipet 5 mL each of these solutions, add exactly 5 mL of alkaline copper TS, and heat for 15 minutes on a steam bath. After cooling, add 1 mL of potassium iodine solution (1 in 40) and 1.5 mL of dilute sulfuric acid and titrate with 0.005 mol/L sodium thiosulfate VS (indicator: 2 mL of starch TS): The titrant consumed for the test solution is NLT that for the control solution.

Loss on drying NMT 5.0% (1, 105 °C, 6 hours).

Residue on ignition NMT 0.1% (1 g).

Bacterial endotoxins Less than 2.5 EU per g of dextran 40 when Dextran 40 is used in a sterile preparation.

Antigenicity Dissolve 10.0 g of Dextran 40 in isotonic sodium chloride injection to make 100 mL, sterilize it, and use this solution as the test solution. Inject 1.0 mL of

the test solution at Days 1, 3 and 5 into the peritoneal cavity of each of 4 well-nourished, healthy guinea pigs weighing between 250 g and 300 g. Separately, inject 0.10 mL of horse serum into the peritoneal cavity of each of 4 guinea pigs in another group as a control. Inject 0.2 mL of the test solution intravenously to each of 2 guinea pigs in the test solution group at Day 15 and each of the remaining 2 guinea pigs in the test solution group at Day 22, and inject 0.2 mL of horse serum intravenously in the same manner to each guinea pig in the horse serum group. Observe the signs of respiratory distress, collapse or death of the animals for 30 minutes after each intravenous injection and 24 hours later; animals in the test solution group exhibit no signs mentioned above. All of the 4 animals in the horse serum group exhibit symptoms of respiratory distress or collapse and NLT 3 animals die.

Microbiological examination of non-sterile products When Dextran 40 is used in the manufacturing of injections, the total aerobic microbial count is NMT 1000 CFU, and the total combined yeasts/molds count is NMT 100 CFU per g of Dextran 40. Also, *Escherichia coli*, *Salmonella*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* are not detected.

Viscosity (1) ***Dextran 40***—Weigh accurately about 0.2 to 0.5 g of Dextran 40, previously dried, dissolve in water to make exactly 100 mL, and use this solution as the test solution. Perform the test solution with water as directed in Method 1 under the Viscosity at 25 ℃; the intrinsic viscosity is between 0.16 and 0.19.

(2) ***High-molecular fraction***—Weigh accurately about 6 g of Dextran 40, previously dried, dissolve in water to make exactly 100 mL, and transfer to a flask. Slowly add an enough amount of methanol to obtain 7% to 10% of the precipitate (usually 80 to 90 mL) at 25 ± 1 ℃ with stirring for mixing. Next, dissolve the precipitate at 35 ℃ on a steam bath with occasional shaking and allow it to stand for NLT 15 hours at 25 ± 1 ℃. Discard the clear supernatant at the top by decantation and evaporate the precipitate in the lower layer to dryness on a steam bath. Dry the residue and determine the intrinsic viscosity of the dried substance as directed in (1); the value is NMT 0.27.

(3) ***Low-molecular fraction***—Weigh accurately about 6 g of Dextran 40, previously dried, dissolve in water to make exactly 100 mL and transfer to a flask. Slowly add an enough amount of methanol to obtain 90% to 93% of the precipitate (usually 115 to 135 mL) at 25 ± 1 ℃ with stirring for mixing. Centrifuge at 25 ℃ and evaporate the clear supernatant at the top to dryness on a steam bath. Dry the residue and determine the intrinsic viscosity of the dried substance as directed in (1); the value is NLT 0.09.

Assay Weigh accurately about 3 g of Dextran 40, previously dried, dissolve in water to make exactly 50 mL, and use this solution as the test solution. Determine the optical rotation α_D with the test solution as directed under the Optical Rotation at the layer length of 100 mm at 20 ± 1 ℃.

$$\text{Amount (mg) of dextran 40} = \alpha_D \times 253.8$$

Packaging and storage Preserve in tight containers.

Dextran 40 Injection
덱스트란 40 주사액

Dextran 40 Injection is an aqueous solution for injection, which contains NLT 9.5 w/v% and NMT 10.5 w/v% of dextran 40.

Method of preparation

Dextran 40	10 g
Isotonic Sodium Chloride Injection	A sufficient quantity
Total volume	100 mL

Prepare as directed under Injections, with the above.
No preservative is added.

Description Dextran 40 Injection occurs as a clear and colorless liquid, and is slightly viscous.

Identification (1) Add water to 1 mL of Dextran 40 Injection to make 200 mL. To 1 mL of this solution, add 2 mL of anthrone TS; the solution exhibits a bluish green color which gradually changes to dark bluish green. To this solution, add 1 mL of diluted sulfuric acid (1 in 2) or 1 mL of acetic acid(100); the solution does not change in color.

(2) Dextran 40 Injection responds to the Qualitative Analysis for sodium salt and chloride.

pH Between 4.5 and 7.0.

Purity (1) ***5-Hydroxymethylfururals***—Take Dextran 40 Injection in the amount equivalent to 1.0 g of Dextran 40 according to the labeled amount, and add water to make exactly 500 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at a wavelength of 284 nm is NMT 0.25.

(2) ***Heavy metal***—Proceed with 2.0 g of Dextran 40 Injection according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 5 ppm).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.50 EU per mL of Dextran 40 Injection.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Viscosity Take 2 mL to 5 mL of Dextran 40 Injection, add isotonic sodium chloride injection to make exactly 100 mL, and use this solution as the test solution. Perform the test with the test solution and isotonic sodium chloride injection according to Method 1 under the Viscosity at 25 ℃; the intrinsic viscosity is between 0.16 and 0.19. Calculate the concentration (g/100 mL) of the test solution as directed under the Assay.

Assay Take exactly 30 mL of Dextran 40 Injection, add water to make exactly 50 mL, and use this solution as the test solution. Determine the optical rotation α_D with the test solution as directed under the Optical Rotation at the layer length of 100 mm at 20 ± 1 ℃.

Amount (mg) of dextran 40 in 100 mL of Dextran 40 Injection
$= \alpha_D \times 846.0$

Packaging and storage Preserve in hermetic containers. Plastic containers for aqueous injections may be used. Avoid storage in a place under a highly variable temperature.

Dextran 70
덱스트란 70

[*9004-54-0*]

Dextran 70 is a product of partial decomposition of polysaccharide, which is produced by sucrose fermentation by *Leuconostoc mesenteroides* van Tieghem (*Lactobacillaceae*), and has the average molecular weight of about 70000.

Dextran 70, when dried, contains NLT 98.0% and NMT 102.0% of dextran 70.

Description Dextran 70 occurs as a white, amorphous, odorless and tasteless powder.
It is practically insoluble in ethanol(95) or ether.
It dissolves gradually in water.
It is hygroscopic.

Identification Perform the test according to the Identification of Dextran 40.

Optical rotation $[\alpha]_D^{20}$: Between +195° and +203° (0.2 g, water, 10 mL, 100 mm), dissolve by warming on a steam bath, if necessary.

pH Dissolve 3.0 of Dextran 70 in 50 mL of water; the pH of this solution is between 5.0 and 7.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Dextran 70 in 10 mL of water with warming; the solution is clear and colorless.

(2) ***Chloride***—Perform the test with 2.0 g of Dextran 70. Prepare the control solution with 1.0 mL of 0.01 mol/L hydrochloric acid (NMT 0.018%)

(3) ***Heavy metal***—Proceed with 2.0 of Dextran 70 according to Method 1 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 5 ppm).

(4) ***Arsenic***—Prepare the test solution with 1.5 g of Dextran 70 according to Method 1 and perform the test (NMT 1.3 ppm).

(5) ***Nitrogen***—Weigh accurately 2 g of Dextran 70, previously dried, and perform the test according to the Nitrogen Determination; the amount of nitrogen (N : 14.007) is NMT 0.010%. The amount of sulfuric acid used for decomposition should be 10 mL and the amount of added sodium hydroxide solution (2 in 5) should be 45 mL.

(6) ***Reducing substances***—Weigh exactly 3.00 g of Dextran 70, previously dried, dissolve in water to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately 0.300 g of glucose, previously dried, dissolve in water to make exactly 500 mL, and use this solution as the control solution. Pipet 5 mL each of the test solution and control solution, and add water to make exactly 50 mL. Pipet 5 mL each of these solutions, add exactly 5 mL of alkaline copper TS, and heat for 15 minutes on a steam bath. After cooling, add 1 mL of potassium iodine solution (1 in 40) and 1.5 mL of dilute sulfuric acid and titrate with 0.005 mol/L sodium thiosulfate VS (indicator: 2 mL of starch TS): The titrant consumed for the test solution is NLT that for the control solution.

Loss on drying NMT 5.0% (1, 105 ℃, 6 hours).

Residue on ignition NMT 0.1% (1 g).

Bacterial endotoxins Less than 0.5 EU per mL of a solution prepared by diluting Dextran 70 with isotonic Sodium Chloride Injection to 6 w/v% when Dextran 70 is used in a sterile preparation.

Antigenicity Dissolve 6.0 g of Dextran 70 in isotonic sodium chloride injection to make 100 mL, sterilize, and use this solution as the test solution. Perform the test with the test solution according to the Antigenicity of Dextran 40.

Microbiological examination of non-sterile products When Dextran 70 is used in the manufacturing of injections, the total aerobic microbial count is NMT 1000 CFU, and the total combined yeasts/molds count is NMT

100 CFU per g of Dextran 70. Also, *Escherichia coli*, *Salmonella*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* are not detected.

Viscosity (1) ***Dextran 70***—Weigh accurately about 0.2 to 0.5 g of Dextran 70, previously dried, dissolve in water to make exactly 100 mL, and use this solution as the test solution. Perform the test with the test solution and water as directed in Method 1 under the Viscosity at 25 ℃; the intrinsic viscosity is between 0.21 and 0.26.

(2) ***High-molecular fraction***—Weigh accurately about 6 g of Dextran 70, previously dried, dissolve in water to make exactly 100 mL, and transfer to a flask. Slowly add an enough amount of methanol to obtain 7% to 10% of the precipitate (usually 75 to 85 mL) at 25 ± 1 ℃ with stirring for mixing. Next, dissolve the precipitate at 35 ℃ on a steam bath with occasional shaking and allow it to stand for NLT 15 hours at 25 ± 1 ℃. Discard the clear supernatant at the top by decantation and evaporate the precipitate in the lower layer to dryness on a steam bath. Dry the residue and determine the intrinsic viscosity of the dried substance as directed in (1); the value is NMT 0.35.

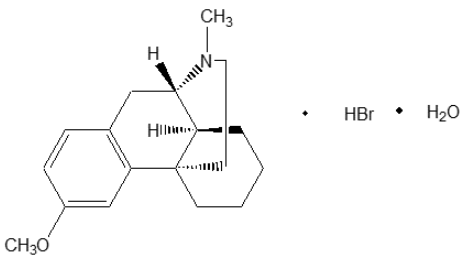
(3) ***Low-molecular fraction***—Weigh accurately about 6 g of Dextran 70, previously dried, dissolve in water to make exactly 100 mL and transfer to a flask. Slowly add an enough amount of methanol to obtain 90% to 93% of the precipitate (usually 110 to 130 mL) at 25 ± 1 ℃ with stirring for mixing. Centrifuge at 25 ℃ and evaporate the clear supernatant at the top to dryness on a steam bath. Dry the residue and determine the intrinsic viscosity of the dried substance as directed in (1); the value is NLT 0.10.

Assay Weigh accurately about 3 g of Dextran 70, previously dried, dissolve in water to make exactly 50 mL, and use this solution as the test solution. Determine the optical rotation α_D with the test solution as directed under the Optical Rotation at the layer length of 100 mm at 25 ± 1 ℃.

$$\text{Amount (mg) of dextran 70} = \alpha_D \times 253.8$$

Packaging and storage Preserve in tight containers.

Dextromethorphan Hydrobromide Hydrate
덱스트로메토르판브롬화수소산염수화물



Dextromethorphan Hydrobromide
$C_{18}H_{25}NO \cdot HBr \cdot H2O$: 370.32
[*6700-34-1*]

Dextromethorphan Hydrobromide Hydrate contains NLT 98.0% and NMT 101.0% of dextromethorphan hydrobromide ($C_{18}H_{25}NO \cdot HBr$: 352.31), calculated on the anhydrous basis.

Description Dextromethorphan Hydrobromide Hydrate occurs as white crystals or a crystalline powder.
It is very soluble in methanol, freely soluble in ethanol(95) or acetic acid(100), sparingly soluble in water, and practically insoluble in ether.

Melting point—About 126 ℃ (Insert the capillary tube into the bath at 116 ℃ and continue heating so that the temperature rise by approximately 3°C per minute).

Identification (1) Determine the absorption spectra of solutions of Dextromethorphan Hydrobromide Hydrate and dextromethorphan hydrobromide hydrate RS (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelength.

(2) Determine the infrared spectra of Dextromethorphan Hydrobromide Hydrate and dextromethorphan hydrobromide hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

(3) Take 50 mL of a solution of Dextromethorphan Hydrobromide Hydrate (1 in 100), add 2 drops of phenolphthalein TS and then sodium hydroxide TS until a red color appears. After adding 50 mL of chloroform and shake to mix, take 40 mL of the water layer and add 5 mL of dilute nitric acid; the solution responds to the Qualitative Analysis for bromide.

Optical rotation $[\alpha]_D^{20}$: Between +26° and +30° (0.34 g, calculated on the anhydrous basis, water, 20 mL, 100 mm).

pH Dissolve 1.0 g of Dextromethorphan Hydrobromide Hydrate in 100 mL of water; the pH of this solution is between 5.2 and 6.5.

Purity (1) ***Clarity and color of solution***—Dissolve 0.20 g of Dextromethorphan Hydrobromide Hydrate in 20 mL of water; the solution is clear and colorless.

(2) ***Dimethylaniline***—To 0.50 g of Dextromethorphan Hydrobromide Hydrate, add 20 mL of water, and dissolve by heating on a steam bath. After cooling, add 2 mL of dilute acetic acid, 1 mL of sodium nitrite TS and water to make 25 mL; the color of the solution is not more intense than that of the following control solution.

Control solution—Dissolve 0.10 g of dimethylaniline in 400 mL of water by warming in the water bath, cool down, and add water to make 500 mL. Pipet 5 mL of

this solution and add water to make 200 mL. To 1.0 mL of this solution, add 2 mL of dilute acetic acid, 1 mL of sodium nitrite TS, and water to make 25 mL.

(3) ***Heavy metal***—Proceed with 1.0 g of Dextromethorphan Hydrobromide Hydrate and perform the test according to the Method 4. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Phenolic compounds***—Dissolve 5 mg of Dextromethorphan Hydrobromide Hydrate in 1 drop of dilute hydrochloric acid and 1 mL of water, add 2 drops of iron(III) chloride TS and 2 drops of potassium hexacyanoferrate(III) TS, shake to mix, and allow to stand for 15 minutes; no bluish green color is observed.

(5) ***Related substances***—Dissolve 0.25 g of Dextromethorphan Hydrobromide Hydrate in exactly 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of toluene, methanol, dichloromethane and 13.5 mol/L ammonia TS (55 : 20 : 13 : 10 : 2) to a distance of about 15 cm, and air-dry the plate. Spray bismuth potassium iodide TS evenly and then spray hydrogen peroxide TS evenly on the plate; spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Water Between 4.0% and 5.5% (0.2 g, volumetric titration, reverse titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Dextromethorphan Hydrobromide Hydrate, dissolve in 10 mL of acetic acid(100), add 40 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 35.231 mg of $C_{18}H_{25}NO \cdot HBr$

Packaging and storage Preserve in well-closed containers.

Dextrose, Sodium Chloride and Sodium Lactate Injection
포도당·염화나트륨·락트산나트륨 주사액

Dextrose, Sodium Chloride and Sodium Lactate Injection contains NLT 90.0% and NMT 110.0% of the labeled amounts of glucose ($C_6H_{12}O_6$: 180.16), sodium chloride (NaCl : 58.44) and sodium lactate ($C_3H_5NaO_3$: 112.06).

Method of preparation Prepare as directed under Injections, with Glucose, Sodium Chloride and Sodium Lactate.

Identification (1) Evaporate Dextrose, Sodium Chloride and Sodium Lactate Injection to concentration to about 1/2 the volume on a steam bath; 5 mL of the solution responds to the Qualitative Analysis for sodium salt, chloride and lactate.

(2) Dissolve an amount of Dextrose, Sodium Chloride and Sodium Lactate Injection equivalent to about 0.1 g of glucose and add 10 mL of hot Fehling's TS; a red precipitate is formed.

pH Between 4.0 and 6.0.

Sterility Meets the requirements.

Pyrogen Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay (1) ***Glucose*—**Pipet an amount of Dextrose, Sodium Chloride and Sodium Lactate Injection equivalent to about 2.5 g of glucose ($C_6H_{12}O_6$) and perform the test as directed under the Korean Pharmacopoeia (KP) for Glucose Injections.

(2) ***Sodium chloride*—**Pipet an amount of Dextrose, Sodium Chloride and Sodium Lactate Injection equivalent to about 0.1 g of sodium chloride (NaCl), add 30 ml of water and 25 mL of 0.1 mol/L silver nitrate, then add 3 mL of nitric acid and 5 mL of nitrobenzene and titrate with 0.1 mol/L ammonium thiocyanate VS. (Indicator: ammonium iron(III) sulfate TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L silver nitrate
= 5.844 mg of NaCl

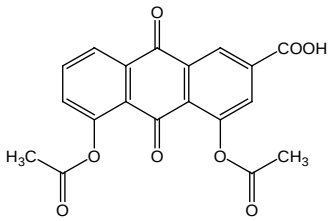
(3) ***Sodium lactate*—**Pipet an amount of Dextrose, Sodium Chloride and Sodium Lactate Injection equivalent to about 0.2 g of sodium lactate ($C_3H_5NaO_3$), evaporate to dryness on a steam bath, slowly ignite and carbonize the residue. Wet the residue with 25 mL of water, add 25.0 mL of 0.05 mol/L sulfuric acid, and heat for 30 minutes on a steam bath, stirring thoroughly with a glass rod. Wash the resulting solution with hot water until the filtrate is neutral, filter, collect the filtrate and washings, then add excess sulfuric acid and titrate with 0.1 mol/L sodium hydroxide VS (indicator: methyl orange TS).

Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L sulfuric acid
= 11.206 mg of $C_3H_5NaO_3$

Packaging and storage Preserve in hermetic containers.

Diacerein
디아세레인



$C_{19}H_{12}O_8$: 368.29

4,5-Bis(acetyloxy)-9,10-dihydro-9,10-dioxo-2-anthracenecarboxylic acid; 9,10-Dihydro-4,5-dihydroxy-9,10-dioxo-2-anthroic acid diacetate, [*13739-02-1*]

Diacerein contains NMT 96.0% and NLT 101.0% of diacerein ($C_{19}H_{12}O_8$), calculated on the anhydrous basis.

Description Diacerein occurs as a yellow crystalline powder and is almost odorless.
It is freely soluble in acetic acid, ethanol or acetone.
It is soluble in a dilute alkaline solution.

Melting point—Between 242 and 248 ℃ (with decomposition).

Identification (1) Dissolve Diacerein in 0.5 mol/L sodium hydroxide; the resulting solution exhibits a dark red color.

(2) Weigh 10 mg of Diacerein, dissolve in 100 mL of *N*,*N*-dimethylacetamide, and use this solution as the test solution. Separately, weigh 10 mg of diacerein RS, dissolve in 100 mL of *N*,*N*-dimethylacetamide, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate of silica gel for thin-layer chromatography (with a fluorescent indicator). Develop the plate with a mixture of n-Propanol, ethyl acetate and water (30 : 15 : 1) to a distance of about 17cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

(3) Determine the absorption spectrum of Diacerein in ethanol (1 in 100,000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at about 217 nm, 255 nm and 340 nm.

(4) Determine the absorption spectra of Diacerein and diacerein RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity ***Free rhein***—Weigh accurately about 0.2g of Diacerein, dissolve in *N*,*N*--Dimethylacetamide to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately 25 mg of the rhein RS, dissolve in *N*,*N*-Dimethylacetamide to make 50 mL. Pipet 1.0 mL of this solution, add the mobile phase to make 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography under the Assay, and determine the peak areas (or heights) A_T and A_S of diacerein; the amount of free rhein is NMT 2.0% of the labeled amount of diacerein.

$$\text{Amount (mg) of rhein } (C_{15}H_8O_6) = \text{Amount (mg) of diacerein RS} \times \frac{A_T}{A_S} \times \frac{1}{50}$$

Loss on drying NMT 2.0% (0.3 g, 60 ℃, in vacuum, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg of Diacerein, dissolve in *N*,*N*-Dimethylacetamide to make 50 mL, and use this solution as the test solution. Separately, weigh accurately 50 mg of diacerein RS, dissolve in *N*,*N*-Dimethylacetamid to make 50 mL, and use this solution as the standard solution. Proceed with 20 μL each of the test solution and the standard solution, and perform the test as directed under the Liquid Chromatography to determine the peak areas (or heights) A_T and A_S, of diacerein in these solutions.

$$\text{Amount (mg) of diacerein } (C_{19}H_{12}O_8) = \text{Amount (mg) of diacerein RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 272 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Mobile phase: A mixture of buffer solution and acetonitrile (55 : 45).

Buffer solution—Mix 19.6 mL of 0.1 mol/L citric acid and 0.4 mL of 0.2 mol/L dibasic sodium phosphate.

Packaging and storage Preserve in well-closed containers.

Diacerein Capsules
디아세레인 캡슐

Diacerein Capsules contain NLT 90.0% and NMT 110.0% the labeled amount of diacerein ($C_{19}H_{12}O_8$: 368.29).

Method of preparation Prepare as directed under Capsules, with Diacerein.

Identification (1) Weigh an amount of the contents of Diacerein Capsules equivalent to 50 mg of diacerein, dissolve in *N*,*N*-dimethylacetamide to make 50 mL, filter, and use the filtrate as the test solution. Separately, weigh 25 mg of diacerein RS, add *N*,*N*-Dimethylacetamide to make 25 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography, develop the plate with a mixture of n-propanol, ethyl acetate and water (30 : 15 : 1) (as the developing solvent) to a distance of about 17cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots obtained from the test solution exhibits R_f values and the colors corresponding to that of the standard solution.

(2) The retention times of the major peaks from the test solution corresponding to those of the standard solution, as obtained in the Assay.

Purity ***Free rhein***—Weigh accurately the contents of NLT 20 capsules of Diacerein Capsules. Weigh accurately an amount equivalent to about 0.2 g of diacerein ($C_{19}H_{12}O_8$), add *N*,*N*-dimethylacetamide, dissolve to make 50 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 25 mg of rhein RS, dissolve in *N*,*N*-dimethylacetamide to make 50 mL. Take 1.0 mL of this solution, add the mobile phase to make 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the condition under the Assay, and determine the peak areas (or heights) A_T and A_S of each rhein; the amount of free rhein is NMT 2.0% of the labeled amount of diacerein.

$$\text{Amount (mg) of rhein } (C_{15}H_8O_6) = \text{Amount (mg) of rhein RS} \times \frac{A_T}{A_S} \times \frac{1}{50}$$

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the content of NLT 20 capsules of Diacerein Capsules. Weigh accurately an amount equivalent to about 50 mg diacerein ($C_{19}H_{12}O_8$), add *N*,*N*-dimethylacetamide, dissolve to make 50 mL, and filter. Take 2.0 mL of the filtrate, add the mobile phase to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of diacerein RS, proceed in the same manner as in the test solution, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following condition, and determine the peak heights (or areas) A_T and A_S, of diacerein in each solution.

$$\text{Amount (mg) of diacerein } (C_{19}H_{12}O_8) = \text{Amount (mg) of diacerein RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 272 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Mobile phase: A mixture of buffer solution and acetonitrile (55 : 45).

Buffer solution—Mix 19.6 mL of 0.1 mol/L citric acid TS and 0.4 mL of 0.2 mol/L dibasic sodium phosphate.

Packaging and storage Preserve in well-closed containers.

Diastase
디아스타제

Diastase is an enzyme mainly prepared from malt and has an amylolytic activity. Diastase contains NLT 440 starch saccharifying activity units per g. Diastase is typically diluted with suitable diluents.

Description Diastase occurs as a pale yellow to pale brown powder.
It is hygroscopic.

Purity ***Rancidity*—**Diastase has no unpleasant or rancid odor and has no unpleasant or rancid taste.

Loss on drying NMT 4.0% (1 g, 105 ℃, 5 hours).

Assay (1) ***Substrate solution***—Use potato starch solution TS for starch digestion activity.

(2) ***Test solution***—Weigh accurately about 0.1 g of Diastase and dissolve in water to make exactly 100 mL.

(3) ***Procedure***—Proceed as directed in (A) Measurement of starch saccharifying activity of (1)

starch digestibility test under the Digestive Power.

Packaging and storage Preserve in tight containers at below 30℃.

Diastase·Protease
디아스타제·프로테아제

Diastase·protease is a complex enzyme prepared from *Aspergillus oryzae* or *Bacillus subtilis*, and has starch digestive activity and protein digestive activity. Diastase·protease contains NLT 90.0% of digestive activity units of the labeled amount.

Description Diastase·protease occurs as a white to yellowish white powder and has a characteristic odor.

Identification Perform the test as directed under the Assay; it exhibits a positive response.

Loss on drying NMT 7.0% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 30.0% (1.0 g).

Assay (1) ***Starch saccharifying activity***—(i) Test solution: Dissolve Diastase·protease in 0.1% sodium chloride solution, adjust to contain 0.4 to 0.8 starch saccharifying activity unit/mL, and use this solution as the test solution.

(ii) Substrate solution: Weigh accurately about 1 g of potato starch in advance, dry at 105 °C for 2 hours, and then measure the loss in weight. Weigh accurately the potato starch, equivalent to about 2.0 g of the dried, dissolve in 20 mL of water, transfer to 30 mL of boiling water, and gelatinize it for NLT 5 minutes. After cooling, add 10 mL of pH 5.6 Mcllvaine buffer solution and water to make exactly 100 mL. Prepare before use.

(iii) Procedure: Proceed as directed under (A) Measurement of starch saccharifying activity of (1) Assay for starch digestion activity under the Digestive Power.

(2) ***Protein digestive activity***—(i) Test solution: Dissolve Diastase·protease in 0.1% sodium chloride solution, adjust to contain 15 to 25 protein digestive activity units/mL, and use this solution as the test solution.

(ii) Substrate solution: Use the substrate solution 2 of the Assay for protein digestive activity under the Digestive Power. However, adjust the pH to 7.2.

(iii) Procedure: Proceed as directed under the Assay for protein digestive activity under the Digestive Power. However, use trichloroacetic acid TS A as the precipitation reagent.

Packaging and storage Preserve in light-resistant, tight containers.

Diastase·Protease 100
디아스타제·프로테아제100

Diastase·protease 100 is a digestive enzyme obtained from culture of *Bacillus subtilis* and mixed a diluent. It contains NLT 100,000 unit of α-amylase, NLT 12000 unit of β-amylase, and NLT 100,000 unit of protease per g.

Description Diastase·protease 100 occurs as a white to yellowish white powder.

Identification Diastase·protease 100 shows positive when tested as directed under the Assay of α-amylase, β-amylase, and protease.

Loss on drying NMT 7.0% (2 g, 105 °C, constant mass).

Residue on ignition NMT 30.0% (2 g).

Assay (1) ***α-amylase***—Weigh accurately about 0.5 g of Diastase·protease 100, add 0.1% sodium chloride, dilute so that the concentration becomes NLT 40000 and NMT 80000 times, and use this solution as the test solution. Add 3 mL of Mcilvaine buffer (pH 5.6) and 1 mL of 0.1% calcium chloride of to 5 mL of 1% soluble starch solution, allow it to stand at 37 ℃ for 5 minutes, add 1 mL of the test solution, and mix well by shaking. Allow the solution to stand at 37 ℃ for 30 minutes, take 0.2 mL of the solution, and add to 10 mL of iodine solution. Use this solution as the control and perform the test as directed under the Ultraviolet-visible Spectroscopy. The absorbance at wavelength 660 nm is A_1 and when operated with water instead of the test solution, the absorbance is A_{ST}. Heat the solution at 100 ℃ for 30 minutes and when the test solution that lost activation is operated according to the above, the absorbance is A_0. Calculate as mg of starch digested according to the following formula.

$$\text{mg of digested starch} = \frac{A_0 - A_1}{A_{ST}} \times 50 \times \text{dilution factor}$$

Definition of potency: Set the unit as 1 when 10 mg of starch is digested according to the above conditions for 30 minutes.

(2) ***β-amylase***—Weigh accurately about 1.0 g of Diastase·protease 100, add 0.1% sodium chloride, dilute so that the concentration becomes 30000 times, and use this solution as the test solution. Transfer 10 mL of 2% soluble starch solution to a 100-mL Erlenmeyer flask, previously warmed at 40 ℃ on a thermostat, add 1.0 mL of the test solution, allow to stand at 40 ℃ for 30 minutes, and add 2 mL of Fehling's alkaline tartaric acid TS to stop the enzyme action. Add 2 mL of Fehling's copper TS and boil on fire for 2 minutes. After cooling with running water, add 2 mL of 30% potassium iodide

and 2 mL of 25% sulfuric acid, and titrate the liberated iodine with 0.05 mol/L sodium thiosulfate. Separately, add water instead of the test solution, operate according to the above, perform a blank test and make any necessary correction. Determine the mg of the produced reducing sugar.

mg of the produced reducing sugar
= 1.6200 (Blank the test solution measurement - Test solution measurement)

Definition of potency: Set the activation as 1 when 10 mg of glucose is created according to the above conditions.

(3) ***Protease***—Weigh accurately about 0.5 g of Diastase·protease 100, add 0.1% sodium chloride, dilute so that the concentration becomes NLT 5000 and NMT 10000 times, and use this solution as the test solution. Transfer 1mL of 0.6% casein solution in a test tube, previously warmed at 37 ℃ on a warm bath, add 1.0 mL of the test solution, and mix well by shaking. Add in a warm water bath at 37 ℃, operate for exactly 10 minutes, add 2 mL of 0.4 mol/L trichloroacetic acid, allow it to stand at 37 ℃ for 20 minutes, and filter. Transfer 1.0 mL of the filtrate in a test tube, add 5 mL of 0.4 mol/L sodium carbonate and 1 mL of Folin's TS (1 in 3), and mix well by shaking. Allow it to stand at 37 ℃ for 20 minutes and perform the test as directed under the Ultraviolet-visible Spectroscopy with the colored solution and water as the control. Determine the absorbance A at the wavelength 660 nm. Separately transfer 1.0 mL of the test solution into a test tube, add 2 mL of 0.4 mol/L trichloroacetic acid, add 1 mL of 0.6% casein solution, and filter after 10 minutes. Operate in the same manner with 1 mL of the filtrate and determine the absorbance A_0. Separately, add 50 mg of tyrosine RS in 0.02 mol/L hydrochloric acid to make 100 mL, pipet 10.0 mL of this solution, add 0.02 mol/L hydrochloric acid to make 100 mL, and use this solution as the standard solution. To 1.0 mL of this standard solution, color like the test solution, perform the test as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance A_S.

$$\text{Potency (unit)} = \frac{A-A_0}{A_S} \times 50 \times \frac{1}{10} \times \text{dilution factor}$$

Definition of potency: Set the unit as 1 for potency creating non-protein material that responds to 1 μg of tyrosine in the above condition.

Packaging and storage Preserve in tight containers

Diastase·Protease 500
디아스타제·프로테아제500

Diastase·protease 500 concentrated and dried *Bacillus subtilis* (hay bacillus) in amylum maydi and soya bean meal and performed concentration drying. Diastase·protease 500 contains 5000 unit of *α*-amylase, 6000 unit of *β*-amylase, and NLT 16000 unit of protease per g.

Description Diastase·protease 500 occurs as a white to yellowish white fine powder.

Identification Diastase·protease 500 shows a positive reaction when tested as directed under the Assay of α-amylase, β-amylase, and protease.

Loss on drying NMT 7.0% (1 g, 105 °C, 1 hours).

Residue on ignition NMT 2.0%.

Assay (1) α-amylase Weigh accurately about 0.5 g of Diastase·protease 500, dissolve in 50 mL of sodium chloride, mix by shaking, and filter with 100 mL of 0.1 mol/L sodium chloride. Pipet 0.6 mL of the filtrate and add 0.1 mol/L sodium chloride to make 100 mL, and use this solution as the test solution. Separately, to 5 mL of 1% soluble starch solution, add 3 mL of McIlvaine buffer solution, pH 5.6, and 1 mL of 0.1% calcium chloride, warm at 37 ℃, and add 1 mL of the test solution. Mix well by shaking and allow it to stand at 37 ℃ for 30 minutes. Add 10 mL of iodine solution to 0.2 mL of this solution, perform the test as directed under the Ultraviolet-visible Spectroscopy using the color solution and water as the control. Determine the absorbance A_1 at the wavelength 660 nm. Separately, perform the test as directed under the Ultraviolet-visible Spectroscopy in the same manner with water, instead of the test solution, and determine the absorbance A_{ST}. Heat the test solution at 100 ℃ for 30 minutes and determine the absorbance A_0 with the test solution that lost activation.

$$\text{Potency of α-amylase} = \frac{A_0-A_1}{A_{ST}} \times 50 \times \text{dilution factor} \times \frac{1}{10}$$

Definition of potency: Set the unit as 1 when 10 mg of starch is decomposed according to the above conditions for 30 minutes.

(2) ***β-amylase***—Weigh accurately Diastase·protease 500 equivalent to about 0.1 g, add 80 mL of 0.1% sodium chloride, mix by shaking, add 100 mL of 0.1% sodium chloride solution, and filter. Take 15.0 mL of this filtrate and add 0.1% sodium chloride to make 100 mL and use this solution as the test solution. Separately, transfer 10 mL of 2% soluble starch solution to a 100-mL Erlenmeyer flask, previously warmed at 40 ℃ on a thermostat, add 1.0 mL of the test solution, allow it to stand at 40 ℃ for 30 minutes, and add 2 mL of Fehling's alkaline tartaric acid TS to stop the enzyme action. Add 2 mL of Fehling's copper TS and boil on fire for 2 minutes. After cooling with running water, add 2 mL of 30% potassium

iodide and 2 mL of sulfuric acid, and titrate the liberated iodine with 0.05 mol/L sodium thiosulfate VS. Separately, add 10 mL of water instead of enzyme liquid, operate in the same manner according to the above conditions, perform a blank test, and make any necessary correction. Determine the mg of the produced reducing sugar.

$$\text{mg of the produced reducing sugar} = 1.6 \times (\text{Measured value of the blank test solution} - \text{Measured value of the test solution})$$

$$\text{}\textit{B-amylase}\text{-amylase potency} = \frac{\text{Produced reducing sugar (mg)}}{10} \times \text{dilution factor}$$

Definition of potency: Set the activation as 1 when 10 mg of glucose is created according to the above conditions.

(3) ***Protease***—Weigh accurately about 0.1 g of Diastase·protease 500, add 80 mL of 0.1% sodium chloride, mix by shaking, add 100 mL of 0.1% sodium chloride solution, and filter. Take 25.0 mL of this filtrate and add 0.1% sodium chloride to make 100 mL and use this solution as the test solution. Separately, put 1 mL of 0.6% casein solution in a test tube, previously warmed at 37 ℃ warm bath, add 1.0 mL of the test solution, and shake well to mix. Add in a warm water bath at 37 ℃, operate it for exactly 10 minutes, add 2.0 mL of 0.4 mol/L trichloroacetic acid, allow it to stand at 37 ℃ for 25 minutes, and filter. Transfer 1.0 mL of the filtrate in a test tube, add 5 mL of 0.4 mol/L sodium carbonate and 1 mL of Folin's TS (1 in 3), and shake well to mix. Allow it to stand at 37 ℃ for 20 minutes and perform the test as directed under the Ultraviolet-visible Spectroscopy with the colored solution and water as the control solution. Determine the absorbance *A*at the wavelength 660 nm. Separately, put 1.0 mL of the test solution in a test tube, add 2.0 mL of 0.4 mol/L trichloroacetic acid solution, mix, add 1 mL of 0.6% casein solution, and filter after 10 minutes. Pipet 1 mL of the filtrate, perform the test in the same manner as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance A_0. Separately, make tyrosine RS with 50 μg per mL. Pipet 1.0 mL of this solution, color like the test solution, perform the test as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance A_S.

$$\text{Potency (unit) of protease} = \frac{A-A_0}{A_S} \times 50 \times \frac{1}{10} \times \text{dilution factor}$$

Definition of potency: Set the unit as 1 for potency creating non-protein Folin TS color material that respond to 1 μg of tyrosine for 1 minute.

Packaging and storage Preserve in light-resistant, tight containers.

Diastase·Protease N_1
디아스타제·프로테아제N_1

Perform the test with Diastase·protease N as directed under the Digestive Power; Diastase·protease N contains NLT 7000 unit and NMT 8800 unit per g for starch saccharifying activity and NLT 32300 unit and NMT 43700 unit per g for protein digestion activity.

Description Diastase·protease N occurs as a pale yellow to yellowish brown powder and has a unique odor.
It is hydroscopic.

Identification (1) Put 1 g of potato starch into two 200-mL glass stoppered Erlenmeyer flask (A and B), respectively, add 5 mL of 40 ℃ water to disperse, and add 15 mL of hot water slowly while shaking to compound. Put a funnel into the opening of flask, heat on a steam bath for 30 minutes, cool to 37 ± 1 ℃, and add 1 mL of acetic acid-sodium acetate buffer solution, pH 5.0. Separately, add 8 mL of acetic acid-sodium acetate buffer solution, pH 5.0 and 4 mL of dilute acetic acid to 1.0 g of Diastase·protease N, shake well occasionally to mix for 10 minutes, allow it to stand, and filter. Put 1 mL of the filtrate into the flask A above, shake intensely to mix for 1 minute, allow it to stand at 37 ± 1 ℃ for 1 hour, and add 2 mL of sodium hydroxide (1 in 10). Put 2 mL of sodium hydroxide (1 in 10) into flask B, shake to mix for 30 minutes, add 1 mL of the above filtrate, shake intensely to mix for 1 minute, and allow it to stand at 37 ± 1 ℃ for 1 hour; the content of flask A exhibits the state of the aqueous solution, but the content of flask B stays in full state. (starch dextrinizing activity).

(2) Add 150 mL of warm water and 1 mL of 3,6-Dinitrophthalic acid-pyridine (1 : 1) to flask A and B in (1), respectively, stopper the flasks, shake well to mix, and heat on a steam bath for 3 minutes; the content of flask A exhibits a red color, but the content of flask B does not exhibit color reactions (starch saccharifying activity).

(3) Add water to 1 mL of casein solution prepared in the protein digestion activity under the Digestive Power to make 10 mL, add 5 mL of this solution in a test tube, and allow it to stand at 37 ± 1 ℃ for 10 minutes. Add 50 mL of 0.1 mol/L phosphate buffer solution, pH 6.0 to 1 g of Diastase·protease N, adjust the pH to 6.0, add 0.1 mol/L phosphate buffer solution, pH 6.0 to make 100 mL, filter, and add 2 mL of the filtrate. Shake well to mix for 15 seconds, allow it to stand at 37 ± 1 ℃ for 1 hour, and add 5 mL of 7.2% trichloroacetate solution; the resulting solution does not become turbid at all (protein digestion activity).

Purity ***Spoilage***—Diastase·protease N does not have a spoiled odor.

Loss on drying NMT 10.0% (1 g, 105 °C, 3 hours).

Digestive power (1) ***Starch saccharifying activity***—Weigh accurately about 0.3 g of Diastase·protease N, and dissolve in water to make 200.0 mL. Pipet 5.0 mL of this solution, add water to make 100.0 mL, and use this solution as the test solution.

Allow 10 mL of potato starch solution, 1% to stand at exactly 37 ± 0.5 ℃ for 10 minutes, add 1.0 mL of the test solution, and shake well to mix. Allow this solution to stand at exactly 37 ± 0.5 ℃ for 10 minutes, add 2.0 mL of Fehling's alkaline tartaric acid solution, shake well to mix, and add 2.0 mL of Ferring's copper solution. After shaking intensely to compound, put a funnel into the opening of a test tube, heat on a steam bath for exactly 15 minutes, and cool with running water to below 25℃. Then, add 2.0 mL of concentrated potassium iodide TS and 2.0 mL of diluted sulfuric acid (1 in 6), and titrate the isolated iodine with 0.05 mol/L sodium thiosulfate VS. However, the endpoint of titration is when the blue color, formed by 1 - 2 drops of starch TS, is decolorized, and make 0.05 mol/L sodium thiosulfate solution used for the test b mL. Separately, proceed in the same manner above with 10 mL of water, instead of 10 mL of potato starch solution, 1% and make 0.05 mol/L sodium thiosulfate solution used for the test b mL.

$$\text{Glucose (mg)} = (a - b) \times 1.6$$

$$\text{Starch saccharifying activity (unit/g)} = \text{Glucose (mg)} \times \frac{1}{10} \times \frac{1}{W}$$

W: Amount (g) of sample in 1mL of the test solution

However, when amylase reacts with potato starch at 37 ℃, the amount of enzymes that bring about an increase in reducing power equivalent to 1 mg of glucose for the initial 1 minute of reaction is defined as 1 unit of starch saccharifying activity.

(2) ***Protein digestion activity***—Weigh accurately about 0.35 g of Diastase·protease N and dissolve in water to make 100 mL. Take exactly 10.0 mL of this solution, add water to make 100 mL, and use this solution as the test solution.

Pipet 5.0 mL of casein solution and allow it to stand at 37 ± 0.5 ℃ for 10 minutes, add 1.0 mL of the test solution, and shake intensely to compound. Allow this solution to stand at 37 ± 0.5 ℃ for 10 minutes, add 5.0 mL of trichloroacetic acid solution, 7.2%, and shake well to compound again. Allow it to stand at 37 ± 0.5 ℃ for 30 minutes, and filter after cooling. Take 2.0 mL of this filtrate, add 5.0 mL of 0.55 mol/L sodium carbonate solution and 1.0 mL of Folin's TS (1 in 3), respectively, and allow it to stand at 37 ± 0.5 ℃ for 30 minutes. Determine the absorption spectrum of this solution, A_T, as directed under the Ultraviolet-visible Spectroscopy at 660 nm wavelength, using water as the control solution. Separately, take 1.0 mL of the test solution, add exactly 5 mL of trichloroacetic acid solution, 7.2%, and shake well to compound. Add 5.0 mL of casein solution, shake well to compound, and allow it to stand at 37 ± 0.5 ℃ for 30 minutes. Determine the absorbance, A_B. in the same manner.

$$\text{Protein digestion activity (unit/g)} = (A_T\text{-}A_B) \times F \times \frac{11}{2} \times \frac{1}{10} \times \frac{1}{W}$$

F: Amount (μg) of tyrosine for absorbance difference of 1 determined from the tyrosine calibration curve

W: Amount (g) of sample in 1mL of the test solution

However, when protease reacts with milk casein at 37 ℃, the amount of enzymes that bring about an increase in non-protein, Folin's TS readily carbonizable substances equivalent to 1 μg of tyrosine for the initial 1 minute of reaction is defined as 1 unit of protein digestion activity.

Creation of tyrosine calibration curve—Dry tyrosine RS at 105 ℃ for 3 hours, weigh accurately 0.5 g of the dried matter, and dissolve in 0.2 mol/L hydrochloric acid TS to make 500 mL. Take 1.0 mL, 2.0 mL, 3.0 mL, and 4.0 mL each of this solution, and add 0.2 mol/L hydrochloric acid TS to make 100.0 mL, respectively. 2 mL each of the solution contains 20 μg, 40 μg, 60 μg and 80 μg of tyrosine. Take 2.0 mL each of the solution, add 5.0 mL of 0.55 mol/L sodium carbonate TS and 1.0 mL of Folin's TS (1 in 3), and allow it to stand at 37 ± 0.5 ℃ for 30 minutes. After cooling, determine the absorption spectra of these solutions, A_1, A_2, A_3 and A_4, as directed under the Ultraviolet-visible Spectroscopy at the 660 nm wavelength. Separately, proceed with 2 mL of 0.2 mol/L hydrochloric acid in the same manner above and determine the absorbance A_0. Measure A_1-A_0, A_2-A_0, A_3-A_0 and A_4-A_0, and create a calibration curve with the difference of absorbance on the longitudinal axis and the amount of tyrosine (μg) in 2 mL of each solution on the horizontal axis. Calculate the amount (F : μg) of tyrosine for the absorbance difference of 1 from this calibration curve.

Packaging and storage Preserve in tight containers.

Diastase·Protease·Cellulase
디아스타제·프로테아제·셀룰라제

Diastase·protease·cellulase is a complex enzyme prepared from beneficial strains of the genus *Aspergillus* or *Trichoderma koningi* with starch digestive activity, protein digestive activity, and cellulose digestive activity. In addition, it may have fat digestive activity. Diastase·protease·cellulase contains NLT 90.0% of digestive activity units of the labeled amount.

Description Diastase·protease·cellulase occurs as a pale yellow powder and has a characteristic odor.

Identification Perform the test as directed under the Assay; it exhibits a positive response.

Purity (1) ***Heavy metals*—**Proceed with 1.0 g of Diastase·protease·cellulase according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 2.0 g of Diastase·protease·cellulase according to Method 3 and perform the test (NMT 1 ppm).

Loss on drying NMT 10.0% (1.0 g, 105 ℃, 4 hours).

Residue on ignition NMT 10.0% (1.0 g).

Assay (1) ***Starch saccharifying activity***—(i) Test solution: Dissolve Diastase·protease·cellulase in acetic acid-sodium acetate buffer solution, pH 5.0, adjust to contain 0.4 to 0.8 starch saccharifying activity unit/mL, and use this solution as the test solution.

(ii) Substrate solution: Use potato starch TS for starch digestion activity.

(iii) Procedure: Proceed as directed under (i) Measurement of starch saccharifying activity of (1) starch digestive activity under the Digestive Power.

(2) **Protein digestive activity**—(i) Test solution: Dissolve Diastase·protease·cellulase in acetate buffer solution, pH 6.0, adjust to contain 15 to 25 protein digestive activity units/mL, and use this solution as the test solution.

(ii) Substrate solution: Use the substrate solution 2 of the Assay for protein digestive activity under the Digestive Power. However, adjust the pH to 6.0.

(iii) Procedure: Proceed as directed under the Assay for protein digestive activity under the Digestive Power. However, use trichloroacetic acid TS A as the precipitation reagent.

(3) ***Cellulose saccharifying activity***—Weigh accurately about 0.1 g of Diastase·protease·cellulase and add water to make 100 mL, and use this solution as the test solution. Take 4 mL of sodium carboxymethyl cellulose solution, allow to stand at 37 ± 0.5 ℃ for 10 minutes, add 1 mL of the test solution, shake to mix, and allow to stand at 37 ± 0.5 ℃ for 30 minutes. Add 2 mL of alkaline copper solution of Fehling's TS, shake to mix, heat on a steam bath for 30 minutes, and cool with running water. Add 2 mL of arsenic molybdate TS, shake well to mix, add 3 mL of 0.5 mol/L sodium hydroxide TS, shake again to mix, dissolve the precipitate, allow to stand for 20 minutes, and add acetic acid-sodium acetate buffer solution, pH 4.5 to make 25 mL. Pipet 1 mL of this solution, add 9 mL of acetic acid-sodium acetate buffer solution, pH 4.5, shake well to mix, and determine the absorbance A_T at the wavelength of 750 nm as directed under the Ultraviolet-visible Spectroscopy. Separately, pipet 1 mL of the test solution, add 2 mL of alkaline copper solution of Fehling's TS, add 4 mL of sodium carboxymethyl cellulose solution, and shake to mix. Proceed in the same manner, and determine the absorbance A_B. Determine the amounts (mg) of glucose, G_T and G_B, corresponding to A_T and A_B, using the glucose calibration curve.

$$\text{Cellulose saccharifying activity (unit/g)} = (G_T - G_B)/30 \times 1/0.18 \times 1/W$$

W: Amount (g) of the sample per mL of the test solution.

Definition of potency—Under the conditions specified above, one cellulose saccharifying activity unit is the amount of enzyme that catalyzes the increases of reducing activity equivalent to 1 μmole of glucose per minute.

Glucose calibration curve—Weigh accurately about 50 mg of the glucose RS, previously dried at 105 °C for 6 hours, and dissolve in water to make exactly 50 mL. Pipet 1, 2, 3, 4, and 5 mL of this solution separately, add water to make exactly 10 mL, respectively, and use these solutions as the standard solutions for the calibration curve. Pipet 1 mL of water and the standard solutions for the calibration curve, separately, add 4 mL of sodium carboxymethyl cellulose solution and 2 mL of alkaline copper solution of Fehling's TS, shake to mix, and heat on a steam bath for 30 minutes, cool with water, add 2 mL of arsenic molybdate TS, and shake to mix. Add 3 mL of 0.5 mol/L sodium hydroxide TS, dissolve the precipitate, allow to stand for 20 minutes, and add acetic acid-sodium acetate buffer solution, pH 4.5 to make 25 mL. Pipet 1 mL of each of these solutions, add 9 mL of acetic acid-sodium acetate buffer solution, pH 4.5, shake to mix, and determine the absorbances, A_0, A_1, A_2, A_3, A_4, and A_5, at the wavelength of 750 nm as directed under the Ultraviolet-visible Spectrophotometry. Construct a calibration curve by plotting the absorbance values $A_1 - A_0$, $A_2 - A_0$, $A_3 - A_0$, $A_4 - A_0$, and $A_5 - A_0$ versus the amounts (mg) of glucose (mg).

Packaging and storage Preserve in tight containers.

Diastase·Protease·Cellulase 1000
디아스타제·프로테아제·셀룰라제1000

Diastase·protease·cellulase 1000 is a digestive enzyme prepared from *Aspergilus aryzae*. About 1 g of Diastase·protease·cellulase 1000, when dried, contains between 7800 and 11000 units of starch saccharifying activity (pH 5.0), between 15000 and 24000 units of starch dextrinizing activity (pH 5.0), between 7000 and 11000 units of protein digestive activity (pH 3.0), between 14000 and 24000 units of protein digestive activity (pH 6.0),between 10000 and 20000 units of protein digestive activity (pH 8.0), and between 60 and 120 units of cellulose saccharifying activity(pH 4.5).

Description Diastase·protease·cellulase 1000 occurs as a pale yellow powder and has a characteristic odor. It is soluble in water and practically insoluble in ethanol.

Identification Perform the test with as directed under the Assay; it exhibits a positive response.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Diastase·protease·cellulase 1000 according to Method 2 and perform the test. Prepare the control solution with 5.0 mL of lead standard solution (NMT 50 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Diastase·protease·cellulase 1000 according to Method 3 and perform the test (NMT 2 ppm).

Loss on drying NMT 10.0% (1.0 g, 105 °C, 4 hours).

Residue on ignition NMT 10.0% (1.0 g).

Assay (1) ***Starch saccharifying activity***—Weigh accurately about 0.5 g of Diastase·protease·cellulase 1000 and add water to make 100 mL. Pipet 1.0 mL of this solution, add water to make 100 mL, and use this solution as the test solution. Pipet 10.0 mL of 1% potato starch solution, allow to stand at 37 ± 0.5 ℃ for 10 minutes, add 1 mL of the test solution, and shake to mix. Allow to stand at 37 ± 0.5 ℃ for exactly 10 minutes, add 2.0 mL of alkaline tartrate solution of Fehling's TS, and shake to mix. Add 2.0 mL of copper solution of Fehling's TS and shake to mix. Insert a funnel into the mouth of the test tube, heat the solution on a steam bath for exactly 15 minutes, cool with running water to below 25 ℃, add 2.0 mL of concentrated potassium iodide TS and 2.0 mL of dilute sulfuric acid (1 in 6), and titrate the liberated iodine with 0.05 mol/L sodium thiosulfate VS. As the endpoint is approached, add 1 to 2 drops of soluble starch TS, and continue the titration to the discharge of blue color. Separately, pipet 10.0 mL of water instead of 10.0 mL of 1% potato starch solution, proceed in the same manner, and titrate (a mL).

$$\text{Starch saccharifying activity (unit/g)} = (a - b) \times 1.6 \times \frac{1}{10} \times \frac{1}{\text{Amount (g) of sample in 1 mL of test solution}}$$

Definition of potency—When amylase reacts with potato starch at 37 ℃, one saccharifying activity unit is the amount of enzyme that catalyzes the increase of reducing activity equivalent to 1 mg of glucose for the initial 1 minute of reaction.

(2) ***Starch dextrinizing activity***—Weigh accurately about 0.5 g of Diastase·protease·cellulase 1000 and add water to make 150 mL. Pipet 1.0 mL of this solution, add water to make 200 mL, and use this solution as the test solution. Pipet 10.0 mL of 1% potato starch solution, allow to stand at 37 ± 0.5 ℃ for 10 minutes, add 1.0 mL of the test solution, shake to mix, and allow to stand at 37 ± 0.5 ℃ for exactly 10 minutes. Pipet 1.0 mL of this solution, add 10.0 mL of 0.1 mol/L hydrochloric acid TS, and shake to mix. Pipet 0.5 mL of this solution, add 10 mL of 0.0002 mol/L iodine TS, shake to mix, and immediately determine the absorbance A_T at the wavelength of 660 nm. Separately, take water instead of the test solution, proceed in the same manner, and determine the absorbance A_B.

$$\text{Starch dextrinizing activity (unit/g)} = \frac{A_B - A_T}{A_B} \times \frac{100}{10 \times 10} \times \frac{1}{\text{Amount (g) of sample in 1 mL of test solution}}$$

Definition of potency—When amylase reacts with 0.1 g of potato starch at 37 ℃, one starch dextrinizing unit is the amount of enzyme required to reduce the coloration of potato starch by iodine by 10% for initial 1 minute of reaction.

(3) ***Protein digestive activity (pH 3.0)***—Weigh accurately about 0.5 g of Diastase·protease·cellulase 1000 and add water to make 75 mL. Pipet 10.0 mL of this solution, add water to make 50 mL, and use this solution as the test solution. Pipet 5.0 mL of casein solution, pH 3.0, allow to stand at 37 ± 0.5 ℃ for 10 minutes, add 1.0 mL of the test solution, and shake to mix. Allow the solution to stand at 37 ± 0.5 ℃ for 10 minutes, add 5 mL of trichloroacetic acid TS, and shake to mix. Allow to stand at 37 ± 0.5 ℃ for 30 minutes and filter. Take 2 mL of the filtrate, add 5 mL of 0.55 mol/L sodium carbonate TS and 1 mL of diluted Folin's TS (1 in 3), allow to stand at 37 ± 0.5 ℃ for 30 minutes, and determine the absorbance A_T at the wavelength of 660 nm. Separately, take 1.0 mL of the test solution, add 5 mL of trichloroacetic acid TS, shake to mix, and add 5 mL of casein solution, pH 3, allow to stand at 37 ± 0.5 ℃ for 30 minutes, proceed in the same manner, and determine the absorbance A_B.

$$\text{Protein digestive activity (unit/g)} = (AT - AB) \times F \times \frac{11}{2} \times \frac{1}{10} \times 750$$

F: Amount (μg) of tyrosine for absorbance difference of 1.000 determined from the tyrosine calibration curve

750: Dilution factor of sample (per g)

$\frac{11}{2}$, $\frac{1}{10}$: Unit conversion factor

Definition of potency—When protease reacts with milk casein at 37 ℃, one protein digestive activity unit is the amount of enzyme that produces non-protein, Folin's TS colorable substance equivalent to 1 μg tyrosine for the initial 1 minute of reaction.

Tyrosine calibration curve—Weigh accurately

about 0.5 g of tyrosine RS, previously dried at 105 ℃ for 4 hours, and dissolve in 0.2 mol/L hydrochloric acid TS to make 500 mL. Pipet 1.0 mL, 2.0 mL, 3.0 mL, and 4.0 mL of this solution separately and add 0.2 mol/L hydrochloric acid TS to make 100 mL. Pipet 2.0 mL of each solution, add 5.0 mL of 0.55 mol/L sodium carbonate TS and 1.0 mL of dilute Folin's TS (1 in 3), allow to stand at 37 ± 0.5 ℃ for 30 minutes, and determine the absorbances A_1, A_2, A_3 and A_4 at the wavelength of 660 nm. Separately, proceed with 2 mL of 0.2 mol/L hydrochloric acid TS in the same manner, and determine the absorbance A_0. Construct a calibration curve by plotting the difference of absorbance versus the content of tyrosine, and determine the amount of tyrosine (F) corresponding to the absorbance difference of 1.000.

(4) ***Protein digestion activity (pH 6.0)***—Weigh accurately about 0.5 g of Diastase·protease·cellulase 1000 and add water to make 75 mL. Pipet 10.0 mL of this solution, add water to make 50 mL, and use this solution as the test solution. Take 5.0 mL of casein solution, pH 6.0, proceed as directed under the protein digestive activity (pH 3.0) under the Assay, and determine the absorbances A_T and A_B.

$$\text{Protein digestive activity (pH 6.0) (unit/g)} = (A_T - A_B) \times F \times \frac{11}{2} \times \frac{1}{10} \times 750$$

F: Amount (μg) of tyrosine for absorbance difference of 1.000 determined from the tyrosine calibration curve

(5) ***Protein digestion activity (pH 8.0)***—Weigh accurately about 0.5 g of Diastase·protease·cellulase 1000 and add water to make 75 mL. Take 10.0 mL of this solution, add water to make 50 mL, and use this solution as the test solution. Take 5.0 mL of casein solution, pH 8.0, proceed as directed under the protein digestive activity (pH 3.0) under the Assay, and determine the absorbances A_T and A_B.

$$\text{Protein digestive activity (pH 8.0) (unit/g)} = (A_T - A_B) \times F \times \frac{11}{2} \times \frac{1}{10} \times 750$$

F: Amount (μg) of tyrosine for absorbance difference of 1.000 determined from the tyrosine calibration curve

(6) ***Cellulose saccharifying activity***—Weigh accurately about 0.5 g of Diastase·protease·cellulase 1000 and add water to make 100 mL. Pipet 1.0 mL of this solution, add water to make 100 mL, and use this solution as the test solution. Take 4.0 mL of sodium carboxymethylcellulose solution, allow to stand at 37 ± 0.5 ℃ for 10 minutes, add 1.0 mL of the test solution, shake to mix, and allow to stand at 37 ± 0.5 ℃ for exactly 30 minutes. Add 2.0 mL of alkaline copper solution of Fehling's TS, shake to mix, heat on a steam bath for 30 minutes, and cool with running water. Add 2.0 mL of arsenic molybdate TS, shake to mix, add 3.0 mL of 0.5 mol/L sodium hydroxide TS, shake again to mix, dissolve the precipitate, allow to stand for 20 minutes, and add acetic acid-sodium acetate buffer solution, pH 4.5 to make 25 mL. Pipet 1.0 mL of this solution, add 9.0 mL of acetic acid-sodium acetate buffer solution, pH 4.5, shake well to mix, and determine the absorbance A_T at the wavelength of 750 nm. Separately, pipet 1.0 mL of the test solution, add 2.0 mL of alkaline copper solution of Fehling's TS, add 4.0 mL of sodium carboxymethyl cellulose solution and shake to mix. Proceed in the same manner, and determine the absorbance A_B. Determine the amount of glucose, G_T and G_B, corresponding to A_T and A_B using the glucose calibration curve.

$$\text{Cellulose saccharifying activity (unit/g)} = \frac{G_T - G_B}{30} \times \frac{1}{0.18} \times \frac{1}{\text{Amont (g) of sample in 1 mL of test solution}}$$

Definition of potency—When cellulase reacts with sodium carboxymethylcellulose at 37 ℃, one cellulose saccharifying activity unit is the amount of enzyme that catalyzes the increases of reducing activity equivalent to 1 μmol of glucose for the initial 1 minute of reaction.

Glucose calibration curve—Weigh accurately about 1.0 g of glucose RS, previously dried at 105 ℃ for 6 hours, and dissolve in water to make 1.0 L. Pipet 1.0, 2.0 mL, 3.0 mL, 4.0 mL, and 5.0 mL of this solution separately, and add water to make 10 mL, respectively. Pipet 1.0 mL of each solution, add 4.0 mL of sodium carboxymethylcellulose solution and 2.0 mL alkaline copper solution of Fehling's TS, shake to mix, insert the stopper, heat on a steam bath for 30 minutes and cool with water. Add 2.0 mL of arsenic molybdate TS, shake to mix, add 3.0 mL of 0.5 mol/L sodium hydroxide TS, dissolve the precipitate, allow to stand for 20 minutes and add acetic acid-sodium acetate buffer solution, pH 4.5 to make 25 mL. Pipet 1.0 mL of each solution and add 9.0 mL of acetic acid-sodium acetate buffer solution, pH 4.5, shake to mix, and determine the absorbances A_1, A_2, A_3, A_4 and A_5 at the wavelength of 750 mm. Separately, proceed in the same manner with 1 mL of water instead of 1 mL of the glucose solution, and determine the absorbance A_0. Construct a calibration curve with the difference of absorbance versus the amounts of glucose.

Packaging and storage Preserve in tight containers.

Diastase·Protease·Cellulase 2000 II
디아스타제·프로테아제·셀룰라제2000II

Diastase·protease·cellulase 2000 II is a digestive

enzyme purified from the enzyme obtained by culturing several fungi belonging to the genus *Aspergillus* in a special media. It contains starch digestive enzymes, α-amylase and *β*-amylase, and also contains a protein digestive enzyme, trypsin and a fat digestive enzyme, lipase.

About 1 g of Diastase·protease·cellulase 2000 II contains between 3900 and 5500 units of starch saccharifying activity (pH 5.0), between 7000 and 12000 units of starch dextrinizing activity (pH 5.0), between 7000 and 12000 units of protein digestive activity (pH 6.0), and between 30 and 60 units of cellulose saccharifying activity.

Description Diastase·protease·cellulase 2000 II occurs as a pale yellowish brown powder. It is soluble in water and insoluble in ethanol.

Identification Perform the test with Diastase·protease·cellulase 2000 II as directed under the Assay; it exhibits a positive response.

Purity (1) ***Heavy metals***—Proceed with 0.4 g of Diastase·protease·cellulase 2000 II according to Method 2 and perform the test. Prepare the control solution with 5.0 mL of lead standard solution (NMT 50 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Diastase·protease·cellulase 2000 II according to Method 3 and perform the test (NMT 2 ppm).

Loss on drying NMT 10.0% (1 g, 105 °C, 4 hours).

Assay (1) ***Starch saccharifying activity***—Weigh accurately about 0.2 g of Diastase·protease·cellulase 2000 II and add acetic acid-sodium acetate buffer solution, pH 5.0, to make 200 mL. Pipet 10 mL of this solution, add acetic acid-sodium acetate buffer solution, pH 5.0 to make 100 mL, and use this solution as the test solution. Pipet 10.0 mL of 1% potato starch solution, allow to stand at 37 ± 0.5 ℃ for 10 minutes, add 1 mL of the test solution, and shake to mix. Allow to stand at 37 ± 0.5 ℃ for exactly 10 minutes, add 2.0 mL of alkaline tartrate solution of Fehling's TS, and shake to mix. Add 2.0 mL of copper solution of Fehling's TS, and shake to mix. Insert a funnel into the mouth of the test tube, heat the solution on a steam bath for exactly 15 minutes, cool with running water to below 25 ℃, add 2.0 mL of concentrated potassium iodide TS and 2.0 mL of dilute sulfuric acid (1 in 6), and titrate the liberated iodine with 0.05 mol/L sodium thiosulfate VS. As the endpoint is approached, add 1 to 2 drops of soluble starch TS, and continue the titration to the discharge of blue color. Separately, pipet 10 mL of water instead of 10 mL of 1% potato starch solution, proceed in the same manner, and titrate (a mL).

$$\text{Starch saccharifying activity (unit/g)} = (a-b) \times 1.6 \times \frac{1}{10} \times \frac{1}{\text{Amount (g) of sample in 1 mL of test solution}}$$

Definition of potency—When amylase reacts with potato starch at 37 ℃, one saccharifying activity unit is the amount of enzyme that catalyzes the increase of reducing activity equivalent to 1 mg of glucose for the initial 1 minute of reaction.

(2) ***Starch dextrinizing activity***—Weigh accurately about 0.1 g of Diastase·protease·cellulase 2000 II, add acetic acid-sodium acetate buffer solution, pH 5.0 to make 200 mL. Pipet accurately 10.0 mL of this solution, add acetic acid-sodium acetate buffer solution, pH 5.0 to make 100 mL, and use this solution as the test solution. Pipet 10 mL of 1% potato starch solution, allow to stand at 37 ± 0.5 ℃ for 10 minutes, add 1.0 mL of the test solution, shake to mix, and allow to stand at 37 ± 0.5 ℃ for exactly 10 minutes. Pipet 1.0 mL of this solution, add 10 mL of 0.1 mol/L hydrochloric acid TS, and shake to mix. Pipet 0.5 mL of this solution, add 10 mL of 0.0002 mol/L iodine TS, shake to mix, and immediately determine the absorbance A_T at the wavelength of 660 nm. Separately, take water instead of the test solution, proceed in the same manner, and determine the absorbance A_B.

$$\text{Starch dextrinizing activity (unit/g)} = \frac{A_B - A_T}{A_B} \times \frac{100}{10 \times 10} \times \frac{1}{\text{Amount (g) of sample in 1 mL of test solution}}$$

Definition of potency—When amylase reacts with 0.1 g of potato starch at 37 ℃, one starch dextrinizing unit is the amount of enzyme required to reduce the coloration of potato starch by iodine by 10% for the initial 1 minute of reaction.

(3) ***Protein digestive activity (pH 6.0)***—Weigh accurately about 0.5 g of Diastase·protease·cellulase 2000 II, add acetate buffer solution, pH 6.0 to make 200 mL, and use this solution as the test solution. Take 5.0 mL of casein solution, pH 6.0, allow to stand at 37 ± 0.5 ℃ for 10 minutes, add 1.0 mL of the test solution, and shake to mix. Allow the solution to stand at 37 ± 0.5 ℃ for exactly 10 minutes, add 5 mL of trichloroacetic acid TS, and shake to mix. Allow to stand at 37 ± 0.5 ℃ for 30 minutes and filter. Take 2.0 mL of the filtrate, add 5.0 mL of 0.55 mol/L sodium carbonate TS and 1 mL of diluted Folin's TS (1 in 3), allow to stand at 37 ± 0.5 ℃ for 30 minutes, and determine the absorbance A_T at the wavelength of 660 nm. Separately, take 1.0 mL of the test solution, add 5 mL of trichloroacetic acid TS, shake to mix, and add 5 mL of casein solution, allow to stand at 37 ± 0.5 ℃ for 30 minutes, proceed in the same manner, and determine the absorbance A_B.

$$\text{Protein digestive activity (unit/g)} = (AT - AB) \times F \times \frac{11}{2} \times \frac{1}{10} \times \frac{1}{\text{Amount (g) of sample in 1 mL of test solution}}$$

F: Amount (μg) of tyrosine for absorbance difference of 1.000 determined from the tyrosine calibration curve

Tyrosine calibration curve—Weigh accurately about 0.5 g of tyrosine RS, previously dried at 105 ℃ for 3 hours, and dissolve in 0.2 mol/L hydrochloric acid TS to make 500 mL. Pipet 1.0 mL, 2.0 mL, 3.0 mL, and 4.0 mL this solution separately and add 0.2 mol/L hydrochloric acid TS to make100 mL. Pipet 2.0 mL of each solution, add 5 mL of 0.55 mol/L sodium carbonate TS and 2.0 mL of diluted Folin's TS (1 in 3), allow to stand at 37 ± 0.5 ℃ for 30 minutes, and determine the absorbances A_1, A_2, A_3 and A_4 at the wavelength of 660 nm. Separately, proceed with 2.0 mL of 0.2 mol/L hydrochloric acid TS in the same manner, and determine the absorbance A_0. Construct a calibration curve by plotting the difference of absorbance versus the content of tyrosine.

(4) ***Cellulose saccharifying activity***—Weigh accurately about 0.1 g of Diastase·protease·cellulase 2000 II, add water to make 100 mL, and use this solution as the test solution. Take 4.0 mL of sodium carboxymethylcellulose solution, allow to stand at 37 ± 0.5 ℃ for 10 minutes, add 1.0 mL of the test solution, shake to mix, and allow to stand at 37 ± 0.5 ℃ for exactly 30 minutes. Add 2.0 mL of alkaline copper TS, shake to mix, heat on a steam bath for 30 minutes, and cool with running water. Add 2.0 mL of arsenic molybdate TS, shake to mix, add 3.0 mL of 0.5 mol/L sodium hydroxide TS, shake again to mix, dissolve the precipitate, allow to stand for 20 minutes, and add 25.0 mL of acetic acid-sodium acetate buffer solution, pH 4.5 to make 25.0 mL. Pipet 1.0 mL of this solution, add 9.0 mL of acetic acid-sodium acetate buffer solution, pH 4.5, shake well to mix, and determine the absorbance A_T at the wavelength of 750 nm. Separately, pipet 1.0 mL of the test solution, add 2.0 mL of alkaline copper TS, and mix. Add 4.0 mL of sodium carboxymethylcellulose solution and shake to mix. Proceed in the same manner, and determine the absorbance A_B. Determine the amount of glucose, G_T and G_B, corresponding to A_T and A_B using the glucose calibration curve.

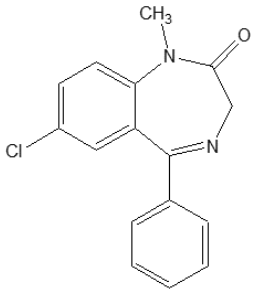
$$\text{Cellulose saccharifying activity (unit/g)} = \frac{G_T - G_B}{30} \times \frac{1}{0.18} \times \frac{1}{\text{Amount (g) of sample in 1 mL of test solution}}$$

Definition of potency—When cellulase reacts with sodium carboxymethylcellulose at 37 ℃, one cellulose saccharifying activity unit is the amount of enzyme that catalyzes the increases of reducing activity equivalent to 1 μmol of glucose for the initial 1 minute of reaction.

Glucose calibration curve—Weigh accurately about 1.0 g of glucose RS, previously dried at 105 ℃ for 6 hours, and add water to make 1000 mL. Pipet 1.0, 2.0 mL, 3.0 mL, 4.0 mL, and 5.0 mL of each solution, and add water to make 10 mL, respectively. Pipet 1.0 mL of each solution, add 4.0 mL of sodium carboxymethylcellulose solution and 2.0 mL of alkaline copper TS, shake to mix, and insert the stopper, heat on a steam bath for 30 minutes and cool with water. Add 2.0 mL of arsenic molybdate TS, shake to mix, add 3.0 mL of 0.5 mol/L sodium hydroxide TS, and dissolve the precipitate, allow to stand for 20 minutes, and add acetic acid-sodium acetate buffer solution, pH 4.5 to make 25 mL. Pipet 1.0 mL of each solution and add 9.0 mL of acetic acid-sodium acetate buffer solution, pH 4.5, shake to mix, and determine the absorbances A_1, A_2, A_3, A_4 and A_5 at the wavelength of 750 mm. Separately, proceed in the same manner with 1 mL of water instead of 1 mL of the glucose solution, and determine the absorbance A_0. Construct a calibration curve y plotting the difference of absorbance versus the amount of glucose.

Packaging and storage Preserve in tight containers.

Diazepam
디아제팜



$C_{16}H_{13}ClN_2O$: 284.74

7-Chloro-1-methyl-5-phenyl-3*H*-1,4-benzo-diazepin-2-one [*439-14-5*]

Diazepam, when dried, contains NLT 98.5% and NMT 101.0% of diazepam ($C_{16}H_{13}ClN_2$ O).

Description Diazepam occurs as a white to pale yellow crystalline powder, is odorless and has a slightly bitter taste.

It is freely soluble in acetone, soluble in ethanol(95) and acetic anhydride, sparingly soluble in ethanol, slightly soluble in ethanol(99.5), and practically insoluble in water.

Identification (1) Dissolve about 10 mg of Diazepam in 3 mL of sulfuric acid and examine the solution under ultraviolet light (wavelength of 365 nm); the resulting solution exhibits a yellowish green fluorescent color.

(2) Dissolve 2 mg each of Diazepam and diazepam RS in 200 mL solution of sulfuric acid in ethanol(99.5) (3 in 1000), and determine the absorption spectra as directed under the Ultraviolet-visible Spectroscopy; both spectra

exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Diazepam and diazepam RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) Perform the test with Diazepam as directed under the Flame Coloration (2); it exhibits a blue to bluish green color.

Melting point Between 130 and 134 ℃.

Absorbance $E_{1cm}^{1\%}$ (285 nm): Between 425 and 445 [2 mg, after drying, solution of sulfuric acid in ethanol(99.5) (3 in 1000), 200 mL].

Purity (1) ***Clarity and color of solution***—Dissolve about 0.10 g of Diazepam in 20 mL of acetone (95); the resulting solution is clear.

(2) ***Chloride***—Take 1.0 g of Diazepam, add 50 mL of water, allow to stand for 1 hour with occasional shaking to mix, and filter. To 25 mL of the filtrate, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.20 mL of 0.01 mol/L hydrochloric acid (NMT 0.014%).

(3) ***Heavy metals***—Proceed with 1.0 g of Diazepam according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Related substances***—Dissolve about 0.10 g of Diazepam in 10 mL of acetone and use this solution as the test solution. Pipet 1 mL of this solution, and add acetone to make exactly 100 mL. Pipet 1 mL of this solution, add acetone to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Then, develop the plate with a mixture of ethyl acetate and hexane (1 :1) to a distance of about 12 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 °C, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.6 g of Diazepam, previously dried, dissolve in 60 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid

= 28.474 mg of $C_{16}H_{13}ClN_2O$

Packaging and storage Preserve in light-resistant, tight containers.

Diazepam Injection
디아제팜 주사액

Diazepam Injection contains NLT 90.0% and NMT 110.0% of diazepam ($C_{16}H_{13}ClN_2O$: 284.74).

Method of preparation Prepare Diazepam Injection as directed under the Injections, with Diazepam.

Description Diazepam Injection occurs as a clear, colorless liquid.

Identification (1) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

(2) Take an appropriate amount equivalent to 10 mg of diazepam according to the labeled amount of Diazepam Injection, transfer to a separatory funnel, add 20 mL of water, and shake well to mix. Add 20 mL of chloroform and shake vigorously. Filter and add the chloroform layer with 5 g of anhydrous sodium sulfate, wash anhydrous sodium sulfate with 20 mL of chloroform, and add the washings with the filtrate. Evaporate the filtrate on a steam bath in air so that it becomes about 5 mL and evaporate the beaker to dryness on a steam bath in air. Strongly rake in the oil layer with a spatula, and dry in vacuum at 60 ℃ for 4 hours in a desiccator with phosphorus pentoxide as a drier. Separately, perform the test in the same manner in the preparation of the sample with diazepam RS and use as the reference standard. Determine the spectra with the sample and reference standards as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

pH Between 6.2 and 6.9.

Sterility Meets the requirements.

Bacterial endotoxins Less than 11.6 EU per mg of diazepam.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Take exactly an amount of Diazepam Injection,

equivalent to about 10 mg of diazepam ($C_{16}H_{13}ClN_2O$), add 10.0 mL of the internal standard solution and methanol to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of diazepam RS, and dissolve in methanol to make a solution containing 1 mg per mL. Pipet 5 mL of this solution, add exactly 5.0 mL of the internal standard solution, add methanol to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and calculate the ratios, Q_T and Q_S, of the peak area of diazepam to that of the internal standard for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of diazepam } (C_{16}H_{13}ClN_2O) = \text{Amount (mg) of diazepam RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of *p*-tolualdehyde in methanol (3 in 10000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 - 10 μm in particle diameter).

Mobile phase: A mixture of methanol and water (65 : 35).

Flow rate: 1.4 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the internal standard and diazepam are eluted in this order with the resolution being NLT 5.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution under the above operating conditions; the relative standard deviation of the ratios of the peak area of diazepam to that of the internal standard is NMT 2.0%.

Packaging and storage Preserve in light-resistant, hermetic containers.

Diazepam Tablets
디아제팜 정

Diazepam Tablets contains NLT 95.0% and NMT 105.0% of diazepam ($C_{16}H_{13}ClN_2O$: 284.74).

Method of preparation Prepare as directed under Tablets, with Diazepam.

Identification Weigh an amount of Diazepam Tablets, previously powdered, equivalent to 50 mg of diazepam according to the labeled amount, add 50 mL of acetone, shake to mix, and filter. Take 1 mL of the filtrate, evaporate to dryness in a water bath, and dissolve the residue in 100 mL of sulfuric acid in ethanol(95) (3 in 1000). Determine the absorption spectra of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 240 nm and 244 nm, between 283 nm and 287 nm, and between 360 nm and 370 nm.

Dissolution Perform the test with 1 tablet of Diazepam Tablets at 100 revolutions per minute according to Method 1, using 900 mL of 0.1 mol/L hydrochloric acid as the dissolution medium. Use the dissolved solution 30 minutes after starting the dissolution test as the test solution by suitably diluting with the dissolution medium, if necessary. Separately, weigh accurately an appropriate amount of diazepam RS, dissolve in 0.1 mol/L hydrochloric acid to make it the same concentration as the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using 0.1 mol/L hydrochloric acid as the control solution, and determine the absorbance at the absorbance maximum wavelength of about 242 nm.

It meets the requirements if the dissolution rate of Diazepam Tablets in 30 minutes is NLT 85%.

Uniformity of dosage units It meets the requirements when the Content uniformity test is performed according to the following procedure. Take 1 tablet of Diazepam Tablets, add 5 mL of water, and disintegrate by shaking to mix. Add 30 mL of methanol, shake for 10 minutes, add methanol to make exactly 50 mL, and centrifuge. Take *V* mL of the clear supernatant, equivalent to 0.4 mg of diazepam ($C_{16}H_{13}ClN_2O$), add 5 mL of internal standard solution, add methanol to make 20 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of diazepam RS, previously dried at 105 °C for 2 hours, and dissolve in methanol to make exactly 100 mL. Pipet 2 mL of this solution, add exactly 5 mL of the internal standard solution, add methanol to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and calculate the ratios, Q_T and Q_S, of the peak area of diazepam to that of the internal standard from the test solution and the standard solution, respectively.

$$\text{Amount (mg) of diazepam } (C_{16}H_{13}ClN_2O) = \text{Amount (mg) of diazepam RS} \times \frac{Q_T}{Q_S} \times \frac{1}{V}$$

Internal standard solution—A solution of ethylparaben in methanol (1 in 25000).

Operating conditions

Proceed as directed under the operating conditions

under the Assay.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the internal standard and diazepam are eluted in this order with the resolution between these peaks being NLT 6.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the ratios of the peak area of diazepam to that of the internal standard is NMT 1.0%.

Assay Weigh accurately and powder NLT 20 tablets of Diazepam Tablets. Weigh accurately a portion of this powder, equivalent to about 50 mg of diazepam ($C_{16}H_{13}ClN_2O$), dissolve in 10 mL of water by shaking to mix, add 60 mL of methanol, shake to mix for 10 minutes, add methanol to make exactly 100 mL, and centrifuge. Pipet 5 mL of the clear supernatant, add exactly 5 mL of the internal standard solution, add methanol to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of diazepam RS, previously dried at 105 ℃ for 2 hours, add 10 mL of water, and add methanol to make exactly 100 mL. Pipet 5 mL of this solution, add exactly 5 mL of the internal standard solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios Q_T and Q_S, of the peak area of diazepam to the peak area of the internal standard from each solution.

$$\text{Amount (mg) of diazepam } (C_{16}H_{13}ClN_2O) = \text{Amount (mg) of diazepam RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of ethylparaben in methanol (1 in 5000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless-steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of methanol and water (13 : 7).

Flow rate: Adjust the flow rate so that the retention time of diazepam is about 10 minutes.

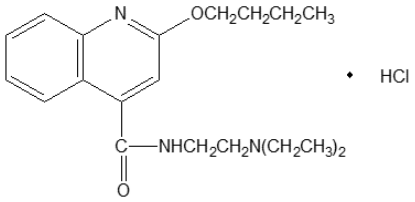
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the internal standard and diazepam are eluted in this order with the resolution being NLT 6.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution each time according to the above conditions; the relative standard deviation of the peak areas of diazepam is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Dibucaine Hydrochloride
디부카인염산염



Cinchocaine Hydrochloride $C_{20}H_{29}N_3O_2 \cdot HCl$: 379.92
2-Butoxy-*N*-(2-(diethylamino)ethyl)quinoline-4-carboxamide hydrochloride [*61-12-1*]

Dibucaine Hydrochloride, when dried, contains NLT 98.0% and NMT 101.0% of dibucaine hydrochloride (C20H29N3O2·HCl).

Description Dibucaine Hydrochloride occurs as white crystals or a crystalline powder.
It is very soluble in water, ethanol(95) or acetic acid(100), freely soluble in acetic anhydride and practically insoluble in ether.
It is hygroscopic.

Identification (1) Determine the absorption spectra of Dibucaine Hydrochloride and dibucaine hydrochloride RS in 1 mol/L hydrochloric acid (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Dibucaine Hydrochloride and dibucaine hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Dibucaine Hydrochloride (1 in 10) responds to the Qualitative Analysis chloride.

Melting point Between 95 and 100 ℃. Put Dibucaine Hydrochloride into a capillary tube for melting point determination, and dry in vacuum over phosphorus pentoxide at 80 °C for 5 hours. Seal immediately the open end of the tube and determine the melting point.

pH Dissolve 1.0 g of Dibucaine Hydrochloride in 50 mL of water; the pH of this solution is between 5.0 and 6.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Dibucaine Hydrochloride in 20 mL of water; the resulting solution is clear and colorless Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy, using water as the control solution; the absorbance at the wavelength of about 430 nm is NMT 0.03.

(2) ***Sulfate***—Weigh 0.3 g of Dibucaine Hydrochloride and perform the test. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid (NMT 0.056%).

(3) ***Heavy metals***—Proceed with 1.0 g of Dibucaine Hydrochloride as directed under Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Related substances***—Dissolve 0.2 g of Dibucaine Hydrochloride in 5 mL of ethanol(95) and use this solution as the test solution. Pipet 1 mL of the test solution, and add ethanol(95) to make exactly 20 mL. Pipet 2 mL of this solution, add ethanol(95) to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, water and acetic acid(100) (3 : 1 : 1) to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 2.0% (1 g, in vacuum, phosphorus pentoxide, 80 ℃, 5 hours).

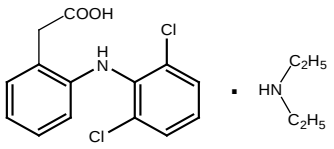
Residue on ignition NMT 0.1% (1 g).

Assay Weigh exactly about 0.3 g of Dibucaine Hydrochloride, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 19.00 mg of $C_{20}H_{29}N_3O_2 \cdot HCl$

Packaging and storage Preserve in tight containers.

Diclofenac Diethylammonium
디클로페낙디에틸암모늄



$C_{18}H_{22}Cl_2N_2O_2$: 369.29
Diethylammonium 2-[(2,6-dichloroanilino) phenyl] acetate, [*78213-16-8*]

Diclofenac Diethylammonium, when dried, contains NLT 99.0% and NMT 101.0% of diclofenac diethylammonium ($C_{18}H_{22}Cl_2N_2O_2$).

Description Diclofenac Diethylammonium occurs as a pale yellow crystalline powder.
It is freely soluble in methanol, ethanol(95) and chloroform, and slightly soluble in acetic acid(100), acetone and water.
It is practically insoluble in 1 mol/L sodium hydroxide.
A solution of Diclofenac Diethylammonium in methanol (1 in 20) is clear.

Melting point—About 154 °C.

Identification Dissolve 25 mg of Diclofenac Diethylammonium in 100 mL of methanol, take 1 mL of this solution, and add methanol to make 10 mL. Determine the absorption spectrum with this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavenumber of about 282 nm.

pH Between 6.5 and 8.3 (1% aqueous solution).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Diclofenac Diethylammonium according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Weigh accurately about 0.10 g of Diclofenac Diethylammonium, dissolve in the mobile phase to make 100 mL, and use this solution as the test solution. Pipet 2 mL of this solution, add the mobile phase to make exactly 100 mL, then pipet1.0 mL of this solution, add the mobile phase to make exactly 10 mL, and use this solution as the standard solution. Perform the test with exactly 20 mL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas by the automatic integration method; the peak area of each related substance other than the major peak from the test solution is NMT the major peak area from the standard solution (NMT 0.2%). The sum of peak areas of related substances other than the major peak from the test solution is not greater than 2.5 times the major peak area from the standard solution (NMT 0.5%). But exclude small peaks that are smaller than 0.25 times the major peak area from the standard solution (NMT 0.05%).

Operating conditions

Detector: An ultraviolet absorption photometer

(wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of a solution, where 0.1% phosphoric acid solution and 0.16% sodium dihydrogen phosphate buffer solution are mixed in the same volume with the pH adjusted to 2.5, and methanol (17 : 33).

Flow rate: 1 mL/minute (the retention time of diclofenac: about 25 minutes, the retention time of related substances A (1-(2,6-dichlorophenyl)-1,3-dihydro-2H-indole-2-one): about 12 minutes).

System suitability

System performance: Weigh 1 mg of related substances A (1-(2,6-dichlorophenyl)-1,3-dihydro-2H-indole-2-one) RS, dissolve in the mobile phase, add 1mL of the test solution and the mobile phase to make exactly 200 mL, and use this solution as the system suitability solution. Proceed with 20 μL of this solution according to the above conditions; the resolution between diclofenac and elated substances A (1-(2,6-dichlorophenyl)-1,3-dihydro-2H-indole-2-one) is NLT 6.5.

Detection sensitivity: Adjust the detection sensitivity so that the peak heights are about 50% of the full scale when proceeding with 20 μL of the system suitability solution according to the above conditions.

Time span of measurement: About 1.5 times the retention time of diclofenac.

Loss on drying NMT 0.1% (3 g, room temperature, 24 hours, in vacuum).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Diclofenac Diethylammonium, previously dried, dissolve in 30 mL of acetic acid(100) for non-aqueous titration, and titrate with 0.1 mol/L perchloric acid VS as directed in the potentiometric titration under the Titrimetry. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 36.929 mg of $C_{18}H_{22}Cl_2N_2O_2$

Packaging and storage Preserve in well-closed containers, protected from heat.

Diclofenac Diethylammonium Cream
디클로페낙디에틸암모늄 크림

Diclofenac Diethylammonium Cream contains NLT 95.0% and NMT 105.0% of the labeled amount of diclofenac diethylammonium ($C_{18}H_{22}Cl_2N_2O_2$: 369.29).

Method of preparation Prepare as directed under Creams, with Diclofenac Diethylammonium.

Identification Weigh an amount of Diclofenac Diethylammonium Cream, equivalent to 50 mg of diclofenac diethylammonium, add 25 mL of 0.5 mol/L lithium chloride-methanol solution, shake to mix to make a homogeneous suspension, then add chloroform to make 50 mL. Shake this solution vigorously to mix, centrifuge for 10 minutes, and use the clear supernatant as the test solution. Separately, weigh accurately 50 mg of diclofenac diethylammonium RS, add 25 mL of 0.5 mol/L lithium chloride-methanol solution, add chloroform to make 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution onto a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of toluene, formic acid and *n*-hexane (20 : 3 : 2) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray 0.5% potassium dichromate-sulfuric acid TS on the plate; the R_f values and colors of the spots from the test solution and the standard solution are the same.

Assay Weigh accurately an amount of Diclofenac Diethylammonium Cream, equivalent to about 50 mg of diclofenac diethylammonium ($C_{18}H_{22}Cl_2N_2O_2$), and add water to make 500 mL. Filter this solution, take 10.0 mL of the filtrate, add methanol to make 20 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of diclofenac diethylammonium RS and dissolve in a mixture of water and methanol (1 : 1) to make 100 mL. Pipet 10.0 mL of the resulting solution, add a mixture of water and methanol (1 : 1) to make 100 mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography and determine the peak area of diclofenac diethylammonium, A_T and A_S, for each solution.

$$\text{Amount (mg) of diclofenac diethylammonium } (C_{18}H_{22}Cl_2N_2O_2) = \text{Amount (mg) of diclofenac diethylammonium} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

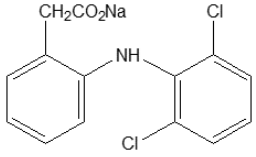
Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Mobile phase: A mixture of 0.1 mol/L sodium acetate-methanol and water (1 : 1).

Flow rate: 2 mL/min

Packaging and storage Preserve in tight containers.

Diclofenac Sodium
디클로페낙나트륨



$C_{14}H_{10}Cl_2NNaO_2$: 318.13
Sodium 2-(2-(2,6-dichlorophenylamino)phenyl)acetate
[*15307-79-6*]

Diclofenac Sodium, when dried, contains NLT 98.5% and NMT 101.0% of diclofenac sodium ($C_{14}H_{10}Cl_2NNaO_2$).

Description Diclofenac Sodium occurs as white to pale yellow crystals or a crystalline powder.
It is freely soluble in methanol or ethanol(95), sparingly soluble in acetic acid(100) and practically insoluble in ether.
It is hygroscopic.

Identification (1) Take 1 mL of Diclofenac Sodium in methanol solution (1 in 250), and add 1 mL of nitric acid; the resulting solution exhibits a dark red color.

(2) Perform the Flame Coloration (2) with 5 mg of Diclofenac Sodium; it exhibits a pale green color.

(3) Determine the infrared spectra of Diclofenac Sodium and diclofenac sodium RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) An aqueous solution of Diclofenac Sodium (1 in 100) to the Qualitative Analysis for sodium salt.

Purity (1) ***Clarity and color of solution***—Dissolve about 1.0 g of Diclofenac Sodium in 20 mL of methanol; the resulting solution exhibits a colorless to pale yellow color. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at the wavelength of 440 nm is NMT 0.050.

(2) ***Heavy metals***—Proceed with about 2.0 g of Diclofenac Sodium and perform the test according to Method 2. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Proceed with about 1.0 g of Diclofenac Sodium according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve about 50 mg of Diclofenac Sodium in 50 mL of the mobile phase, and use this solution as the test solution. Pipet 1.0 mL of this solution and add the mobile phase to make exactly 50 mL. Pipet5 mL of the test solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of each solution by the automatic integration method; the total area of the peaks other than diclofenac sodium obtained the test solution is NMT the peak area from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (7 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of methanol and diluted acetic acid(100) (3 in 2500) (4 : 3).

Flow rate: Adjust the flow rate so that the retention time of diclofenac is about 20 minutes.

System suitability

System performance: Dissolve 35 mg of ethylparaben and 50 mg of propyl p-hydroxybenzoate in 100 mL of the mobile phase and take 1 mL of this solution to make 50 mL. Proceed with 20 μL of this solution according to the above operating conditions, ethylparaben and propyl p-hydroxybenzoate are eluted in this order with the resolution between these peaks being NLT 5.

System repeatability: Perform the test six times with 20 μL of the standard solution according to the above operating conditions, the relative standard deviation of the peak area of diclofenac is NMT 2.0%

Time span of measurement: About 2 times of the retention time of diclofenac beginning after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 °C, 3 hours).

Assay Weigh accurately about 0.5 g of Diclofenac Sodium, previously dried, transfer to a separatory funnel, dissolve in 40 mL of water, and add 2 mL of dilute hydrochloric acid. Extract the precipitate with 50 mL of chloroform. Extract 2 times with 20 mL each of chloroform, and filter the extracts using a cotton wool wet with chloroform each time. Wash the end of the separatory funnel and the cotton wool with 15 mL of chloroform, add the washings to the extract, add 10 mL of 1 mol/L hydrochloric acid in ethanol(99.5) solution (1 in 100), and titrate with 0.1 mol/L potassium hydroxide and ethanol VS (99.5) from the equivalence point 1 to the equivalence point 2 (potentiometric titration under the Titrimetry).

Each mL of 0.1 mol/L potassium hydroxide VS
= 31.813 mg of $C_{14}H_{10}Cl_2NNaO_2$

Packaging and storage Preserve in tight containers.

Diclofenac Sodium Injection
디클로페낙나트륨 주사액

Diclofenac Sodium Injection contains NLT 95.0% and NMT 105.0% the labeled amount of diclofenac sodium ($C_{14}H_{10}Cl_2NNaO_2$: 318.13).

Method of preparation Prepare Diclofenac Sodium Injection as directed under Injections, with Diclofenac Sodium.

Identification Weigh an amount of Diclofenac Sodium Injection, equivalent to 50 mg of diclofenac sodium, add methanol to make 25 mL, and use this solution as the test solution. Separately, weigh 50 mg of diclofenac sodium RS, add methanol to make 25 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, methanol and acetic acid(100) (30 : 10 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f value and the color of the spots obtained from the test and the standard solutions are the same.

pH Between 8.0 and 9.0.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

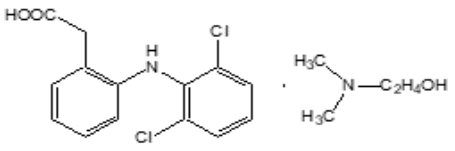
Extractable volume of injections Meets the requirements.

Assay Weigh accurately an amount of Diclofenac Sodium Injection, equivalent to 50 mg of diclofenac sodium ($C_{14}H_{10}Cl_2NNaO_2$), add 0.01 mol/L methanolic sodium hydroxide to make exactly 200 mL. Pipet 5 mL of this solution, add 0.01 mol/L methanolic sodium hydroxide to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of diclofenac sodium RS, add 0.01 mol/L methanolic sodium hydroxide to make exactly 200 mL. Pipet 5 mL of this solution, add 0.01 mol/L methanolic sodium hydroxide to make 100 mL, and use this solution as the standard Solution. With the test solution and the standard solution, perform the test as directed under the Ultraviolet-visible Spectroscopy, using 0.01 mol/L methanolic sodium hydroxide solution as the control solution, and determine the absorbances, A_T and A_S at a wavelength of 282 nm.

Amount (mg) of diclofenac sodium ($C_{14}H_{10}Cl_2NNaO_2$)
= Amount (mg) of diclofenac sodium RS × (A_T / A_S)

Packaging and storage Preserve in hermetic containers.

Diclofenac β-Dimethylaminoethanol
디클로페낙β-디메틸아미노에탄올



$C_{18}H_{22}Cl_2N_2O_3$: 385.28
2-[(2,6-Dichlorophenyl)amino]-benzeneacetic acid 2-dimethylaminoethanol salt, [*81811-14-5*]

Diclofenac β-Dimethylaminoethanol contains NLT 99.0% and NMT 101.0% of diclofenac β-dimethylaminoethanol when weighing with diclofenac ($C_{14}H_{11}Cl_2NO_2$: 296.15) and *β*-dimethylaminoethanol ($C_4H_{11}NO$: 89.14) (1 : 1), calculated on the anhydrous basis.

Description Diclofenac β-Dimethylaminoethanol occurs as a white crystalline powder and has a slight, characteristic odor.
It is very soluble in ethanol, methanol, chloroform and acetic acid(100), soluble in hot water, and practically insoluble in ether.
It is soluble in 0.1 mol/L sodium hydroxide and practically insoluble in 0.1 mol/L hydrochloric acid.

Identification (1) Determine the absorption spectra of Diclofenac β-Dimethylaminoethanol in ethanol solution (1 in 67000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelength of 282 nm.

(2) Determine the infrared spectra of Diclofenac β-Dimethylaminoethanol and diclofenac β-dimethylaminoethanol RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 119 and 127 ℃.

Purity (1) ***Heavy metals***—Add 3 mL of 2 mol/L hydrochloric acid in the residue of the ignition test, and dissolve by warming. Cool, add 2 mL of water, 5 mL of 2 mol/L ammonia water, and 2 drops of sodium sulfide TS; the resulting solution does not exhibit a change in color.

Sodium sulfide TS—Dissolve sodium sulfide in a mixture of glycerin and water (35 : 65) to make the concentration of the solution 6%.

(2) ***Related substances***—Dissolve about 0.5 g of Diclofenac β-Dimethylaminoethanol in 10 mL of ethanol and use this solution as the test solution. Separately, weigh accurately about 25 mg of diclofenac β-dimethylaminoethanol RS and add ethanol to make 100.0 mL. Take 5.0 mL of this solution, add ethanol to make 50.0 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of benzene, dioxane, and acetic acid(100) (90 : 25 : 4) to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (wavelength 254 nm, diclofenac), and soak in iodine steam (β-dimethylaminoethanol) saturation; the spots other than the principal spot is not more intense or larger than the major peak from the standard solution.

Water NMT 1.0% (0.2 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 200 mg of Diclofenac β-Dimethylaminoethanol, dissolve in 80 mL of acetic acid(100) for non-aqueous titration and 10 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 38.528 mg of $C_{18}H_{22}Cl_2N_2O_3$

Packaging and storage Preserve in tight containers.

Diclofenac β-Dimethylaminoethanol Injection
디클로페낙 β-디메틸아미노에탄올 주사액

Diclofenac β-Dimethylaminoethanol Injection contains NLT 95.0% and NMT 105.0% the labeled amount of diclofenac β-dimethylaminoethanol ($C_{18}H_{22}Cl_2N_2O_3$: 385.28).

Method of preparation Prepare as directed under Injections, with Diclofenac β-dimethylaminoethanol.

Identification Determine the absorption spectrum of the test solution in the Assay as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelength of about 282 nm.

pH Between 7.5 and 9.5.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

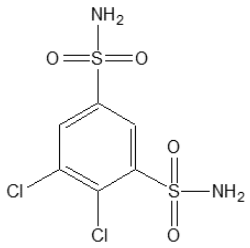
Extractable volume of injections Meets the requirements.

Assay Weigh accurately an amount of Diclofenac β-Dimethylaminoethanol Injection, equivalent to 0.15 g of diclofenac β-dimethylaminoethanol, and add ethanol(95) to make exactly 100 mL. Take 2 mL of this solution, add ethanol(95) to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.15 g of diclofenac β-dimethylaminoethanol, proceed in the same manner as in the test solution, and use this solution as the standard solution. Perform the test with the test solution and standard solution as directed under the Ultraviolet-visible Spectroscopy, using ethanol(95) as a control solution, and determine the absorbances, A_T and A_S at a wavelength of 282 nm.

Amount (mg) of Diclofenac *β*-dimethylaminoethanol ($C_{18}H_{22}Cl_2N_2O_3$)
= Amount (mg) of diclofenac *β*-dimethylaminoethanol RS × (A_T / A_S)

Packaging and storage Preserve in light-resistant, hermetic containers.

Diclofenamide
디클로페나미드



$C_6H_6Cl_2N_2O_4S_2$: 305.16
4,5-Dichlorobenzene-1,3-disulfonamide [*120-97-8*]

Diclofenamide, when dried, contains NLT 98.0% and NMT 101.0% of diclofenamide ($C_6H_6Cl_2N_2O_4S_2$).

Description Diclofenamide occurs as a white crystalline powder.
It is very soluble in *N*,*N*-dimethylformamide, soluble in ethanol(95), slightly soluble in ether, and very slightly soluble in water.
It dissolves in sodium hydroxide TS.

Identification (1) Dissolve 10 mg of Diclofenamide and diclofenamide RS in 100 mL of 0.01 mol/L sodium hydroxide TS. To 10 mL each of these solutions, add 0.1 mL of hydrochloric acid, and determine the absorption spectra as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Diclofenamide and diclofenamideRS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 237 and 240 ℃.

Purity (1) ***Chloride***—Dissolve about 0.10 g of Diclofenamide in 10 mL of *N*,*N*-Dimethylformamide and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.45 mL of 0.01 mol/L hydrochloric acid VS, 10 mL of *N*,*N*-Dimethylformamide, 6 mL of dilute nitric acid and water to make 50 mL (NMT 0.160%).

(2) ***Selenium***—Add 0.5 mL of a mixture of 0.5 mL of perchloric acid and sulfuric acid (1 : 1), 2 mL of nitric acid to about 0.10 g of Diclofenamide, and heat on a steam bath. When a brown gas is not produced and the solution becomes clear with a pale yellow color, cool the solution. Then, add 4 mL of nitric acid and water to make exactly 50 mL, and use this solution as the test solution. Separately, pipet 3 mL of selenium standard solution, add 0.5 mL of a mixture of perchloric acid and sulfuric acid (1 : 1), 6 mL of nitric acid and water to make exactly 50 mL, and use this solution as the standard solution. Perform the test with the standard and the test solution as directed under the Atomic Absorption Spectroscopy, and determine the absorbance A_T for the test solution and A_S for the standard solution when the reading of the display rapidly rises and, then, reaches a plateau; A_T is less than A_S (NMT 30 ppm). This test is performed using a hydride generator and a heating cell.

Lamp: Selenium hollow-cathode lamp
Wavelength: 196.0 nm
Atomizing temperature: When an electric furnace is used, the temperature is set at about 1000℃.
Carrier gas: Nitrogen or argon

(3) ***Heavy metals***—Proceed with about 2.0 g of Diclofenamide and perform the test according to Method 2. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Related substances***—Dissolve about 0.10 g of Diclofenamide in 50 mL of the mobile phase and use this solution as the test solution. Pipet 2 mL of the test solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of each solution by the automatic integration method; the total area of the peaks other than the peak of diclofenamide from the test solution is not greater than the peak area of diclofenamide from the standard solution.

Operating conditions
For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.
System suitability
For system performance, follow the system suitability under the Assay.
Test for required detectability: Pipet 5 mL of the standard solution and add water to make 100 mL. Confirm that the peak area of diclofenamide obtained with 10 μL of this solution is equivalent to NLT 3.5% and NMT 6.5% of the peak area of diclofenamide in the standard solution.
System repeatability: Perform the test six times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of diclofenamide is NMT 1.0%.
Time span of measurement: About 5 times the retention time of diclofenamide.

Loss on drying NMT 1.0% (1 g, NMT 0.67 kPa, 100 ℃, 5 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Dissolve about 50 mg each of Diclofenamide and diclofenamide RS, previously dried and accurately weighed, in 30 mL of the mobile phase, add exactly 10 mL each of the internal standard solution, and add the mobile phase to make 50 mL. Use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of the peak area of the internal standard to diclofenamide peak area.

$$\text{Amount (mg) of diclofenamide } (C_6H_6Cl_2N_2O_4S_2) = \text{Amount (mg) of diclofenamide} \times \frac{Q_T}{Q_S}$$

Internal Standard solution—A solution of butyl p-hydroxybenzoate in the mobile phase (3 in 5000).

Operating conditions
Detector: An ultraviolet absorption photometer (wavelength: 280 nm).
Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of sodium phosphate TS and acetonitrile (1 : 1).

Flow rate: Adjust the flow rate so that the retention time of diclofenamide is about 7 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; diclofenamide and internal standard are eluted in this order with the resolution between their peaks being NLT 9.

System repeatability: Perform the test six times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of diclofenamide is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Diclofenamide Tablets
디클로페나미드 정

Diclofenamide Tablets contain NLT 92.0% and NMT 108.0% of dichlorphenamide ($C_6H_6Cl_2N_2O_4S_2$: 305.16) of the labeled amount.

Method of preparation Diclofenamide Tablets are prepared as directed under Tablets, with Dichlorphenamide.

Identification Weigh an amount of Diclofenamide Tablets, previously powdered, equivalent to 0.2 g of dichlorphenamide according to the labeled amount, add 20 mL of methanol, shake to mix, and filter. Evaporate the filtrate on a steam bath to dryness and dissolve 10 mg of the residue in 100 mL of 0.01 mol/L sodium hydroxide TS. To 10 mL of this solution, add 0.1 mL of hydrochloric acid and determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 284 nm and 288 nm and 293 nm and 297 nm.

Dissolution Perform the test with 1 tablet of Diclofenamide Tablets at 50 revolutions per minute according to Method 2, using 900 mL of water as the dissolution medium. Take NLT 20 mL of the dissolved solution 60 minutes after starting the test and filter by a membrane filter with a pore size of not exceeding 0.8 μm. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add the dissolution solution to make exactly *V'* mL to obtain a solution having known concentration of 55 μg of diclofenamide per mL, and use this solution as the test solution. Separately, weigh accurately about 55 mg of diclofenamide RS, previously dried at a pressure not exceeding 0.67 kPa at 100 °C for 5 hours, dissolve in 10 mL of ethanol(95) and add water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at 285 nm as directed under the Ultraviolet-visible Spectroscopy.

It meets the requirements if the dissolution rate of Glimepiride Tablets in 60 minutes is NLT 70%.

Dissolution rate (%) with respect to the labeled amount of diclofenamide

$$= W_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 90$$

*W*s: Amount (mg) of dichlorphenamide RS

C: Labeled amount (mg) of dichlorphenamide ($C_6H_6Cl_2N_2O_4S_2$) in 1 tablet.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately NLT 20 tablets of Diclofenamide Tablets and powder. Weigh accurately an amount of Diclofenamide Tablets equivalent to about 50 mg of diclofenamide ($C_6H_6Cl_2N_2O_4S_2$), add exactly 25 mL of the mobile phase and shake for 15 minutes and centrifuge. Pipet 10.0 mL of the clear supernatant, add 4.0 mL of the internal standard solution and the mobile phase to make exactly 20 mL and use this solution as the test solution. Separately, weigh accurately about 50 mg of diclofenamide RS, previously dried at 100 °C at a pressure not exceeding 0.67 kPa for 5 hours, dissolve in 30 mL of the mobile phase, add 10.0 mL of the internal standard solution and the mobile phase to make exactly 50 mL and use this solution as the standard solution. Perform the test as directed under the Assay of Dichlorphenamide.

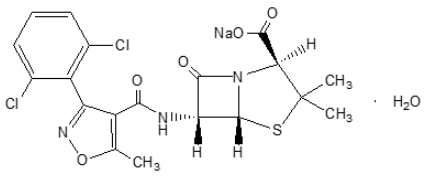
Amount (mg) of diclofenamide ($C_6H_6Cl_2N_2O_4S_2$)

$$= \text{Amount (mg) of diclofenamide} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of butyl p-hydroxybenzoate in the mobile phase (3 in 5000).

Packaging and storage Preserve in well-closed containers.

Dicloxacillin Sodium Hydrate
디클록사실린나트륨수화물



$C_{19}H_{16}Cl_2N_3NaO_5S \cdot H_2O$: 510.33

Sodium(2*S*,5*R*,6*R*)-6-[[3-(2,6-dichlorophenyl)-5-methyl-1,2-oxazole-4-carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-

carboxylate hydrate [*13412-64-1*]

Dicloxacillin Sodium Hydrate contains NLT 910 μg and NMT 1020 μg (potency) of dicloxacillin ($C_{19}H_{17}Cl_2N_3O_5S$: 470.33) per mg, calculated on the anhydrous basis.

Description Dicloxacillin Sodium Hydrate occurs as a white to pale yellow crystalline powder.
It is freely soluble in water and methanol, and soluble in ethanol(95).

Identification (1) Determine the absorption spectra of aqueous solutions of Dicloxacillin Sodium Hydrate and dicloxacillin sodium RS (1 in 2500) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelength.

(2) Determine the infrared spectra of Dicloxacillin Sodium Hydrate and dicloxacillin sodium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Dicloxacillin Sodium Hydrate responds to the Qualitative Analysis (1) for sodium salt.

Crystallinity Meets the requirements.

pH Dissolve 1.0 g of Dicloxacillin Sodium Hydrate in 10 mL of water; the pH of this solution is between 4.5 and 7.5.

Purity ***Dimethylaniline***—Weigh accurately about 1.0 g of Dicloxacillin Sodium Hydrate, add 5 mL of 1 mol/L sodium hydroxide TS and 1 mL of the internal standard solution, centrifuge, if necessary, and use the clear supernatant as the test solution. Separately, weigh accurately about 50 mg of dimethylaniline, add 2.0 mL of hydrochloric acid, and add water to make 50 mL. Pipet 5.0 mL of this solution and add water to make exactly 250 mL. Pipet 1.0 mL of this solution, add 5.0 mL of 1 mol/L sodium hydroxide TS and 1.0 mL of the internal standard solution, centrifuge, if necessary, and use the clear supernatant as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the ratios of the peak area, Q_T and Q_S, of dimethylaniline to that of the internal standard in the test solution and the standard solution, respectively (NMT 20 ppm).

$$\text{Content (ppm) of dimethylaniline} = \text{Amount (mg) of dimethylaniline taken} \times \frac{Q_T}{Q_S} \times \frac{\text{Purity (\%) of dimethylaniline}}{\text{Amount (mg) of Dicloxacillin Sodium Hydrate}} \times 4$$

Internal standard solution—Dissolve 50.0 mg of naphthalene in cyclohexane to make 50 mL. Take 5.0 mL of this solution, add cyclohexane to make 100 mL, and use this solution as the internal standard solution.

Operating conditions

Detector: A flame ionization detector

Column: A column about 2 mm in internal diameter and about 2 m in length, packed with diatomaceous earth for gas chromatography, which is coated with 50% phenyl-50% methylpolysiloxane for gas chromatography equivalent to 3% of the mass of the diatomaceous earth for gas chromatography.

Column temperature: 120 °C

Temperatures of the sample injection port and the detector: 150 °C

Carrier gas: Nitrogen

Flow rate: 30 mL/min

Water Between 3.0% and 4.5% (0.1 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing process of sterile preparations.

Pyrogen It meets the requirements when used in the manufacturing of sterile preparations. Weigh an appropriate amount of Dicloxacillin Sodium Hydrate, dissolve in isotonic sodium chloride injection to prepare a solution containing 20 mg (potency) per mL, and use this solution as the test solution. However, the test solution injected to a rabbit should be 1.0 mL per kg of the rabbit weight.

Assay Weigh accurately about 230 mg (potency) each of Dicloxacillin Sodium Hydraten and dicloxacillin sodium RS, dissolve each in 0.1% phosphate buffer solution (pH 5.0), and add water to make exactly 200 mL. Use this solution as the test solution. Use these solutions promptly after preparation. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S of dicloxacillin sodium from each solution, respectively.

$$\text{Potency (μg) of dicloxacillin } (C_{19}H_{16}Cl_2N_3NaO_5S) = \text{Potency (μg) of dicloxacillin sodium RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless-steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of 0.02 mol/L potassium dihydrogen phosphate buffer solution and acetonitrile (65 : 35).

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above operating conditions; the number of theoretical plates is NLT 700 and the symmetry factor is NMT 2.0.

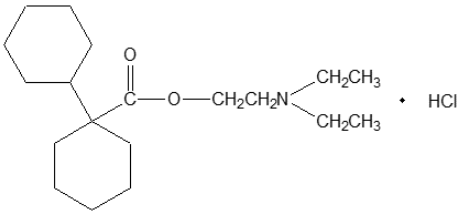
System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of dicloxacillin is NMT 2.0%.

1% phosphate buffer solution (pH 5.0)—Dissolve 5.444 g of potassium dihydrogen phosphate in water to make 2000 mL, and add phosphoric acid to adjust the pH to 5.0.

0.20 mol/L potassium dihydrogen phosphate buffer solution—Dissolve 2.7 g of potassium dihydrogen phosphate to make 1000 mL, and add phosphoric acid to adjust the pH to 5.0.

Packaging and storage Preserve in tight containers.

Dicyclomine Hydrochloride
디시클로민염산염



$C_{19}H_{35}NO_2 \cdot HCl$: 345.95

2-(Diethylamino)ethyl-1-cyclohexylcyclohexane-1-carboxylate hydrochloride [*67-92-5*]

Dicyclomine Hydrochloride contains NLT 99.0% and NMT 102.0% of dicyclomine hydrochloride ($C_{19}H_{35}NO_2 \cdot HCl$), calculated on an anhydrous basis.

Description Dicyclomine Hydrochloride occurs as a white fine crystalline powder, which is odorless and has a bitter taste.

It is soluble in water, freely soluble in ethanol(95) or chloroform, and very slightly soluble in ether.

Identification (1) To 5 mL of an aqueous solution of Dicyclomine Hydrochloride (1 in 500), add 2 mL of 2 mol/L nitric acid, mix, and 2 mL of silver nitrate TS; a white precipitate is formed. The precipitate does not dissolve in nitric acid and dissolves in an excessive amount of ammonia TS.

(2) Determine the infrared spectra of Dicyclomine Hydrochloride and dicyclomine hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 169 and 174 ℃.

pH Dissolve 1.0 g of Dyclomine Hydrochloride in 100 mL of water; the pH of this solution is between 5.0 and 5.5.

Purity ***Readily carbonizable substances***—Proceed with 0.5 g of Dicyclomine Hydrochloride and perform the test. The color of the solution is not more intense than that of the matching fluids for D.

Loss on drying NMT 1.0% (1 g, 105 ℃, 4 hours).

Assay Weigh accurately about 40 mg of Dicyclomine Hydrochloride, add dilute solution to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of dicyclomine hydrochloride RS, add dilute solution to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of dicyclomine dydrochloride A_T and A_S.

Amount (mg) of dyclomine hydrochloride ($C_{19}H_{35}NO_2 \cdot HCl$)
= Amount (mg) of dyclomine hydrochloride RS
× (A_T / A_S) × 4

Diluent—A mixture of acetonitrile and water (7 : 3).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless-steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octylsilane silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and potassium dihydrogen phosphate buffer solution, pH 7.5 (70 : 30).

Potassium dihydrogen phosphate buffer solution, pH 7.5—Dissolve 2.72 g of potassium dihydrogen phosphate in 900 mL of water, adjust pH to 7.5 by adding sodium hydroxide (1 in 10), and then add water to make 1000 mL.

Flow rate: 1 mL/min

System suitability

System performance: Proceed with 50 μL of the standard solution according to the above conditions; the symmetry factor of the dicyclomine hydrochloride peak is NMT 2.0.

System repeatability: Perform the test six times with 50 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of dicyclomine hydrochloride is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Dicyclomine Hydrochloride and Papaverine Hydrochloride Tablets
디시클로민염산염·파파베린염산염 정

Dicyclomine Hydrochloride and Papaverine Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of dicyclomine hydrochloride ($C_{19}H_{35}NO_2$·HCl : 345.95) and papaverine hydrochloride ($C_{20}H_{21}NO_4$·HCl : 375.85).

Method of preparation Prepare as directed under Tablets, with Dicyclomine Hydrochloride and Papaverine Hydrochloride.

Identification The retention times of the major peaks of dicyclomine hydrochloride and papaverine hydrochloride, and the ultraviolet absorption spectrum between 190 and 300 nm obtained from the test solution and the standard solution under the Assay are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Dicyclomine Hydrochloride and Papaverine Hydrochloride Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 10 mg of dicyclomine hydrochloride ($C_{19}H_{35}NO_2$·HCl) and 30 mg of papaverine hydrochloride ($C_{20}H_{21}NO_4$·HCl), and add 50% methanol to make 100 mL. Sonicate this solution for 20 minutes, filter through a membrane filter with a pore size of NMT 0.45 μm, discard the first 2 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately about 10 mg of dicyclomine hydrochloride RS and about 30 mg of papaverine hydrochloride RS respectively, add 50% methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_{T1}, A_{S1}, A_{T2} and A_{S2} of dicyclomine hydrochloride and papaverine hydrochloride from each solution.

Amount (mg) of dicyclomine hydrochloride ($C_{19}H_{35}NO_2$·HCl)
= Amount (mg) of dicyclomine hydrochloride RS × $\frac{A_{T1}}{A_{S1}}$

Amount (mg) of papaverine hydrochloride ($C_{20}H_{21}NO_4$·HCl)
= Amount (mg) of papaverine hydrochloride RS × $\frac{A_{T2}}{A_{S2}}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm). However, a photo-diode array detector (190 nm - 300 nm) is used when the Identification is performed.

Column: A stainless-steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Use mobile phases A and B to control a stepwise or gradient elution-wise as follows.

Mobile phase A: Dissolve 1.74 g of potassium monohydrogen phosphate in 900 mL of water, adjust the pH to 7.2 ± 0.1 with phosphoric acid, and add water to make 1000 mL. To 300 mL of this solution, add 700 mL of methanol.

Mobile phase B: Methanol

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 1	100	0
1 - 5	100 → 5	0 → 95
5 - 10	5	95

Flow rate: 1.0 mL/min

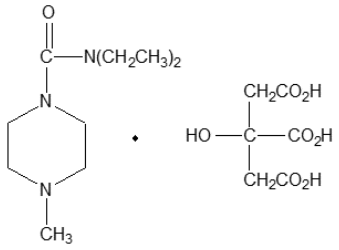
System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; papaverine hydrochloride and dicyclomine hydrochloride are eluted in this order with the resolution between these peaks being NLT 31.0.

System repeatability: Repeat the test 6 times with each 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak areas of papaverine hydrochloride and dicyclomine hydrochloride is NMT 1.0%

Packaging and storage Preserve in well-closed containers.

Diethylcarbamazine Citrate
디에틸카르바마진시트르산염



$C_{10}H_{21}N_3O \cdot C_6H_8O_7$: 391.42

N,*N*-Diethyl-4-methylpiperazine-1-carboxamide; 2-hydroxypropane-1,2,3-tricarboxylic acid [*1642-54-2*]

Diethylcarbamazine Citrate, when dried, contains NLT 98.0% and NMT 101.0% of diethylcarbamazine citrate ($C_{10}H_{21}N_3O \cdot C_6H_8O_7$).

Description Diethylcarbamazine Citrate occurs as a white crystalline powder, which is odorless and has an acid and bitter taste.
It is very soluble in water, freely soluble in ethanol(95) and practically insoluble in acetone, chloroform and ether.
An aqueous solution of Diethylcarbamazine Citrate (1 in 20) is acidic.
It is hygroscopic.

Identification (1) Dissolve about 0.5 g of Diethylcarbamazine Citrate in 2 mL pf water, add 10 mL of sodium hydroxide TS, and extract 4 times with 5 mL of chloroform. Combine all the chloroform extracts, wash with 10 mL of water, evaporate the chloroform on a steam bath, and add 1 mL of ethyl iodide in the residue. Boil gently under a reflux condenser for 5 minutes. Evaporate excess ethyl iodide in a current of air, add 4 mL of ethanol(95), and cool in an ice water. Add ether while stirring until precipitate forms, and stir to mix until the precipitate becomes crystals. Allow to stand in iced water for 30 minutes, filter the crystals, dissolve the filtrate in 4 mL of ethanol(95), and repeat the same procedure. Recrystalize, dry at 105 ℃ for 4 hours; the melting point is between 151 and 155 ℃.

(2) Put dilute hydrochloric acid into the remaining solution, extracted with chloroform of (1), and neutralize the solution; the resulting solution responds to the Qualitative Analysis (2) and (3) for citrate.

Melting point Between 135.5 and 138.5 ℃.

Purity (1) ***Heavy metals***—Proceed with about 2.0 g of Diethylcarbamazine Citrate according to Method 4 and perform the test. Prepare the control solution with 4.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Weigh exactly 300 mg of Diethylcarbamazine Citrate, add 100 mL of phosphate buffer solution, mix, and filter or centrifuge. Use this solution as the test solution. Separately, weigh accurately an appropriate amount of diethylcarbamazine citrate RS, dissolve in phosphate buffer solution so that 1 mL of the solution contains about 3 μg of Diethylcarbamazine Citrate, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution according to the following conditions as directed under the Liquid Chromatography. Measure each peak area A_i other than the major peak obtained from the test solution and the peak area A_S of diethylcarbamazine from the standard solution, and calculate the amount of each related substances in the test solution according to the following formula; it is NMT 0.1%.

$$\text{Content (\%) of each related substance} = 10000 \times \frac{C}{W} \times \frac{A_i}{A_S}$$

C: Concentration (mg/mL) of diethylcarbamazine citrate in the standard solution.
W: Amount (mg) of Diethylcarbamazine Citrate.

Phosphate buffer solution—Dissolve 31.24 g of potassium dihydrogen phosphate in 1000 mL of water.

Operating conditions
Detector: An ultraviolet absorption photometer (wavelength: 220 nm).
Column: A stainless steel column about 3.9 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).
Mobile phase: A mixture of 1% potassium dihydrogen phosphate aqueous solution and methanol (900 : 100).
Flow rate: 0.8 mL/min
System suitability
System repeatability: Perform the test six times with 20 μL of the standard solution according to the above operating conditions; the relative standard deviation of the major peak area is NMT 2.0%.

Loss on drying NMT 1.0% (2 g, 105 °C, 4 hours).

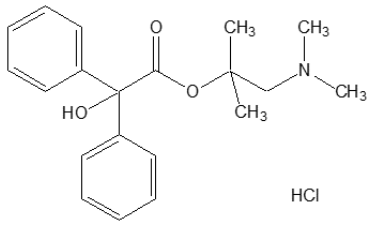
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.75 g of Diethylcarbamazine Citrate, dissolve in 50 mL of acetic acid(100), and dissolve by warming. Cool it down and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry) Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 39.142 mg of $C_{10}H_{21}N_3O \cdot C_6H_8O_7$

Packaging and storage Preserve in tight containers.

Difemerine Hydrochloride
디페메린염산염



$C_{20}H_{25}NO_3 \cdot HCl$: 363.88

α-Hydroxy-α-phenylbenzeneacetic acid 2-(dimethylamino)-2-methyl propyl ester hydrochloride, [*70280-88-5*]

Difemerine Hydrochloride, when dried, contains NLT 98.0% and NMT 102.0% of difemerine hydrochloride ($C_{20}H_{25}NO_3 \cdot HCl$: 363.88).

Description Difemerine Hydrochloride occurs as a white, crystalline powder. It is odorless and has a slightly bitter taste.

It is freely soluble in water, ethanol or chloroform, and sparingly soluble in isopropanol.

The pH of an aqueous solution of Difemerine Hydrochloride (5 in 100) is between 4.0 and 5.0.

Identification (1) Put a small portion of Difemerine Hydrochloride on the watch glass and add 1 mL of sulfuric acid; the red color appears.

(2) Add 0.5 mL of dilute nitric acid and 1 mL of silver nitrate TS to 2 mL of an aqueous solution of Difemerine Hydrochloride (5 in 100); white precipitates are formed, which are soluble in an excessive amount of ammonium hydroxide TS.

(3) Dissolve 0.5 g of Difemerine Hydrochloride in a mixture of methanol and diethylamine (100 : 0.2) to make 100 mL and use this solution as the test solution. Dissolve 0.5 g of Difemerine Hydrochloride RS in a mixture of methanol and diethylamine (100 : 2) to make 100 mL and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol and diethylamine (100 : 0.2) and air-dry the plate. Spray a mixture of a solution prepared by dissolving 0.85 g of bismuth nitrate in 40 mL of water and 10 mL of acetic acid(100) and a solution prepared by dissolving 8.0 g of potassium iodide in 20 mL of water (1 : 1) on the plate; the *Rf* value and color of spots obtained from the test solution and the standard solution are the same.

(4) Determine the infrared spectra of Difemerine Hydrochloride and Difemerine Hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

Purity (1) ***Clarity and color of solution***—Dissolve 2.5 g of Difemerine Hydrochloride in 50 mL of water; the solution is colorless and clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Difemerine Hydrochloride as directed under Method 1 of the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Benzilic acid***—Weigh accurately about 0.75 g of Difemerine Hydrochloride and dissolve by adding water to make 50.0 mL. Put 10.0 mL of this solution into a 20-mL volumetric flask, add 2.0 mL of 1.085% iron(III) chloride TS, and shake to mix. Add water to make 20 mL, and use this solution as the test solution. Separately, weigh accurately about 0.25 g of benzilic acid ($C_{14}H_{12}O_3$) RS, dissolve by adding 25 mL of ethanol, and put water to make 100.0 mL. Take 2.0 mL of this solution into a 20-mL volumetric flask, add 2.0 mL of 1.085% iron(III) chloride TS, and shake to mix. Add water to make 20 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using a solution prepared by adding water to 2.0 mL of 1.085% iron(III) chloride TS to make 20.0 mL as the control solution, and determine the absorbances A_T and A_S at 376 nm wavelength. The content of benzilic acid in Difemerine Hydrochloride is NMT 0.5%.

(4) ***Isodifemerine hydrochloride***—Weigh accurately about 0.50 g of Difemerine Hydrochloride, dissolve in chloroform to make 5.0 mL, and use this solution as the test solution. Separately, weigh accurately about 0.50 g of Isodifemerine hydrochloride RS and dissolve by adding chloroform to make 100.0 mL. Take 10.0 mL of this solution, add chloroform to make 250.0 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak height from the chromatograms of the test solution (retention time: about 0.5 minutes) and the standard solution (retention time: about 2.5 minutes), respectively. The content of isodifemerine hydrochloride in Difemerine Hydrochloride is NMT 1.0%.

Operating conditions

Detector: A differential refractometer

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with porous silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of hexane, butanol, and triethylamine (87.5 : 12.5 : 0.2).

Flow rate: 2 mL/min

Loss on drying NMT 1.0% (1 g, 105 ℃ constant mass).

Assay Weigh accurately about 0.2 g of Difemerine Hy-

drochloride, previously dried, and dissolve by adding 30 mL of acetic acid(100) and 20 mL of acetic anhydride. Titrate with 0.1 mol/L perchloric acid VS (potentiometric titration in the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each of 0.1 mol/L perchloric acid
= 36.388 mg of $C_{20}H_{25}NO_3 \cdot HCl$

Packaging and storage Preserve in tight containers.

Difemerine Hydrochloride Capsules
디페메린염산염 캡슐

Difemerine Hydrochloride Capsules contain NLT 95.0% and NMT 105.0% the labeled amount of difemerine hydrochloride ($C_{20}H_{25}NO_3O6$ HCl : 363.88).

Method of preparation Prepared as directed under Capsules, with Difemerine Hydrochloride.

Identification (1) Put a small amount of Difemerine Hydrochloride Capsules on the watch glass and add 1 mL of sulfuric acid; the solution exhibits a red color.

(2) Add a small amount of Difemerine Hydrochloride Capsules in 5 mL of water, shake to mix, and filter. Take 2 mL of the filtrate in a test tube, add 0.5 mL of dilute nitric acid and 1 mL of silver nitrate TS; a white precipitate is formed and the precipitate dissolves in excess ammonia water.

(3) Weigh an amount of Difemerine Hydrochloride Capsules equivalent to 5 mg of difemerine hydrochloride, dissolve in the developing solvent, filter, and use the filtrate as the test solution. Separately, dissolve 0.5 g of difemerine hydrochloride RS in a mixture of methanol and diethylamine (100 : 2) to make 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot these solutions on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol and ethylamine (100 : 0.2) as the developing solvent and air-dry the plate. Spray a mixture of a solution prepared by dissolving 0.85 g of bismuth nitrate in 40 mL of water and 10 mL of acetic acid(100) and a solution prepared by dissolving 8.0 g of potassium iodide in 20 mL of water (1 : 1) on the plate; the R_f values and colors of spots obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 capsules of Difemerine Hydrochloride Capsules and shake well to mix. Weigh accurately an amount equivalent to 25 mg of difemerine hydrochloride ($C_{20}H_{25}NO_3 \cdot HCl$), add 50 mL of 50% methanol, and use this solution as the test solution. Separately, weigh accurately about 25 mg of difemerine hydrochloride, add 50% methanol to make 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of difemerine hydrochloride from each solution, A_T and A_S, respectively.

Amount (mg) of difemerine hydrochloride ($C_{20}H_{25}NO_3 \cdot HCl$)
$= \text{Amount (mg) of difemerine hydrochloride RS} \times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column, about 4.0 μm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography.

Mobile phase: A mixture of water, methanol and acetic acid (50 : 50 : 1).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Difemerine Hydrochloride Injection
디페메린염산염 주사액

Difemerine Hydrochloride Injection contains NLT 95.0% and NMT 105.0% the labeled amount of difemerine hydrochloride ($C_{20}H_{25}NO_3 \cdot HCl$: 363.88).

Method of preparation Prepare Difemerine Hydrochloride Injection as directed under Injections, with Difemerine Hydrochloride.

Description Difemerine Hydrochloride Injection occurs as a clear, colorless liquid.

Identification (1) Put 2 to 3 spots of Difemerine Hydrochloride Injection on a watch glass and add 1 mL of sulfuric acid; the resulting solution exhibits a red color.

(2) Add 0.5 mL of dilute nitric acid and 1 mL of silver nitrate TS to 2 mL of Difemerine Hydrochloride Injection; precipitates are formed, which are soluble in an excessive amount of ammonium hydroxide TS.

(3) Weigh an amount equivalent to about 0.5 g of difemerine hydrochloride according to the labeled amount, add a mixture of methanol and diethylamine (100 : 0.2) to make 100 mL, and use this solution as the test solution. Dissolve 0.5 g of difemerine hydrochloride RS in a mixture of methanol and diethylamine (100 : 0.2) to make 100 mL, and use this solution as the standard

solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol and diethylamine (100 : 0.2) as the developing solvent and air-dry the plate. Spray a mixture of a solution prepared by dissolving 0.85 g of bismuth nitrate in 40 mL of water and 10 mL of acetic acid(100) and a solution prepared by dissolving 8.0 g of potassium iodide in 20 mL of water (1 : 1) on the plate; the R_f value and color of spots obtained from the test solution and the standard solution are the same.

pH Between 3.2 and 5.2.

Sterility Meets the requirements.

Bacterial endotoxins Less than 150 EU per mg of difemerine hydrochloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

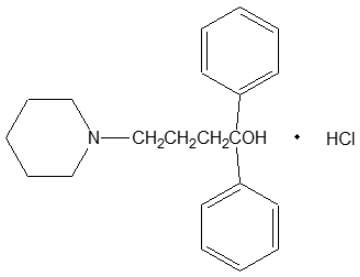
Extractable volume of injections Meets the requirements.

Assay Weigh accurately an amount equivalent to 10 mg of difemerine hydrochloride ($C_{20}H_{25}NO_3$·HCl) according to the labeled amount, transfer to a 25-mL volumetric flask, add water to make 25 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of difemerine hydrochloride RS, add water to make 25 mL, and use this solution as the standard solution. Determine the absorbance of the test solution and the standard solution, A_T and A_S at 258 nm using water as a control solution as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of difemerine hydrochloride } (C_{20}H_{25}NO_3\cdot HCl) = \text{Amount (mg) of difemerine hydrochloride RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in hermetic containers.

Difenidol Hydrochloride
디페니돌염산염



$C_{21}H_{27}NO$·HCl: 345.91

1,1-Diphenyl-4-piperidin-1-ylbutan-1-ol hydrochloride [*3254-89-5*]

Difenidol Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of difenidol hydrochloride ($C_{21}H_{27}NO$·HCl).

Description Difenidol Hydrochloride occurs as white crystals or a crystalline powder. It is odorless.
It is freely soluble in methanol, soluble in ethanol acid (95), sparingly soluble in water or acetic anhydride and practically insoluble in ether.

Melting point—About 217 °C (with decomposition).

Identification (1) Dissolve 10 mg of Difenidol Hydrochloride in 1 mL of sulfuric acid; the resulting solution exhibits an orange color. Add carefully 3 drops of water to this solution; the solution appears a yellowish brown color. Add 10 mL again; the solution appears as colorless.

(2) Add 2 mL of reinecke salt TS to 5 mL of an aqueous solution of Difenidol Hydrochloride (1 in 100); a pale red precipitate develops.

(3) Add 2 mL of sodium hydroxide TS to 10 mL of an aqueous solution of Difenidol Hydrochloride (1 in 100), and extract twice with 15 mL of chloroform. Combine the extracted solutions, wash three times with 10 mL each of water, evaporate chloroform on a steam bath, and dry the residue in a desiccator (in vacuum, silica gel, 55 ℃) for 5 hours; the melting point is between 103 and 106 ℃.

(4) An aqueous solution of Difenidol Hydrochloride (1 in 100) responds to the Qualitative Analysis for chloride.

pH Dissolve 1.0 g of Difenidol Hydrochloride in 100 mL of freshly boiled and cooled water; the pH of this solution is between 4.7 and 6.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Difenidol Hydrochloride in 10 mL of methanol; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Difenidol Hydrochloride as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 2.0 g of Difenidol Hydrochloride as directed under Method 3 and perform the test (NMT 1 ppm).

(4) ***Related substances***—Weigh 0.10 g of Difenidol Hydrochloride, dissolve in methanol to make exactly 10 mL, and use this solution as the test solution. Separately, weigh 10 mg of 1.1-diphenyl-4-piperidino-1-butene hydrochloride RS, dissolve in methanol to make exactly 20 mL. Pipet 1 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (fluorescent indicator added). Next, develop the plate with a mixture of toluene, methanol and acetic acid(100) (10 : 10 : 1) to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, silica gel, 5 hours).

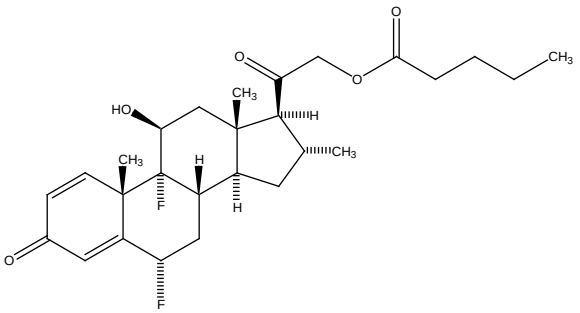
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.35 g of Difenidol Hydrochloride, previously dried, add 30 mL of acetic acid(100), and dissolve by warming, if necessary. After cooling, add 30 mL of acetic anhydride and titrate with 0.05 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L perchloric acid VS
= 17.295 mg of $C_{21}H_{27}NO \cdot HCl$

Packaging and storage Preserve in well-closed containers.

Diflucortolone Valerate
디플루코르톨론발레레이트



$C_{27}H_{36}F_2O_5$: 478.57

[2-[(6*S*,8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*R*,17*S*)-6,9-Difluoro-11-hydroxy-10,13,16-trimethyl-3-oxo-7,8,11,12,14,15,16,17-octahydro-6*H*-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl]pentanoate [*59198-70-8*]

Diflucortolone Valerate contains NLT 97.0% and NMT 102.0% of diflucortolone valerate ($C_{27}H_{36}F_2O_5$), calculated on the dried basis.

Description Diflucortolone Valerate occurs as a white crystalline powder.
It is freely soluble in dichloromethane or 1,4-dioxane, sparingly soluble in ether, slightly soluble in methanol and practically insoluble in water.

Identification (1) Determine the absorption spectra of solutions of Diflucortolone Valerate and Diflucortolone Valerate RS in methanol (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Optical rotation $[\alpha]_D^{20}$: Between +110° and +115° (0.1 g, calculated on the dried basis, ethanol(95), 10 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Diflucortolone Valerate according to Method 2 under the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Perform the test with 10 μL of the test solution obtained from the Assay as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of the test solution as directed in the automatic integration method and calculate the amount of each peak according to the percentage peak area method; the amount of each peak of flucortolone valerate, 12α-diflucortolone valerate, and ⊿4-diflucortolone valerate is NMT 0.6%, and the amount of clocortolone valerate is NMT 0.3%. The amount of other individual related substances is NMT 0.1%, and the sum of the amounts of related substances other than diflucortolone valerate is NMT 2.0%.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed under the operating conditions in the Assay.

System suitability

System performance and system repeatability: Proceed as directed under the system suitability in the Assay.

Test for required detectability: Pipet 1.0 mL of the test solution, add a mixture of water and acetonitrile (1 : 1) to make exactly 10 mL, and use this solution as the system suitability solution. Pipet 1 mL of the system suitability solution and add a mixture of water and acetonitrile (1 : 1) to make exactly 20 mL. Confirm that the peak area of diflucortolone valerate obtained from 10 μL of this solution is equivalent to between 3.5% and 6.5% of the peak area of diflucortolone valerate from the system suitability solution.

Relative retention time: The relative retention

time of flucortolone valerate, 12α-diflucortolone valerate, ⊿4-diflucortolone valerate, and clocortolone valerate for the diflucortolone valerate peak is about 0.97, 1.03, 1.05, and 1.09, respectively.

Time span of measurement: About 1.4 times the retention time of diflucortolone valerate after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 ℃, constant mass).

Residue on ignition NMT 0.1% (1 g, platinum crucible).

Assay Weigh accurately about 5 mg each of Diflucortolone Valerate and diflucortolone valerate RS (previously measure the loss on drying in the same manner as Diflucortolone Valerate), dissolve by adding a mixture of water and acetonitrile (1 : 1) to make exactly 10 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test as directed under the Liquid Chromatography according to the following conditions and calculate the peak areas of A_T and A_S of diflucortolone valerate from each solution.

$$\text{Amount (mg) of diflucortolone valerate } (C_{27}H_{36}F_2O_5) = W_S \times \frac{A_T}{A_S}$$

W_S: Amount (mg) of diflucortolone valerate RS taken, calculated on the dried basis.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 238 nm).

Column: A stainless steel column, 4.6 mm in internal diameter and 25 cm in length, packed with hexyl silyl silica gel for liquid chromatography bound to sulfonamides (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Control the gradient elution by modifying the mixing ratio of mobile phases A and B as follows.

Mobile phase A: A mixture of 0.02 mol/L potassium dihydrogen phosphate TS, adjusted pH to 3.0 with phosphoric acid, and acetonitrile (11:9).

Mobile phase B: Acetonitrile

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
Between 0 and 10	100 → 90	0 → 10
Between 10 and 25	90	10
Between 25 and 45	90 → 35	10 → 65
Between 45 and 50	35	65

Flow rate: 1.0 mL/min

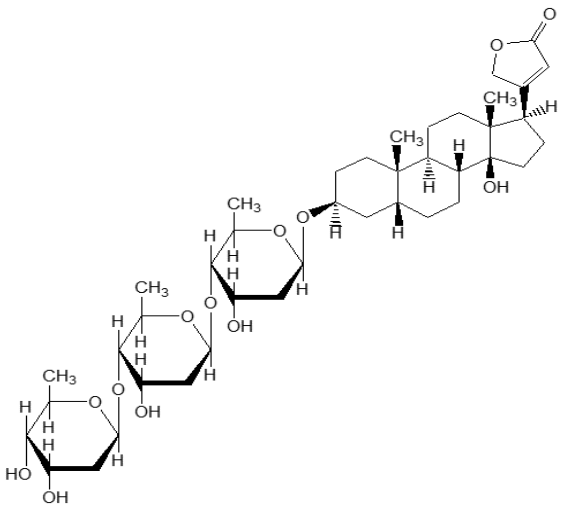
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the number of theoretical plates of diflucortolone valerate is NLT 10000 and the symmetry factor is NMT 1.5.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of diflucortolone valerate is NMT 1.0%.

Packaging and storage Preserve in light-resistant, well-closed containers.

Digitoxin
디기톡신



$C_{41}H_{64}O_{13}$: 764.94

4-[(3*S*,5*R*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-3-[(2*S*,4*S*,5*R*,6*R*)-5-[(2*S*,4*S*,5*R*,6*R*)-5-[(2*S*,4*S*,5*R*,6*R*)-4,5-Dihydroxy-6-methyl-oxan-2-yl]oxy-4-hydroxy-6-methyl-oxan-2-yl]oxy-4-hydroxy-6-methyl-oxan-2-yl]oxy-14-hydroxy-10,13-dimethyl-1,2,3,4,5,6,7,8,9,11,12,15,16,17-tetradecahydrocyclopenta[a]phenanthren-17-yl]-5*H*-furan-2-one [*71-63-6*]

Digitoxin, when dried, contains NLT 90.0% and NMT 101.0% of digoxin ($C_{41}H_{64}O_{13}$).

Description Digitoxin occurs as a white to pale yellow crystalline powder and is odorless.
It is soluble in chloroform, sparingly soluble in methanol or ethanol(95) and practically insoluble in water or ether.

Identification (1) Transfer 1 mg of Digitoxin to a small test tube, about 10 mm in internal diameter, dissolve in 1 mL of a solution of iron(III) chloride hexahydrate in acetic acid(100) (1 in 10000), and underlay gently with 1 mL of sulfuric acid; at the boundary layer of the two liquids, a brown ring free from a reddish color is observed, and the color of the upper layer near the contact zone changes

to purple, and then to green. Finally, the color of the entire acetic acid layer turns dark blue, and then to green.

(2) To 2 mg of Digitoxin, add 25 mL of a freshly prepared solution of *m*-dinitrobenzene in ethanol(95) (1 → 100) and shake to dissolve. Take 2 mL of this solution, add 2 mL of a solution of Tetramethylammonium hydroxide in ethanol(95) (1 in 200), and shake to dissolve; this solution slowly turns reddish purple, and then becomes colorless.

(3) Dissolve 1 mg each of Digitoxin and digitoxin RS in a mixture of ethanol(95) and chloroform (1 : 1), and use these solutions as the test solution and the standard solution, respectively. Perform the test with these solutions as directed under the Thin-layer chromatography. Spot 20 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate using a mixture of dichloromethane, methanol and water (84 : 15 : 1) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Spray dilute sulfuric acid evenly on the plate, and heat it at 110 ℃ for 10 minutes; the R_f values of the spots obtained from the test and standard solutions are the same.

Specific optical rotation $[\alpha]_D^{20}$: Between +16° and +18° (after drying 0.5 g, chloroform, 20 mL, 200 mm).

Purity ***Digitonin***—Weigh 10 mg of Digitoxin and transfer it into a flawless test tube, dissolve it in 2 mL of a solution of cholesterol in ethanol(95) (1 in 200), mix gently, and allow it to stand for 10 minutes; the solution does not become cloudy.

Loss on drying NMT 1.5% (0.5 g, in vacuum, 100 ℃, 2 hours).

Ignition residue NMT 0.5% (0.1 g).

Assay Weigh accurately about 20 mg each of Digitoxin and digitoxin RS, previously dried, and dissolve in methanol to make exactly 200 mL. Pipet 5 mL each of these solutions, add exactly 10 ml of the internal standard solution to each, add 12.5 mL of water, add methanol to make 50 mL, and use these solutions as the test solution and the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak area of digitoxin to that of the internal standard, Q_T and Q_S.

$$\text{Amount (mg) digitoxin } (C_{41}H_{64}O_{13}) = \text{Amount (mg) of digitoxin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of acenaphthene in methanol (3 in 1000000).

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 230 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm to 20 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

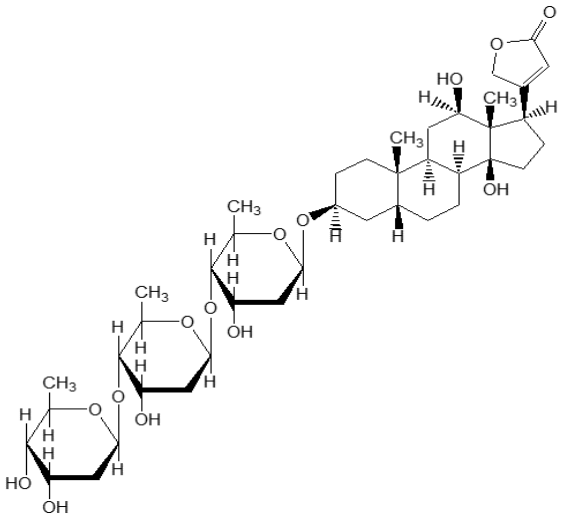
Mobile phase: A mixture of methanol and water (3 : 1).

Flow rate: Adjust the flow rate so that the retention time of digitoxin is about 5 minutes.

Selection of column: Proceed with 50 μL of the standard solution under the above operating conditions. At this time, use a column from which digitoxin and the internal standard are eluted in this order with the resolution between these peaks being NLT 6.

Packaging and storage Preserve in light-resistant, tight containers.

Digoxin
디곡신



$C_{41}H_{64}O_{14}$: 780.94

4-[(3*S*,5*R*,8*R*,9*S*,10*S*,12*R*,13*S*,14*S*,17*S*)-3-[(2*S*,4*S*,5*R*,6*R*)-5-[(2*S*,4*S*,5*R*,6*R*)-5-[(2*S*,4*S*,5*R*,6*R*)-4,5-Dihydroxy-6-methyl-oxan-2-yl]oxy-4-hydroxy-6-methyl-oxan-2-yl]oxy-4-hydroxy-6-methyl-oxan-2-yl]oxy-12,14-dihydroxy-10,13-dimethyl-1,2,3,4,5,6,7,8,9,11,12,15,16,17-tetradecahydrocyclopenta[a]phenanthren-17-yl]-5*H*-furan-2-one [*20830-75-5*]

Digoxin, when dried, contains NLT 96.0% and NMT 106.0% of digoxin ($C_{41}H_{64}O_{14}$).

Description Digoxin occurs as colorless to white crystals or a white, crystalline powder.

It is freely soluble in pyridine, slightly soluble in ethanol(95), very slightly soluble in acetic acid(100), and practically insoluble in water.

Identification (1) Transfer 1 mg of Digoxin to a small test tube, about 10 mm in internal diameter, dissolve in 1 mL of a solution of iron(III) chloride hexahydrate in acetic acid(100) (1 in 10000), and underlay gently with 1 mL of sulfuric acid; at the boundary layer of the two liquids, a brown ring free from a reddish color is observed, and the color of the upper layer near the contact zone changes to purple, and then to green. Finally, the color of the entire acetic acid layer turns dark blue, and then to green.

(2) Determine the infrared spectra of Digoxin and digoxin RS, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between + 10.0° and + 13.0° (after drying 0.2 g, pyridine, 10 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Digoxin in 15 mL of diluted ethanol(4 in 5) by warming to 70 ℃; the solution is clear and colorless.

(2) ***Related substances***—Weigh accurately about 25.0 mg of Digoxin, dissolve in 50 mL of warm ethanol, cool, and add ethanol(95) to make exactly 100 mL. Pipet 10 mL of this solution, add 10 mL of water, add dilute ethanol to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately 5.0 mg of gitoxin RS, previously dried in vacuum at 105 ºC for 1 hour, and add a mixture of acetonitrile and water (7 : 3) to make exactly 200 mL. Pipet 2 mL of this solution, add dilute ethanol to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography and determine the peak areas, A_T and A_S, of gitoxin in each solution; A_T is not larger than A_S. Also, the sum of the areas of all peaks obtained from the test solution, other than those of digoxin and gitoxin, is NMT 3%, when calculated by the percentage peak area method.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

Test for required detectability: Weigh accurately about 25.0 mg of Digoxin, dissolve in 50 mL of warm ethanol, cool, and add ethanol(95) to make exactly 100 mL. Pipet 10 mL of this solution, add 10 mL of water, add dilute ethanol to make exactly 50 mL, and use this solution as the system suitability solution. Pipet 2 mL of the system suitability solution, and add dilute ethanol to make exactly 100 mL. Pipet 5 mL of this solution, and add dilute ethanol to make exactly 100 mL. The peak area of digoxin obtained from 10 μL of this solution is between 0.07 - 0.13% of that obtained from the system suitability solution.

System performance: Take about 25 g of Digoxin, dissolve in 50 mL of warm ethanol, cool, and add ethanol(95) to make exactly 100 mL. Pipet 10 mL of this solution, add exactly 5 mL of propyl *p*-hydroxybenzoate in ethanol(95) (1 in 4000), add 10 mL of water, and add dilute ethanol to make 50 mL. Proceed with 10 μL of this solution under the above operating conditions; digoxin and propyl *p*-hydroxybenzoate are eluted in this order with the resolution between these peaks being NLT 5.

System repeatability: Repeat the test 6 times with 10 μL of the system suitability solution under the above operating conditions; the relative standard deviation of the peak area of digoxin is NMT 2.5%.

Time span of measurement: A range of about 4 times the retention time of digoxin after the solvent peak.

Loss on drying NMT 1.0% (0.5 g, in vacuum, 105 ℃, 1 hours).

Ignition residue NMT 0.5% (0.1 g).

Assay Weigh accurately about 25 mg of Digoxin and digoxin RS, previously dried, dissolve each in 50 mL of warm ethanol, cool, and add ethanol(95) to make exactly 100 mL. Pipet 10 mL each of these solutions, add exactly 5 ml of the internal standard solution to each, add 10 mL of water, add dilute ethanol to make 50 mL, and use these solutions as the test solution and the standard solutions. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak area of digoxin to that of the internal standard, Q_T and Q_S.

$$\text{Amount (mg) of digoxin } (C_{41}H_{64}O_{14}) = \text{Amount (mg) of digoxin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of propyl *p*-hydroxybenzoate in ethanol(95) (1 in 4000).

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 220 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 ℃.

Mobile phase: A mixture of water and acetonitrile (7 : 3).

Flow rate: Adjust the flow rate so that the retention time of digoxin is about 10 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; digoxin and the internal standard are eluted in this order with the resolution between these peaks being NLT 5.

System repeatability: Repeat the test 6 times with

10 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area of digoxin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Digoxin Injection
디곡신 주사액

Digoxin Injection is an aqueous injection and contains NLT 90.0% and NMT 105.0% the labeled amount of digoxin ($C_{41}H_{64}O_{14}$: 780.94).

Method of preparation Prepare as directed under the Injections, dissolving Digoxin between 10 and 50 vol% ethanol.

Description Digoxin Injection occurs as a clear, colorless liquid.

Identification (1) To contain 0.25 mg of digoxin per mL according to the labeled amount of Digoxin Injection, add methanol if necessary, and use this solution as the test solution. Separately, dissolve 0.5 mg of digoxin RS in 2 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol and water (7 : 3) as the developing solvent to a distance of about 10 cm, and air-dry the plate. To this, spray evenly a mixture of 4 volumes of a solution of trichloroacetic acid in ethanol(95) (1 in 4) and 1 volume of sodium toluenesulfonchloramide trihydratesolution (3 in 100), heat at 110 ℃ for 10 minutes, and examine the plate under ultraviolet light (wavelength: 366 nm); the R_f values of the principal spots obtained from the test solution to that of the standard solution are the same.

(2) The retention times of the major peaks obtained from the test solution and the standard solution in the Assay are the same.

Purity ***Related substances***—Take exactly an appropriate amount of Digoxin Injection equivalent to 2.5 mg of digoxin according to the labeled amount, dissolve in 50 mL of dilute ethanol, and use this solution as the test solution. With 10 μL of the test solution, perform the test as directed under the Liquid Chromatography according to the following conditions. Measure each of the peak area from the test solution according to the automatic integration method and obtain each amount according to the percentage peak area method; the total area of the peak of the related substance to that of the major peak is NMT 5%.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

Test for required detectability: Dissolve 25 mg of digoxin in 50 mL of warm ethanol(95), cool it down, and add ethanol(95) to make exactly 100 mL. Pipet 10 mL of this solution, add 10 mL of water, add dilute ethanol to make exactly 50 mL, and use this solution as the system suitability solution. Pipet 2 mL of the system suitability solution and add dilute ethanol to make exactly 100 mL. Pipet 5 mL of this solution and add dilute ethanol to make exactly 100 mL. The peak area of digoxin obtained from 10 μL of this solution is 0.07% to 0.13% of the peak area of digoxin from the system suitability solution.

System performance: Dissolve 25 mg of digoxin in 50 mL of warm ethanol(95), cool it down, and add ethanol(95) to make exactly 100 mL. Pipet 10 mL of this solution, add 5 mL of propyl *p*-hydroxybenzoate in ethanol(95) (1 in 4000), add 10 mL of water, and add dilute ethanol to make 50 mL. Proceed with 10 μL of this solution under the above operating conditions; digoxin and propyl *p*-hydroxybenzoate are eluted in this order with the resolution being NLT 5.

System repeatability: Repeat the test 6 times with 10 μL of the system suitability solution under the above operating conditions; the relative standard deviation of the peak area of digoxin is NMT 2.5%.

Time span of measurement: About 4 times of the retention time of digoxin after the solvent peak.

Sterility Meets the requirements.

Bacterial endotoxins Less than 200 EU per mg of digoxin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Alcohol number Between 0.8 and 1.2 (Method 1).

Assay Take exactly an amount of Digoxin Injection equivalent to about 2.5 mg of digoxin ($C_{41}H_{64}O_{14}$), add exactly 5 mL of the internal standard solution and dilute ethanol to make exactly 50 mL, and use this solution as the test solution. Separately, dry digoxin RS at 105 ℃ for 1 hour in vacuum, weigh accurately 25 mg of digoxin RS, dissolve in 50 mL of warm ethanol, and cool it down. Add ethanol(95) to make exactly 100 mL. Pipet 10 mL of this solution, add 5 mL of the internal standard, add 10 mL of water, and dilute in ethanol to make 50 mL. Use

this solution as the internal standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions and determine the ratio of the peak area of digoxin to that of the internal standard, Q_T and Q_S.

$$\text{Amount (mg) of digoxin } (C_{41}H_{64}O_{14}) = \text{Amount (mg) of digoxin RS} \times \frac{Q_T}{Q_S} \times \frac{1}{10}$$

Internal standard solution—A solution of propyl *p*-hydroxybenzoate in ethanol(95) (1 in 4000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of water and acetonitrile (7 : 3).

Flow rate: Adjust the flow rate so that the retention time of digoxin is about 10 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; digoxin and the internal standard are eluted in this order with the resolution being NLT 5.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area of digoxin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, hermetic containers.

Digoxin Tablets
디곡신 정

Digoxin Tablets contain NLT 90.0% and NMT 105.0% of the labeled amount of digoxin ($C_{41}H_{64}O_{14}$: 780.94).

Method of preparation Prepare Digoxin Tablets as directed under Tablets, with Digoxin.

Identification (1) Take a portion of powdered Digoxin Tablets, equivalent to 0.5 mg of Digoxin according to the labeled amount, add 2 mL of methanol, shake for 10 minutes, and filter. Use this solution as the test solution. Separately, dissolve about 0.5 mg of digoxin RS in 2 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol and water (7 : 3) as the developing solvent to a distance of about 10 cm, and air-dry the plate. To this, spray evenly a mixture of 1 volume of sodium toluenesulfonchloramide trihydrate (3 in 100), freshly prepared, and 4 volumes of a solution of trichloroacetic acid in methanol, heat at 110 ℃ for 10 minutes, and examine the plate under ultraviolet light (wavelength: 366 nm); the R_f value of spots obtained from the test solution and the standard solution are the same.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Purity (1) ***Related substances*—**Weigh accurately the mass of NLT 20 tablets of Digoxin Tablets and powder. Weigh accurately equivalent to about 2.5 mg of digoxin, add 30 mL of dilute ethanol, sonicate for 20 minutes, and shake well to mix for 5 minutes. Cool it down, add 50 mL of dilute ethanol, filter, and use this solution as the test solution. With 10 μL of the test solution, perform the test as directed under the Liquid Chromatography according to the following conditions. Measure each of the peak area from the test solution according to the automatic integration method and obtain each amount according to the percentage peak area method; the total area of the peak of the related substance to that of the major peak is NMT 5%.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

Test for required detectability: Weigh accurately 25.0 mg of Digoxin Tablets, dissolve in 50 mL of warm ethanol, cool, and add ethanol(95) to make exactly 100 mL. Pipet 10 mL of this solution, add 10 mL of water, add dilute ethanol to make exactly 50 mL, and use this solution as the system suitability solution. Pipet 2 mL of the system suitability solution and add dilute ethanol to make exactly 100 mL. Pipet 5 mL of this solution and add dilute ethanol to make exactly 100 mL. The peak area of digoxin obtained from 10 μL of this solution is between 0.07% and 0.13% of that obtained from the system suitability solution.

System performance: Weigh accurately 25.0 mg of Digoxin Tablets, dissolve in 50 mL of warm ethanol, cool, and add ethanol(95) to make exactly 100 mL. Pipet 10 mL of this solution, add exactly 5 mL of propyl *p*-hydroxybenzoate in ethanol(95) (1 in 4000), add 10 mL of water, and add dilute ethanol to make 50 mL. Proceed with 10 μL of this solution under the above operating conditions; digoxin and propyl *p*-hydroxybenzoate are eluted in this order with the resolution between these

peaks being NLT 5.

System repeatability: Repeat the test 6 times with 10 μL of the system suitability solution under the above operating conditions; the relative standard deviation of the peak area of digoxin is NMT 2.5%.

Time span of measurement: About 4 times the retention time of digoxin after the solvent peak.

Dissolution Perform the test with 1 tablet of Digoxin Tablets at 100 revolutions per minutes according to Method 1, with 500 mL of hydrochloric acid diluted with the dissolution medium (3 in 500). Take 30 mL of the dissolved solution 60 minutes after starting the Dissolution, filter through a membrane filter with a pore diameter of 0.8 μm, discard the first 10 mL of the filtrate, and use this solution as the test solution. Separately, dry digoxin RS at 105 ℃ for 1 hour in vacuum, weigh accurately 25 mg of digoxin RS, dissolve in a small amount of ethanol(95), and add a solution of 4 volumes of ethanol(95) and 1 volume of water to make exactly 500 mL. Pipet 5 mL of this solution, add the dissolution medium to make exactly 500 mL, and use this solution as the standard solution. Pipet 2 mL each of the test solution, the standard solution and the dissolution medium, and transfer to a test tube T, S and B with a brown stopper. To this, add exactly 10 mL each of 0.012 g/dL ascorbic acid-hydrochloric acid TS and shake well to mix. Add exactly 1 mL each of dilute hydrogen peroxide TS, shake well to mix, and allow it to stand for 45 minutes at a constant temperature of 25 to 30 ℃. Determine the fluorescence intensities, F_T, F_S and F_B, of these solutions, at 360 nm as the excitation wavelength and at 485 nm as the fluorescence wavelength as directed under the Fluorescence Spectroscopy.

It meets the requirements if the dissolution rate of Digoxin Tablets in 60 minutes is NLT 65%.

The retest requirements do not apply to Digoxin Tablets.

$$\text{Dissolution rate (\%) of the labeled amount of digoxin } (C_{41}H_{64}O_{14}) = W_S \times \frac{F_T - F_B}{F_S - F_B} \times \frac{1}{C}$$

W_S: Amount (mg) of digoxin RS

C: Labeled amount (mg) of digoxin ($C_{41}H_{64}O_{14}$) in 1 tablet

Uniformity of dosage units It meets the requirements when tested according to the following procedure. Take 1 tablet of Digoxin Tablets, add 0.5 mL of water to disintegrate, pipet 0.5 mL of the internal standard solution, and add V mL of dilute ethanol so that Each mL of the solution contains about 21 μg of digoxin ($C_{41}H_{64}O_{14}$). Sonicate, shake well to mix for 5 minutes, filter, and use the filtrate as the test solution. Separately, dry digoxin RS at 105 ℃ for 1 hour in vacuum, weigh accurately 25 mg of digoxin RS, dissolve in 50 mL of warm ethanol, and cool it down. Add ethanol(95) to make exactly 100 mL. Pipet 10 mL of this solution and add ethanol(95) to make exactly 20 mL. Pipet 1 mL of this solution, add exactly 0.5 mL of the internal standard solution, add 1.5 mL of water and *dilute ethanol (V*-2), and use this solution as the standard solution. Perform the test as directed under the Assay below.

$$\text{Amount (mg) of digoxin } (C_{41}H_{64}O_{14}) = \text{Amount (mg) of digoxin RS} \times \frac{Q_T}{Q_S} \times \frac{1}{200}$$

Internal standard solution—Dissolve 1 g of propyl p-hydroxybenzoate in ethanol(95) to make 40000/V.

Assay Weigh accurately NLT 20 tablets of Digoxin Tablets and powder them. Weigh accurately an amount, equivalent to ($C_{41}H_{64}O_{14}$) about 2.5 mg of digoxin ($C_{41}H_{64}O_{14}$), add 30 mL of dilute ethanol, sonicate for 20 minutes, and shake well to mix for 5 minutes. Add exactly 5 mL of the internal standard solution and add dilute ethanol to make exactly 50 mL. Centrifuge this solution, and use the clear supernatant as the test solution. Separately, dry digoxin RS at 105 ℃ for 1 hour in vacuum, weigh accurately 25 mg of digoxin RS, dissolve in 50 mL of warm ethanol, and cool it down. Add ethanol(95) to make exactly 100 mL. Pipet 10 mL of this solution, add 5 mL of the internal standard, add 10 mL of water, and dilute in ethanol to make 50 mL. Use this solution as the internal standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak area, Q_T and Q_S, of digoxin to that of the internal standard.

$$\text{Amount (mg) of digoxin } (C_{41}H_{64}O_{14}) = \text{Amount (mg) of digoxin RS} \times \frac{Q_T}{Q_S} \times \frac{1}{10}$$

Internal standard solution—A solution of propyl *p*-hydroxybenzoate in ethanol(95) (1 in 4000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 25 length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of water and acetonitrile (7 : 3).

Flow rate: Adjust the flow rate so that the retention time of digoxin is about 10 minutes.

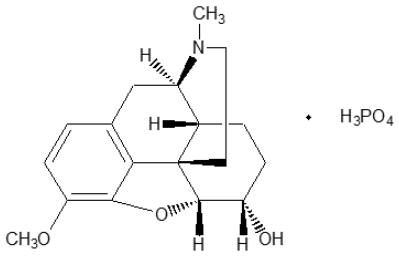
System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; digoxin and the internal standard are eluted in this order with the resolution between these peaks being NLT 5.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area of digoxin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Dihydrocodeine Phosphate
디히드로코데인인산염



$C_{18}H_{23}NO_3 \cdot H_3PO_4$: 399.38
4,5-alpha-Epoxy-3-methoxy-17-methyl-morphinan-6-ol
[*24204-13-5*]

Dihydrocodeine Phosphate contains NLT 98.0% and NMT 101.0% of dihydrocodeine phosphate ($C_{18}H_{23}NO_3 \cdot H_3PO_4$), calculated on the dried basis.

Description Dihydrocodeine Phosphate occurs as a white to yellow crystalline powder.
It is freely soluble in water or acetic acid(100), slightly soluble in ethanol and practically insoluble in ether.
Dissolve 1.0 g of Dihydrocodeine Phosphate in 10 mL of water; the pH of this solution is between 3.0 and 5.0.
It is affected by light.

Identification (1) Determine the absorption spectra of Dihydrocodeine Phosphate and an aqueous solution of Dihydrocodeine Phosphate RS (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelength.

(2) Determine the infrared spectra of Dihydrocodeine Phosphate and Dihydrocodeine Phosphate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) A solution of Dihydrocodeine Phosphate (1 in 20) responds to the Qualitative Analysis (1) for phosphate.

Purity (1) ***Chloride***—Perform the test with 0.5 g of Dihydrocodeine Phosphate. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.021%).

(2) ***Sulfate***—Perform the test with 0.20 g of Dihydrocodeine Phosphate. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.240%).

(3) ***Related substances***—Dissolve 0.2 g of Dihydrocodeine Phosphate in 10 mL of diluted ethanol (1 in 2) and use this solution as the test solution. Pipet 1 mL of this solution, add diluted ethanol (1 in 2) to make exactly 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (fluorescent indicator added). Next, develop the plate with a mixture of anhydrous ethanol, toluene, acetone and strong ammonia water (14 : 14 : 7 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 1.0% (0.5 g, 105 ℃, 4 hours).

Assay Weigh accurately about 0.5 g of Dihydrocodeine Phosphate, dissolve in 70 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 3 drops of methylrosaniline chloride TS). However, the endpoint of the titration is when the violet color changes to blue and then finally to greenish blue. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 39.938 mg of $C_{18}H_{23}NO_3 \cdot H_3PO_4$

Packaging and storage Preserve in light-resistant, tight containers.

1% Dihydrocodeine Phosphate Powder
디히드로코데인인산염 100 배산

1% Dihydrocodeine Phosphate

1% Dihydrocodeine Phosphate Powder contains NLT 0.90% and NMT 1.10% of Dihydrocodeine Phosphate ($C_{18}H_{23}NO_3 \cdot H_3PO_4$: 399.38).

Method of preparation

Dihydrocodeine phosphate	10 g
Lactose hydrate	A sufficient quantity
Total amount	1000 g

Prepare as directed under Powders, with the above ingredients.

Identification (1) Determine the absorption spectrum with an aqueous solution of 1% Dihydrocodeine Phosphate Powder (1 in 100) as directed under the Ultraviolet-

visible Spectroscopy; it exhibits a maximum between 281 nm and 285 nm.

Particle size distribution estimation by analytical sieving Meets the requirements.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Weigh accurately about 5 g of 1% Dihydrocodeine Phosphate Powder and dissolve in water to make exactly 100 mL. Pipet 10 mL of this solution, add exactly 10 mL of the internal standard solution, and use this solution as the test solution. Separately, weigh accurately about 50 mg of Dihydrocodeine Phosphate RS (previously measured the loss on drying) and dissolve in water to make exactly 100 mL. Pipet 10 mL of this solution, add exactly 10 mL of the internal standard solution, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of Dihydrocodeine to the peak area of the internal standard.

Amount (mg) of Dihydrocodeine Phosphate ($C_{18}H_{23}NO_3 \cdot H_3PO_4$) = Amount (mg) of Dihydrocodeine Phosphate RS, calculated on the anhydrous basis $\times \frac{Q_T}{Q_S}$

Internal standard solution—An aqueous solution of etilefrine hydrochloride (3 in 10000).

Operating conditions

Proceed as directed under the Assay for 10% Dihydrocodeine Phosphate Powder.

Packaging and storage Preserve in tight containers.

10% Dihydrocodeine Phosphate Powder
디히드로코데인인산염 10 배산

10% Dihydrocodeine Phosphate

10% Dihydrocodeine Phosphate Powder contains NLT 9.3% and NMT 10.7% of Dihydrocodeine Phosphate ($C_{18}H_{23}NO_3 \cdot H_3PO_4$: 399.38).

Method of preparation

Dihydrocodeine phosphate	100 g
Lactose hydrate	A sufficient quantity
Tot	

Prepare as directed under Powders, with the above ingredients.

Identification (1) Determine the absorption spectrum with an aqueous solution of 10% Dihydrocodeine Phosphate Powder (1 in 1000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 281 nm and 285 nm.

Particle size distribution estimation by analytical sieving Meets the requirements.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Weigh accurately about 2.5 g of 10% Dihydrocodeine Phosphate Powder and dissolve in water to make 100 mL exactly. Take exactly 2 mL of this solution, add exactly 10 mL of the internal standard solution, add water to make 20 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of Dihydrocodeine Phosphate RS (previously measured the loss on drying) and dissolve in water to make exactly 100 mL. Pipet 10 mL of this solution, add exactly 10 mL of the internal standard solution, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of Dihydrocodeine to the peak area of the internal standard.

Amount (mg) of Dihydrocodeine Phosphate ($C_{18}H_{23}NO_3 \cdot H_3PO_4$) = Amount (mg) of Dihydrocodeine Phosphate RS, calculated on the dried basis $\times \frac{Q_T}{Q_S} \times 5$

Internal standard solution—An aqueous solution of etilefrine hydrochloride (3 in 10000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless-steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 1.0 g of sodium lauryl sulfate in 500 mL of diluted phosphoric acid (1 in 1000), then adjust the pH to 3.0 with sodium hydroxide TS. Mix 70 mL of tetrahydrofuran to 240 mL of this solution.

Flow rate: Adjust the flow rate so that the retention time of Dihydrocodeine is about 9 minutes.

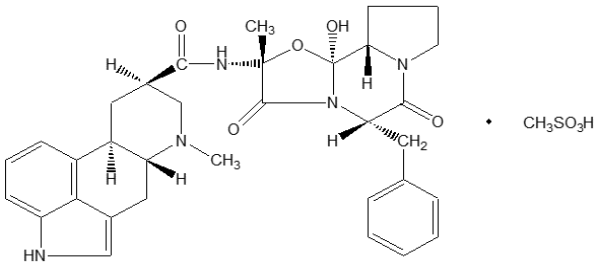
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above operating conditions; dihydrocodeine and the internal standard are eluted in this order with the resolution between their peaks being NLT 4.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratios of Dihydrocodeine to the peak area of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Dihydroergotamine Mesilate
디히드로에르고타민메실산염



$C_{33}H_{37}N_5O_5 \cdot CH_4O_3S$: 679.78

(2*R*,4*R*,7*R*)-*N*-[(1*S*,2*S*,4*R*,7*S*)-7-Benzyl-2-hydroxy-4-methyl-5,8-dioxo-3-oxa-6,9-diazatricyclo[7.3.0.02,6]dodecan-4-yl]-6-methyl-6,11-diazatetracyclo[7.6.1.02,7.012,16]hexadeca-1(16),9,12,14-tetraene-4-carboxamide; methanesulfonic acid [*6190-39-2*]

Dihydroergotamine Mesilate contains NLT 97.0% and NMT 101.0% of dihydroergotamine mesylate ($C_{33}H_{37}N_5O_5 \cdot CH_4O_3S$), calculated on the dried basis.

Method of preparation If there is any possibility of alkyl (methyl, ethyl, isopropyl, etc.) methanesulfonate esters to be mixed according to the manufacturing process of Dihydroergotamine Mesilate, take cautions for starting material, manufacturing process, and intermediate to minimize the residue of impurities in consideration of risk assessment results. If necessary, the manufacturing process may be verified by the test data proving that no quality risk exists in the final drug substance.

Description Dihydroergotamine Mesilate occurs as a white to yellowish white or pale gray to reddish white powder.

It is freely soluble in acetic acid(100), sparingly soluble in methanol or chloroform, slightly soluble in water or ethanol(95) and practically insoluble in acetic acid(100) or ether.

It is gradually affected by light.

Melting point—About 214 °C (with decomposition).

Identification (1) Dissolve about 1 mg of Dihydroergotamine Mesilate in 5 mL of L-tartaric acid (1 in 100), add 2 mL of 4-dimethylaminobenzaldehyde-iron(III) chloride TS to 1 mL of this solution, and shake to mix; the resulting solution exhibits the blue color.

(2) Put 0.4 g of sodium hydroxide in about 0.1 g of Dihydroergotamine Mesilate, stir well to mix, and heat gradually to incinerate. After cooling, add 10 mL of water to the residue, heat to boil, cool, and filter. Add 0.5 mL of hydrochloric acid to the filtrate; the resulting solution responds to the Qualitative Analysis for sulfate. Separately, add 5 mL of dilute hydrochloric acid to 0.1 g of Dihydroergotamine Mesilate, shake to mix for 5 minutes, and filter. Add 1 mL of barium chloride TS to the filtrate; the resulting solution is clear.

(3) Determine the absorption spectra of Dihydroergotamine Mesylate and a solution of Dihydroergotamine Mesilate RS in methanol (1 in 20000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared spectra of Dihydroergotamine Mesylate and Dihydroergotamine Mesilate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -16.7° and -22.7° [0.5 g calculated on the dried basis, a mixture of ethanol(99.5), chloroform and ammonia water(28) (10 : 10 : 1), 20 mL, 100 mm].

pH Dissolve 50 mg of Dihydroergotamine Mesylate in 50 mL of water; the pH of this solution is between 4.4 and 5.4.

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Dihydroergotamine Mesylate in 0.1 mL of methanesulfonic acid (7 in 100) and 50 mL of water; the resulting solution is clear and the color is not more intense than that of Control solution (1) or (2) below.

Control solution (1)—Pipet 0.6 mL of iron(III) chloride hexahydrate colorimetric stock solution and 0.15 mL of cobaltous(II) chloride hexahydrate colorimetric stock solution to mix and add diluted hydrochloric acid (1 in 40) to make exactly 100 mL.

Control solution (2)—Pipet 0.6 mL of iron(III) chloride hexahydrate colorimetric stock solution, 0.25 mL of cobaltous(II) chloride hexahydrate colorimetric stock solution and 0.1 mL of copper(II) sulfate pentahydrate colorimetric stock solution, respectively, mix, and add diluted hydrochloric acid (1 in 40) to make exactly 100 mL.

(2) ***Related substances***—Proceed with light-resistant containers, away from the light. Dissolve 0.10 g of Dihydroergotamine Mesilate in 5 mL of a mixture of chloroform and methanol (9 : 1) and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of chloroform and methanol (9 : 1) to make exactly 200 mL, and use this solution as the standard solution (1).

Pipet 10 mL of this solution, add a mixture of chloroform and methanol (9 : 1) to make exactly 25 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution, the standard solution (1), and the standard solution (2) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of dichloromethane, ethyl acetate, methanol, and ammonia water (50 : 50 : 6 : 1) as the developing solvent to a distance of about 15 cm, and dry the plate with cool air within 1 minute. In an instant, develop again the plate with a new mixture of dichloromethane, ethyl acetate, methanol and ammonia water (50 : 50 : 6 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray evenly 4-dimethylaminobenzaldehyde TS for spraying and dry the plate with warm air; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution (1) and number of the spots, which are more intense than the spots from the standard solution (2), are NMT 2.

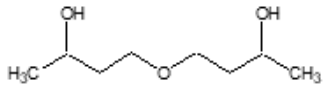
Loss on drying NMT 4.0% (0.5 g, NMT 0.67 kPa, 100 ℃, 6 hours).

Assay Weigh accurately 0.2 g of Dihydroergotamine Mesilate, dissolve in 170 mL of a mixture of acetic anhydride and acetic acid(100) (10 : 1), and titrate with 0.02 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.02 mol/L perchloric acid VS
= 13.596 mg of $C_{33}H_{37}N_5O_5 \cdot CH_4O_3S$

Packaging and storage Preserve in light-resistant, tight containers.

Dihydroxydibutyl Ether
디히드록시디부틸에테르



$C_8H_{18}O_3$: 162.23

4,4'-Oxybix-1-butanol; 4,4'-Dihydroxydibutyl ether, [*3403-82-5*]

Dihydroxydibutyl Ether contains dihydroxydibutyl ether ($C_8H_{18}O_3$: 162.23) NLT 95.0% and NMT 101.0%, calculated on the anhydrous basis.

Description Dihydroxydibutyl Ether occurs as a colorless and clear liquid, which is almost odorless and has a bitter taste.

It is soluble in general organic solvents such as water, acetic acid(100), ethanol(95), ether, acetone or chloroform etc. and practically insoluble in petroleum ether.

The specific gravity of Dihydroxydibutyl Ether is about 0.994 (20 ℃).

Identification (1) Use a solution of Dihydroxydibutyl Ether in 1% acetone as the test solution. Separately, weigh about 0.1 g of dihydroxydibutyl ether RS, dissolve in 10 mL of acetone, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of *n*-butanol and water (9 : 1) to a distance of about 10 cm, and air-dry the plate. Allow the plate to stand for a while in a developing chamber for iodine vapor; the R_f values and colors of the spots from the test solution and the standard solution are the same.

(2) Weigh 0.125 g each of Dihydroxydibutyl Ether and dihydroxydibutyl ether RS, add acetone to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 2 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following the conditions; the retention times of peaks from the test solution and the standard solution are the same.

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A steel column about 0.32 mm in internal diameter and about 30.0 m in length, coated with polyethylene glycol (0.25 μm in particle diameter).

Column temperature: Increase the temperature from 170 ℃ to 180 ℃ by 1 ℃ per minute and then to 240 ℃ by 60 ℃ per minute.

Sample injection port temperature: 240 ℃

Detector temperature: 250 ℃

Carrier gas: Nitrogen

Flow rate: 2 mL/min

Total flow: About 25 mL.

Refractive index $[\alpha]_D^{20}$: Between 1.4480 and 1.4495.

pH Between 5.0 and 7.0 (5% aqueous solution).

Boiling point Between 260 and 265 ℃.

Water NMT 0.5% (1 g, volumetric titration, direct titration).

Assay (1) ***Hydroxyl group*—**Weigh accurately 0.5 g of Dihydroxydibutyl Ether, transfer into a stoppered Erlenmeyer flask, put 5 mL of tetrahydrofuran and 20 mL of acetylation TS, and stopper the flask. After compounding, allow it to stand. Separately, put 5 mL of tetrahydrofuran and 20 mL of acetylation TS into a stoppered Erlenmeyer flask, stopper the flask, mix, and allow to stand. Heat

these two stoppered Erlenmeyer flasks on a steam bath at 67 ℃ for 2 hours, take out, and cool down at room temperature. After adding 5 mL of anhydrous pyridine to each flask, mix, and perform the test with Karl Fischer TS as directed under the Water. Remove the volume (mL) consumed by the blank test, obtain the amount of water produced by the reaction. 1 mL of water corresponds to 4.502 mg of dihydroxydibutyl ether.

Preparation of acetylation TS—Dissolve 100 g of trifluoroboron in acetic acid(100), add 1 - 2 mL of water, and put acetic acid(100) to make 1000 mL.

(2) ***Acid or alkali*—**Weigh accurately about 0.3 g of Dihydroxydibutyl Ether, transfer into a stoppered Erlenmeyer flask, add 5 mL of acetylation TS, and allow to stand for 30 minutes. Put 5 mL of water and 5 mL of a mixture of pyridine and water (3 : 1), allow to stand for 5 minutes, and titrate with 0.5 mol/L sodium hydroxide VS (indicator: phenolphthalein TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.5 mol/L sodium hydroxide VS
= 40.56 mg of $C_8H_{18}O_3$

Acetylation TS—Add 30 mL of acetic anhydride and 0.4 mL of 12% perchloric acid to 180 mL of ethyl acetate and agitate for 5 hours. After allowing to stand for 3 - 4 hours, and use it.

Packaging and storage Preserve in tight containers.

Dihydroxydibutyl Ether Capsules
디히드록시디부틸에테르 캡슐

Dihydroxydibutyl Ether Capsules contain NLT 95.0% and NMT 105.0% the labeled amount of dihydroxydibutyl ether ($C_8H_{18}N_3O6$: 162.23).

Method of preparation Prepare as directed under Capsules, with Dihydroxydibutyl Ether.

Identification Weigh an amount of the contents of Dihydroxydibutyl Ether Capsules equivalent to 0.5 g of dihydroxydibutyl ether, dissolve in 5 mL of acetone, and use this solution as the test solution. Separately, use a solution of dihydroxydibutyl ether RS in 1% acetone as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography, develop the plate with a mixture of *n*-butanol and water (100) (9 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray the iodine fume; the R_f values and colors of the spots from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the contents of NLT 20 capsules of Dihydroxydibutyl Ether Capsules. Weigh accurately an amount equivalent to about 0.125 g of dihydroxydibutyl ether ($C_8H_{18}O_3$), add 25 mL of acetone, sonicate, and add exactly 1 mL of the internal standard solution and acetone to make exactly 50 mL. Filter and use the filtrate as the test solution. Separately, weigh accurately 0.125 g of dihydroxydibutyl ether RS, add exactly 1 mL of the internal standard solution, add acetone to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 2 μL each of the test solution and the standard solution according to the following operating conditions as directed under the Liquid Chromatography, and determine the ratio of peak areas for dihydroxydibutyl ether, Q_T and Q_S, to the internal reference for each solution.

Amount (mg) of dihydroxydibutyl ether ($C_8H_{18}O_3$)
= Amount (mg) of dihydroxydibutyl ether RS × (Q_T / Q_S)

Internal standard solution—A solution of phenol in acetone (1 in 5).

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A column about 0.32 mm in internal diameter and about 30.0 m in length, packed with polyethylene glycol (0.25 μm in particle diameter).

Column temperature: Raise the temperature from 170 ℃ to 180 ℃ by 1 ℃ per minute and then to 240 ℃ by 60 ℃ per minute.

Sample injection port temperature: 240 ℃

Detector temperature: 250 ℃

Carrier gas: Nitrogen

Flow rate: 2 mL/min

Total flow: About 25 mL.

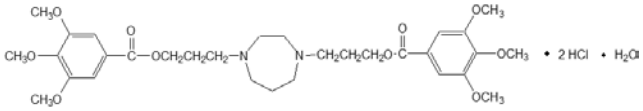
System suitability

System performance: Proceed with 2 μL of the standard solution under the above operating conditions; the internal standard and dihydroxydibutyl ether are eluted in this order.

System repeatability: Repeat the test 6 times with 2 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak area ratios of dihydroxydibutyl ether to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Dilazep Hydrochloride Hydrate
딜라제프염산염수화물



Dilazep Hydrochloride $C_{31}H_{44}N_2O_{10}\cdot 2HCl\cdot H_2O$: 695.63
3-[4-[3-(3,4,5-Trimethoxybenzoyl)oxypropyl]-1,4-diazepan-1-yl]propyl3,4,5-trimethoxybenzoate hydrate dihydrochloride [*20153-98-4*, anhydrous]

Dilazep Hydrochloride Hydrate contains NLT 98.0% and NMT 101.0% of dilazep hydrochloride ($C_{31}H_{44}N_2O_{10}\cdot 2HCl$: 677.61), calculated on the dried basis.

Description Dilazep Hydrochloride Hydrate occurs as a white crystalline powder, which is odorless.
It is freely soluble in acetic acid(100) or chloroform, soluble in water, slightly soluble in ethanol(95) or acetic anhydrideand practically insoluble in ether.

Melting point—Between 200 and 204 ℃. In a 110 ℃ bath fluid, heat to increase by about 3 ℃/min between 140 ℃and 150 ℃, about 10 ℃/min between 160 and 195 ℃, and about 1 ℃/min thereafter.

Identification (1) Add 0.1 mL of hydroxylamine hydrochloride (1 in 10) and 8 mol/L potassium hydroxide TS to 0.1 mL of an aqueous solution of Dilazep Hydrochloride Hydrate (1 in 100) and heat at 70 ℃ on a steam bath for 10 minutes. After cooling, add 0.5 mL of dilute hydrochloric acid and 0.1 mL of iron(III) chloride TS; the resulting solution exhibits a violet color.

(2) Add 0.3 mL of Reinecke salt TS to 5 mL of an aqueous solution of Dilazep Hydrochloride Hydrate (3 in 500); a pale red precipitate develops.

(3) Determine the absorption spectra of Dilazep Hydrochloride Hydrate and an aqueous solution of dilazep hydrochloride RS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared spectra of Dilazep Hydrochloride Hydrate and dilazep hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(5) An aqueous solution of Dilazep Hydrochloride Hydrate (1 in 50) responds to the Qualitative Analysis for chloride.

pH Dissolve 1.0 g of Dilazep Hydrochloride Hydrate in 100 mL of water; the pH is between 3.0 and 4.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Dilazep Hydrochloride Hydrate in 20 mL of water; the resulting solution is clear and colorless.

(2) ***Sulfate***—Perform the test with 0.5 g of Dilazep Hydrochloride Hydrate. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid VS (NMT 0.048%).

(3) ***Heavy metals***—Proceed with 2.0 g of Dilazep Hydrochloride Hydrate as directed under Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Proceed with 1.0 g of Dilazep Hydrochloride Hydrate as directed under Method 3 and perform the test (NMT 2 ppm).

(5) ***Related substances***—Dissolve 0.40 g of Dilazep Hydrochloride Hydrate in 10 mL of chloroform and use this solution as the test solution. Pipet 1.0 mL of this solution, add chloroform to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol, ethyl acetate, dichloromethane and hydrochloric acid (500 : 200 : 100 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly Dragendorff's TS for spray on the plate; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying Between 2.0% and 3.0% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Dilazep Hydrochloride Hydrate, dissolve in 40 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 33.881 mg of $C_{31}H_{44}N_2O_{10}\cdot 2HCl$

Packaging and storage Preserver in tight containers.

Dilazep Hydrochloride Tablets
딜라제프염산염 정

Dilazep Hydrochloride Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of dilazep hydrochloride ($C_{31}H_{44}N_2O_{10}\cdot 2HCl$: 677.61).

Method of preparation Prepare as directed under Tablets, with Dilazep Hydrochloride.

Identification Weigh an amount of Dilazep Hydrochloride Tablets, equivalent to 50 mg of dilazep hydrochloride according to the labeled amount, dissolve in 5 mL of

ethyl acetate, centrifuge, and use the clear supernatant as the test solution. Weigh about 50 mg of dilazep hydrochloride RS, dissolve in 5 mL of ethyl acetate, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol, ethyl acetate, and hydrochloric acid (50 : 30 : 0.1) as the developing solvent and air-dry the plate. Examine the plate under ultraviolet light and spray chloroplatinic acid-potassium iodide TS; the R_f value and color (dark blue on a bright red background) of the spots obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 tablet of Dilazep Hydrochloride Tablets at 100 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of the first solution as the dissolution solution. Take the dissolved solution after 60 minutes from the start of the test and filter. Discard the first 10 mL of the filtrate and pipet V mL of the next filtrate, add the first solution in the Dissolution to obtain a solution having known concentration of about 55 μg of dilazep hydrochloride per mL according to the labeled amount to make exactly *V' mL*, and use this solution as the test solution. Separately, weigh exactly 55 mg of dilazep hydrochloride RS and dissolve in the first solution in the dissolution test to make exactly 100 mL. Pipet 10 mL of this solution, add this to the first solution in the dissolution test to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak areas, A_T and A_S, of dilazep ($C_{31}H_{44}N_2O_{10}$) in each solution, respectively. Meets the requirements if the dissolution rate of Dilazep Hydrochloride Tablets in 60 minutes is NLT 75%.

Dissolution rate (%) with respect to the labeled amount of dilazep ($C_{31}H_{44}N_2O_{10}$)

$$= W_S \times (V' / V) \times (A_T / A_S) / C$$

W_S: Amount (mg) of dilazep hydrochloride RS

C: Labeled amount (mg) of dilazep ($C_{31}H_{44}N_2O_{10}$) in 1 tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 265 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of 0.05 mol/L sodium dihydrogen phosphate TS (pH 3.0) and acetonitrile (3 : 7).

Flow rate: 1.0 mL/min

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tables of Dilazep Hydrochloride Tablets and powder. Weigh accurately an amount, equivalent to about 55 mg of dilazep hydrochloride ($C_{31}H_{44}N_2O_{10}\cdot 2HCl$), and add the mobile phase to make exactly 100 mL. After filtering this solution, pipet 10 mL of the filtrate, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 55 mg of dilazep hydrochloride RS and add the mobile phase to make exactly 100 mL. Pipet 10 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test as directed under the Liquid Chromatography with 10 mL each of the test solution and the standard solution under the following conditions, and determine the peak areas A_T and A_S of dilazep.

Amount (mg) of dilazep ($C_{31}H_{44}N_2O_{10}$)

$$= \text{Amount (mg) of dilazep RS} \times (A_T / A_S)$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 265 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of 0.05 mol/L sodium dihydrogen phosphate TS (pH 3.0) and acetonitrile (3 : 7).

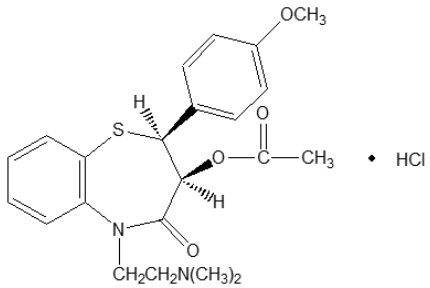
Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 mL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of dilazep hydrochloride is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Diltiazem Hydrochloride
딜티아젬염산염



$C_{22}H_{26}N_2O_4S \cdot HCl$: 450.98

[(2*R*,3*R*)-5-[2-(Dimethylamino)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3-dihydro-1,5-benzothiazepin-3-yl]ethanoate hydrochloride [*33286-22-5*]

Diltiazem Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$).

Description Diltiazem Hydrochloride occurs as a white crystals or a crystalline powder, which is odorless.
It is very soluble in formic acid, freely soluble in water, methanol, or chloroform, sparingly soluble in acetonitrile, slightly soluble in ethanol(99.5) or acetic anhydride and practically insoluble in ether.

Identification (1) Dissolve about 50 mg of Diltiazem Hydrochloride in 1 mL of 1 mol/L hydrochloric acid TS, add 2 mL of ammonium thiocyanate-cobalt nitrate TS and 5 mL of chloroform, shake well to mix, and allow to stand; the chloroform layer exhibits a blue color.

(2) Proceed with 30 mg of Diltiazem Hydrochloride as directed under the Oxygen Flask Combustion, using 20 mL of water as an absorbent to prepare the test solution. The test solution responds to the Qualitative Analysis (1) for sulfate.

(3) Dissolve Diltiazem Hydrochloride and 10 mg of Diltiazem Hydrochloride RS in 0.01 mol/L hydrochloric acid TS to make 100 mL. Pipet 2 mL of this solution and add 0.01 mol/L hydrochloric acid TS to make 20 mL. Determine the absorption spectrum of the resulting solution as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared spectra of Diltiazem Hydrochloride and diltiazem hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(5) An aqueous solution of Diltiazem Hydrochloride (1 in 50) responds to the Qualitative Analysis (2) for chloride.

Optical rotation $[\alpha]_D^{20}$: Between +115° and +120° (0.20 g after drying, water, 20 mL, 100 mm).

Melting point Between 210 and 215 ℃ (with decomposition).

pH Dissolve 1.0 g of Diltiazem Hydrochloridein 100 mL of water; the pH is between 4.3 and 5.3.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Diltiazem Hydrochloride in 20 mL of water; the solution is clear and colorless.

(2) ***Sulfate***—Weigh 1.0 g of Diltiazem Hydrochlorideand perform the test. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid (NMT 0.024%).

(3) ***Heavy metals***—Proceed with 2.0 g of Diltiazem Hydrochloride as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Put 1.0 g of Diltiazem Hydrochlorideinto a decomposition flask, add 5 mL of nitric acid and 2 mL of sulfuric acid, put a small funnel in the mouth of the flask, and heat carefully until white smoke is produced. After cooling, add 2 mL of nitric acid and heat. Repeat the above procedure twice, add 2 mL of strong hydrogen peroxide several times, and heat until the solution changes to colorless to pale yellow. After cooling, add 2 mL of saturated ammonium oxalate and heat again until white smoke is produced. After cooling, add water to make 5 mL. Perform the test with this resulting solution as the test solution; the solution is not more intense than the control solution below (NMT 2 ppm).

Control solution—Proceed in the same manner without using Diltiazem Hydrochloride, add 2.0 mL of arsenic standard solution and water to make 5 mL, and proceed according to the method of preparation of the test solution as follows.

(5) ***Related substances***—Dissolve 50 mg of Diltiazem Hydrochloride in 50 mL of diluted ethanol(99.5) (4 in 5) and use this solution as the test solution. Pipet 1 mL of this solution, add diluted ethanol(99.5) (4 in 5) to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine peak area of each solution by the automatic integration method; the total area of the peaks other than diltiazem of the test solution is NMT three fifth of the peak area of diltiazem from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4 mm internal diameter and 15 cm to 30 cm length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 50 °C.

Mobile phase: Dissolve 8 g of sodium acetate trihydrate and 1.5 g of *d*-camphorsulfonic acid in 500 mL of water and filter through a membrane filter (0.4 μm in pore diameter). Add 250 mL of acetonitrile and 250 mL of methanol to the filtrate and adjust the pH to 6.6 by adding sodium acetate trihydrate. Adjustments can be made if necessary.

Flow rate: Adjust the flow rate so that the retention time of diltiazem is about 9 minutes.

System suitability

Test for required detectability: Pipet 2 mL of the standard solution and add diluted ethanol(99.5) (4 in 5) to make exactly 10 mL. Confirm that the peak area of diltiazem obtained from 20 μL of this solution is equivalent to 15% to 25% of the peak area of diltiazem from the standard solution.

System performance: Weigh 30 mg of Diltiazem Hydrochloride, 20 mg of *d*-3-hydroxy-cis-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(*p*-methoxyphenyl)-1,5-benzodiazepine-4(5*H*)-diltiazem hydrochloride (hereafter, deacetylated agent) and 20 mg of phenyl benzoate, dissolve in 160 mL of ethanol(99.5), and add water again to make 200 mL. Proceed with 20 μL of this solution according to the above conditions; deacetylated agent, diltiazem and phenyl benzoate are eluted in this order with the resolution between deacetylated agent and diltiazem and between diltiazem and phenyl benzoate being NLT 2.5, respectively.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of diltiazem is NMT 2.0%.

Time span of measurement: About 2 times the retention time of diltiazem after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.7 g of Diltiazem Hydrochloride, previously dried, dissolve in 2.0 mL of formic acid, add 60 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 45.10 mg of $C_{22}H_{26}N_2O_4S \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Diltiazem Hydrochloride Extended-Release Tablets
딜티아젬염산염 서방정

Diltiazem Hydrochloride Extended-Release Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$: 450.98).

Method of preparation Prepare as directed under Tablets, with Diltiazem Hydrochloride.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Uniformity of dosage units Meets the requirements.

Related substances Weigh accurately the mass of NLT 20 tablets of Diltiazem Hydrochloride Extended-Release Tablets, and powder. Weigh accurately an amount equivalent to about 50 mg of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$), add 30 mL of anhydrous ethanol, warm it for 5 minutes, and shake to mix for 10 minutes. After cooling, add 10 mL of water and shake for 15 minutes. Add anhydrous ethanol to make 50 mL and filter. Discard the first 20 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 5 mg of diltiazem hydrochloride RS and add anhydrous ethanol to make 100 mL. Pipet 15 mL of this solution, and add 10 mL of water and anhydrous ethanol to make 50 mL. Use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the operating conditions in the Assay. The peak area of the related substance of the test solution is NMT that of the standard solution (NMT 1.5%).

Dissolution Perform the test with 1 tablet of Diltiazem Hydrochloride Extended-Release Tablets at 100 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take the dissolved solution 1, 3, and 10 hours after the start of the Dissolution, filter it, and use the filtrate as the test solution. Separately, weigh accurately about 0.10 g of diltiazem hydrochloride RS, and dissolve it in water to make 1000 mL. Use this solution as the standard solution. Determine the absorbances of the test solution and the standard solution at 280 nm and 320 nm, respectively, as directed under the Atomic Absorption Spectroscopy using water as the control solution. Put the test solution, of which absorbance is measured, into the dissolution tester again. The dissolution rate of Diltiazem Hydrochloride Extended-Release Tablets in 1, 3, and 10 hours should be between 30% and 50%, between 55% and 75%, and NLT 80%, respectively.

Amount (mg) of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$)
= Amount (mg) of diltiazem hydrochloride RS
$$\times \frac{A_{T280} - A_{T320}}{A_{S280} - A_{S320}}$$

Assay Weigh accurately the mass of NLT 20 tablets of Diltiazem Hydrochloride Extended-Release Tablets and powder. Weigh accurately an amount equivalent to about 30 mg of Diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$), add 80 mL of anhydrous ethanol, and warm it. Shake for 10 minutes to mix. Add 40 mL of water, 20 mL of the internal standard solution, and anhydrous ethanol to make 200 mL. Filter, discard the first 20 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately about 30 mg of diltiazem hydrochloride RS, proceed in the same manner with the test solution, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and determine the peak area ratios, Q_T and Q_S, to the internal standard in each solution.

$$\text{Amount (mg) of diltiazem hydrochloride } (C_{22}H_{26}N_2O_4S \cdot HCl) = \text{Amount (mg) of diltiazem hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of phenyl benzoate in ethanol (1 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 to 10 μm in particle diameter).

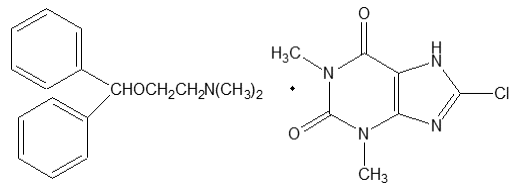
Column temperature: A constant temperature of about 50 °C.

Mobile phase: A solution prepared by dissolving 8 g of sodium acetate and 1.5 g of *d*-camphorsulfonic acid in 500 mL of water, filtering the solution, then adding 250 mL of methanol and 250 mL of acetonitrile and adjusting the pH to 6.6 with sodium acetate.

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Dimenhydrinate
디멘히드리네이트



$C_{17}H_{21}NO \cdot C_7H_7ClN_4O_2$: 469.96

2-Benzhydryloxy-*N*,*N*-dimethylethanamine; 8-chloro-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)dione [*523-87-5*]

Dimenhydrinate, when dried, contains NMT 53.0% and NLT 55.5% of diphenhydramine ($C_{17}H_{21}NO$: 255.36) and NLT 44.0% and NMT 47.0% of 8-chlorotheophylline ($C_7H_7ClN_4O_2$: 214.61).

Description Dimenhydrinate occurs as a white crystalline powder, is odorless, and has a bitter taste.
It is very soluble in chloroform, freely soluble in ethanol(95), and slightly soluble in water or ether.

Identification Determine the infrared spectra of Dimenhydrinate and dimenhydrinate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 102 and 107 ℃.

Purity (1) ***Chloride***—Transfer 50 mL of the filtrate obtained in the Assay (2) to a Nessler tube, add 1 mL of nitric acid, and allow to stand for 5 minutes; the turbidity of the solution is not greater than that of the following control solution.

Control solution—Dilute 0.25 mL of 0.01 mol/L hydrochloric acid with 6 mL of dilute nitric acid and with water to make 50 mL, add 1 mL of silver nitrate TS and allow to stand for 5 minutes (NMT 0.044%).

(2) ***Bromide and iodide*** —Place 0.10 g of Dimenhydrinate in a stoppered test tube and add 50 mg of sodium nitrite, 10 mL of chloroform and 10 mL of dilute hydrochloric acid. Stopper, shake well to mix, and allow to stand; the chloroform layer remains colorless.

Loss on drying NMT 0.5% (3 g, in vacuum, phosphorus pentoxide, 24 hours).

Residue on ignition NMT 0.3% (1 g).

Assay (1) ***Diphenhydramine***—Weigh accurately about 0.5 g of Dimenhydrinate, previously dried, transfer to a 250 mL separatory funnel, and add 50 mL of water, 3 mL of ammonia TS and 10 g of sodium chloride. Extract with six 15 mL portions of ether by shaking to mix. Combine all the ether extracts, wash the combined extract with three 50 mL portions of water, add accurately 25 mL of 0.05 mol/L sulfuric acid and 25mL of water to the ether extract, and shake well to mix. Evaporate the ether gently, allow to cool, and titrate the excess sulfuric acid with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of methyl red TS). Perform a blank test in the same manner.

$$\text{Each mL of 0.05 mol/L sulfuric acid VS} = 25.536 \text{ mg of } C_{17}H_{21}NO$$

(2) ***8-Chlorotheophylline*** —Weigh accurately about 0.8 g of Dimenhydrinate, previously dried, transfer to a 200-mL volumetric flask, add 50 mL of water, 3 mL of

ammonia TS and 6 mL of ammonium nitrate (1 in 10), and heat on a steam bath for 5 minutes. Add exactly 25.0 mL of 0.1 mol/L silver nitrate, and heat on a steam bath for 15 minutes with occasional shaking. After cooling, add water to make exactly 200 mL. Allow to stand overnight to settle the precipitate and filter through a dry filter paper. Discard the initial 20 mL of filtrate, take exactly 100 mL of the subsequent filtrate, acidify by adding nitric acid dropwise, add 3 mL of nitric acid, and titrate the excess silver nitrate with 0.1 mol/L ammonium thiocyanate VS (indicator: 2 mL of ammonium iron(III) sulfate TS). Perform a blank test in the same manner.

Each mL of 0.1 mol/L silver nitrate VS
= 21.461 mg of $C_7H_7ClN_4O_2$

Packaging and storage Preserve in well-closed containers.

Dimenhydrinate Tablets
디멘히드리네이트 정

Dimenhydrinate Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of dimenhydrinate ($C_{17}H_{21}NO \cdot C_7H_7ClN_4O_2$: 469.96).

Method of preparation Prepare Dimenhydrinate Tablets as directed under Tablets, with Dimenhydrinate.

Identification (1) Powder Dimenhydrinate Tablets, weigh an appropriate amount, equivalent to 0.5 g of dimenhydrinate, according to the labeled amount, dissolve in 25 mL of warm ethanol, mix by grinding, and filter. Add 40 mL of water to the filtrate, filter again, and use the filtrate as the test solution. Take 30 mL of the test solution, transfer into a separatory funnel, and perform the test as directed under the Identification (1) of Dimenhydrinate.

(2) Take 30 mL of the test solution from (1) and perform the test as directed under the Identification (2), (3) and (4) of Dimenhydrinate.

Dissolution Perform the test with 1 tablet of Dimenhydrinate Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take NLT 20 mL of the dissolved solution after 15 minutes from the start of the Dissolution, and filter through a membrane filter with a pore diameter of NMT 0.45 μm. Discard the first 10 mL of the filtrate, pipet V mL of the subsequent filtrate, add water to make exactly V' mL so that each mL contains about 28 μg of dimenhydrinate ($C_{17}H_{21}NO \cdot C_7H_7ClN_4O_2$) according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 28 mg of dimenhydrinate RS (previously dry for 24 hours in vacuum using phosphorus pentoxide as the desiccating agent), and add water to make exactly 50 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength of about 276 nm as directed under the Ultraviolet-visible Spectroscopy, using the test solution as the control solution. Meets the requirements if the dissolution rate of Dimenhydrinate Tablets in 15 minutes is NLT 85%.

Dissolution rate (%) of the labeled amount of dimenhydrinate ($C_{17}H_{21}NO \cdot C_7H_7ClN_4O_2$)
= Amount (mg) of dimenhydrinate RS

$$\times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 90$$

C: Labeled amount (mg) of dimenhydrinate ($C_{17}H_{21}NO \cdot C_7H_7O_4ClN_4O_2$) in 1 tablet.

Uniformity of dosage units Meets the requirements.

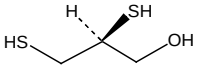
Assay Weigh accurately NLT 20 Dimenhydrinate Tablets and powder them. Weigh accurately an amount, equivalent to about 50 mg of dimenhydrinate ($C_{17}H_{21}NO \cdot C_7H_7ClN_4O_2$), add 80 mL of methanol, and shake well to mix. Add methanol again to make exactly 100 mL, and filter. Pipet 5 mL of the filtrate, add 5 mL of the internal standard solution, and use this solution as the test solution. Separately, weigh accurately about 25 mg of dimenhydrinate RS and dissolve in methanol to make exactly 50 mL. Pipet 5 mL of this solution, add 5 mL of the internal standard solution, and use this solution as the standard solution. Perform the test with exactly 25 μL each of the test solution and the standard solution as directed under the Assay of Dimenhydrinate Injections.

Amount (mg) of dimenhydrinate ($C_{17}H_{21}NO \cdot C_7H_7ClN_4O_2$)
= Amount (mg) of dimenhydrinate RS $\times \frac{A_T}{A_S} \times 2$

Internal standard solution—A solution of 2-hydroxybenzyl alcohol in methanol (2.0 mg/mL).

Packaging and storage Preserve in well-closed containers.

Dimercaprol
디메르카프롤



and enantiomer

$C_3H_8OS_2$: 124.23

2,3-Disulfanylpropan-1-ol [*59-52-9*]

Dimercaprol contains NLT 98.5% and NMT

101.5% of dimercaprol ($C_3H_8OS_2$).

Description Dimercaprol occurs as a colorless to pale yellow liquid and has a mercaptan-like, unpleasant odor.
It is soluble in peanut oil and sparingly soluble in water.
It is miscible with methanol or with ethanol(99.5).
It shows no optical rotation.

Identification (1) Add 1 drop of Dimercaprol to a mixture of 1 drop of a solution of cobalt chloride hexahydrate (1 in 200) and 5 mL of water; the resulting solution exhibits a yellowish brown color.

(2) Determine the infrared spectra of Dimercaprol and dimercaprol RS as directed under the liquid film method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Refractive index n_D^{20}: Between 1.570 and 1.575.

Specific gravity d_{20}^{20}: Between 1.238 and 1.248.

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 mL of Dimercaprol in 20 mL of peanut oil; the resulting solution is clear and colorless to pale yellow.

(2) ***Bromide*—**Add 25 mL of dilute potassium hydroxide-ethanol TS to 2.0 g of Dimercaprol, heat on a steam bath under a reflux condenser for 2 hours, and evaporate the ethanol in a current of warm air. Add 20 mL of water and allow to cool. Add a mixture of 10 mL of hydrogen peroxides (30) and 40 mL of water to this solution, boil gently under a reflux condenser for 10 minutes, and filter immediately after cooling. Wash the residue with two 10 mL portions of water, combine the washings with the filtrate, exactly add 10 mL of dilute nitric acid and 5 mL of 0.1 mol/L silver nitrate, and titrate the excess silver nitrate with 0.1 mol/L ammonium thiocyanate VS (Indicator: 2 mL of ammonium iron(III) sulfate TS). Perform a blank test in the same manner. NMT 1.0 mL of 0.1 mol/L silver nitrate is consumed.

(3) ***Heavy metals*—**Proceed with 1.0 g of Dimercaprol and perform the test according to Method 2. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 20 ppm).

(4) ***1,2,3-Trimercaptopropane and other related substances*—**Weigh exactly 250 mg of hydrogen sulfide-free Dimercaprol, add the mobile phase to make exactly 5 mL, and use this solution as the test solution. Test Dimercaprol for the presence of hydrogen sulfide using lead acetate paper. If the paper darkens, this indicates the presence of hydrogen sulfide; remove hydrogen sulfide by bubbling dry, oxygen-free nitrogen or carbon dioxide through the liquid until a fresh strip of paper does not darken. Weigh accurately 20 g of 100-mesh silicic acid for column chromatography, dissolve in 20 mL of a solution prepared by dissolving 100 mg of sodium sulfite heptahydrate in 100 mL of pH 6.0 phosphate buffer solution, add 100 mL of chloroform, and use this as the filler. Transfer the filler to a column for liquid column chromatography, 13 mm in diameter and 600 mm in length, to pack tightly, and wash the column free from chloroform with the mobile phase, taking cautions to prevent air from entering. Put 2.0 mL of the test solution into the top of the prepared column and wash with the mobile phase. Collect 20 mL of eluate containing 1,2,3-trimercaptopropane and use this solution as the test solution (1), and collect 3 mL of eluate and use this solution as the test solution (2) for the separation test. Add the same volume of ethanol(95) to the test solution (1) and the test solution (2), respectively. Confirm that the test solution (2) is not decolorized by 1 drop of 0.1 mol/L iodine VS, and titrate the test solution (1) with 0.1 mol/L iodine VS until a yellow color is produced. Separately, perform a blank test with 20 mL of the solution that has been passed through the column in the same manner, and make any necessary correction; the amount of 1,2,3-trimercaptopropane is NMT 1.5%.

Each mL of 0.1 mol/L iodine VS
= 4.676 mg of $C_3H_8S_2$

Mobile phase—A mixture of diisopropyl ether and acid-washed hexane (1 : 1).

Diisopropyl ether—Put 100 mL of diisopropyl ether into a distilling flask and distill, retaining only that portion distilling between 68 and 69 °C. Do not evaporate to the point of dryness, since diisopropyl ether forms explosive peroxides. Use only the freshly distilled material.

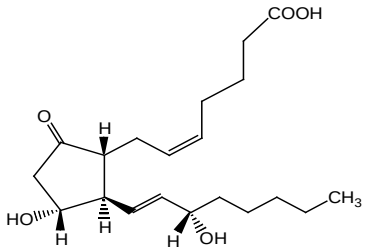
Acid-washed hexane—Put 100 mL of hexane and 10 mL of sulfuric acid into a separatory funnel, shake for NLT 12 hours to mix and allow the layers to be separated. Put the hexane layer into a distilling flask and distills slowly, retaining only the portion that distills between 35and 50 °C. Use only the freshly distilled portion.

Assay Weigh accurately about 0.15 g of Dimercaprol into a stoppered flask, dissolve in 10 mL of methanol, and titrate immediately with 0.05 mol/L iodine VS until a pale yellow color is observed. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L iodine VS
= 6.212 mg of $C_3H_8OS_2$

Packaging and storage Preserve in tight containers and store at below 5 ℃.

Dinoprostone
디노프로스톤



Prostaglandin E_2 $C_{20}H_{32}O_5$: 352.47

(*Z*)-7-((1*R*,2*R*,3*R*)-3-Hydroxy-2-((3*S*,*E*)-3-hydroxyoct-1-en-1-yl)-5-oxocyclopentyl)hept-5-enoic acid [*363-24-6*]

Dinoprostone contains NLT 97.0% and NMT 103.0% of dinoprostone ($C_{20}H_{32}O_5$), calculated on the anhydrous basis.

Description Dinoprostone occurs as a white or pale gray, crystalline powder and is odorless.

Identification (1) Determine the infrared spectra of Dinoprostone and dinoprostone RS, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Optical rotation $[\alpha]_D^{20}$: Between -82° and -90° (0.1 g, ethanol(95) 20 mL, 100 mm).

Purity (1) ***Related substances***—Weigh 25.0 mg of Dinoprostone, add the mobile phase to make exactly 10 mL, and use this solution as the test solution. Separately, weigh 25.0 mg of dinoprostone RS, add the mobile phase to make exactly 10 mL, and use this solution as the standard solution (1). To 0.5 mL of the standard solution (1), add the mobile phase to make exactly 50 mL, and use this solution as the standard solution (2). Perform the test with 20 μL each of the test solution and the standard solution (2) as directed under the Liquid Chromatography according to the following conditions. Determine each peak area in each solution by the automatic integration method and calculate the amount of each related substance in the test solution with respect to dinoprostone; the sum of the dinoprostone related substance I {15-oxo-1-dinoprostone} having a relative retention time of about 0.79, the dinoprostone related substance II {15-epi-dinoprostone} having a relative retention time of about 0.85, and the dinoprostone related substance III {8-isodinoprostone} having a relative retention time of about 0.90 is NMT 1.0%, the dinoprostone related substance IV {5,6-trans-dinoprostone} having a relative retention time of about 1.15 is NMT 2.0%, and the dinoprostone related substance V {(5Z,13E,15S)-15-hydroxy-9-oxoprosta-5,10,13-triene-1-oic acid} having a relative retention time of about 1.80 and the related substance VI {(5Z,13E,15S)-15-hydroxy-9-oxoprosta-5,8(12),13-triene-1-oic acid} having a relative retention time of about 1.90 are 1.0% each. The amount of any other related substance is 0.1%. Determine the peak areas of the dinoprostone related substances I, II, V and VI by dividing the peak areas obtained from the automatic integration method by the correction factors 5, 1.1, 5 and 1.43, respectively.

$$\text{Content (\%) of each related substance} = \frac{\mathrm{C}}{\mathrm{W}} \times \frac{1}{\mathrm{F}} \times \frac{A_\mathrm{i}}{A_\mathrm{S}}$$

C: Concentration (μg/mL) of dinoprostone RS in the standard solution (2).

W: Weight (mg) of sample taken.

F: Relative correction factor

A_i: Peak area for each related substance obtained from the test solution.

A_S: Peak area for dinoprostone obtained from the standard solution.

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 ℃.

Mobile phase: A mixture of methanol and 0.2% acetic acid(100) (58 : 42).

Flow rate: 1 mL/min

System suitability

System performance: When the procedure is run with 20 μL of the standard solution (1) under the above operating conditions, the number of theoretical plates is NLT 6000. The resolution between dinoprostone peak and any other adjacent peak in the chromatogram obtained from the injection of the test solution is NLT 1.0.

System repeatability: Repeat the test 5 times with 20 μL each of the standard solution (1) under the above operating conditions; the relative standard deviation of the areas of the major peaks is NMT 2.0%.

Water NMT 0.5% (0.5 g, volumetric titration, direct titration).

Ignition residue NMT 0.5% (1 g).

Assay Weigh accurately about 25 mg of Dinoprostone, add the mobile phase to make exactly 10 mL, and use this solution as the test solution. Separately, weigh 25 mg of dinoprostone RS, add the mobile phase to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution according to the operating conditions for testing related substances under the Liquid Chromatography, and determine the peak areas, A_T and A_S, of dinoprostone in each solution.

Amount (mg) of dinoprostone ($C_{20}H_{32}O_5$)
= Amount (mg) of dinoprostone RS × $\frac{A_T}{A_S}$

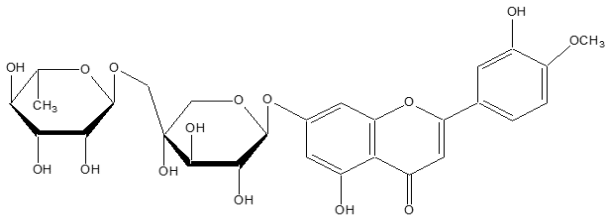
System suitability

System performance: Proceed with 20 μL of the standard solution under the operating conditions for testing related substances; the resolution between dinoprostone peak and any other adjacent peak is NLT 1.0.

System repeatability: Repeat the test 5 times with 20 μL each of the standard solution under the operating conditions for testing related substances; the relative standard deviation of the areas of the major peaks is NMT 2.0%.

Packaging and storage Preserve in light-resistant, well-closed containers.

Diosmin
디오스민



$C_{28}H_{32}O_{15}$: 608.55

5-Hydroxy-2-(3-hydroxy-4-methoxyphenyl)-7-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-[[(2*R*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyl-oxan-2-yl]oxy-methyl]oxan-2-yl]oxychromen-4-one [*520-27-4*]

Diosmin contains NLT 90.0% and NMT 102.0% of diosmin ($C_{28}H_{32}O_{15}$), calculated on the anhydrous basis.

Description Diosmin occurs as a pale grayish yellow or bright yellow powder.
It is soluble in dimethylsulfoxide and practically insoluble in water or ethanol(95).
It is soluble in dilute sodium hydroxide TS.
It is hygroscopic.

Identification (1) Determine the infrared spectra of Diosmin and diosmin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Proceed as directed under the Assay; the retention times of the major peaks obtained from the test solution and the standard solution are the same.

Purity (1) ***Heavy metals***—Proceed with about 2.0 g of Diosmin and perform the test according to Method 2. Prepare the control solution with 4.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Iodine***—Weigh about 0.1 g of Diosmin, prepare the solution with 50 mL of 0.02 w/v% hydrazine solution as an absorbent as directed under the Ooxygen flask combustion, and use this solution as the test solution. Separately, weigh exactly 1.66 g of potassium iodide and dissolve in water to make exactly 100 mL. Pipet 2 mL of this solution, add water to make exactly 100 mL, then pipet 10 mL of this solution, add water to make exactly 100 mL, and use this solution as the control solution. Weigh 20 g of potassium nitrate and dissolve in 0.1 mol/L nitric acid to make 100 mL. Transfer 30 mL of this solution in a beaker, soak iodine ion selective electrodes, stir for 10 minutes, and stir for 10 minutes until the transposition (n_{T1}) of this solution stabilizes. Add1 mL of the test solution and determine transposition (n_{T2}). Separately, weigh 20 g of potassium nitrate and dissolve in 0.1 mol/L nitric acid to make 100 mL. Transfer 30 mL of this solution in a beaker, soak iodine ion selective electrodes, stir for 10 minutes, and stir for 10 minutes until the transposition (n_{R1}) of this solution stabilizes. Add 80 μL of the control solution and determine the transposition (n_{R2}). Thea absolute value of $|n_{T2} - n_{T1}|$ is smaller than the absolute value of $|n_{R2} - n_{R1}|$.

(3) ***Related substances***—Weigh accurately about 25 mg of Diosmin, add dimethylsulfoxide to make exactly 25 mL, and use this solution as the test solution. Separately, weigh exactly 25 mg of diosmin RS and dissolve in dimethylsulfoxide to make exactly 25 mL. Pipet 5 mL of this solution, add dimethylsulfoxide to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of each solution according to the automatic integration method. However, when determining the content of related substances I and related substances VI, multiply 0.38 and 0.61 to each peak area and calibrate. Related substances I is NMT 0.2 times (1%) the peak area from the standard solution, related substances II is NMT (5%) of the peak area from the standard solution, related substances III, V and VI each is NMT 0.6 times (3%) the peak area from the standard solution. Any peak area from the related substances is NMT 0.2 times the major peak area from the standard solution, the total area of related substances I and related substances peak is NMT 0.2 (1%) times the major peak area from the standard solution, and the total sum area of related substances peak is NMT 2 times (10%) the major peak area from the standard solution. However, exclude the peak which is NMT 0.02 times the area of the major peak of the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 275 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in

particle diameter).

Column temperature: 40 °C

Mobile phase: A mixture of water, methanol, acetic acid(100) and acetonitrile (66 : 28 : 6 : 2).

Flow rate: 1.5 mL/min

Relative retention time: The retention time of diosmin peak is about 4.6 minutes. The retention time of related substances I, II, III, IV, V and VI is about 0.5, 0.6, 0.8, 2.2, 2.6 and 4.5 minutes.

System suitability

System performance: Weigh 25 mg of diosmin and dissolve in dimethylsulfoxide to make 25 mL. Proceed with 10 μL of this solution according to the above operating conditions, the resolution between related substances II and III is NLT 2.5.

Water NMT 6.0% (0.3 g, volumetric titration, direct titration).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 25 mg of Diosmin and diosmin RS, dissolve in dimethylsulfoxide to make exactly 25 mL, and use these solutions as the test solution and the standard solution. Perform the test with 10 mL each of the test solution and the standard solution as directed under the Liquid Chromatography according to above the related substances' conditions, and determine the ratios, A_T and A_S, of the peak area of the test solution to that from the standard solution.

$$\text{Amount (mg) of diosmin } (C_{28}H_{32}O_{15}) = \text{Amount (mg) of diosmin RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers.

Diosmin Capsules
디오스민 캡슐

Diosmin Capsules contain NLT 95.0% and NMT 105.0% the labeled amount of diosmin ($C_{28}H_{32}O_{15}$: 608.55).

Method of preparation Prepare as directed under Capsules, with Diosmin.

Identification Weigh accurately an amount of the contents of Diosmin Capsules equivalent to 50 mg of diosmin, add 10 mL of 0.1 mol/L sodium hydroxide methanolic solution, warm on a steam bath, and cool. Filter and use this solution as the test solution. Separately, weigh 50 mg of diosmin RS, dissolve in 10 mL of 0.1 mol/L sodium hydroxide methanolic solution, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with fluorescence indicator), develop the plate with a mixture of ethyl acetate, methyl ethyl acetone, water and formic acid (5 : 3 : 1 : 1) (as the developing solvent) to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots obtained from the test solution exhibits R_f values and the colors corresponding to that of the standard solution.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the contents of NLT 20 capsules of Diosmin Capsules. Weigh accurately an amount equivalent to about 10 mg of diosmin ($C_{28}H_{32}O_{15}$), add 70 mL of 0.1 mol/L sodium hydroxide methanolic solution, warm on a steam bath, and dissolve. Cool it down and add 0.1 mol/L sodium hydroxide methanolic solution to make 100 mL. Filter this solution, take 10.0 mL of the filtrate, add 0.1 mol/L sodium hydroxide methanolic solution to make 50 mL, and use this solution as the test solution. Separately, weigh accurately an amount equivalent to 10 mg of diosmin RS, as a dried basis, proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S of the test solution and the standard solution, at the wavelength of 374 nm as directed under the Ultraviolet-visible Spectroscopy, using 0.1 mol/L sodium hydroxide methanolic solution as a control solution.

$$\text{Amount (mg) of diosmin } (C_{28}H_{32}O_{15}) = \text{Amount (mg) of diosmin RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in well-closed containers.

Diosmin Tablets
디오스민 정

Diosmin Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of diosmin ($C_{28}H_{32}O_{15}$: 608.55).

Method of preparation Prepare as directed under Tablets, with Diosmin.

Identification Weigh an amount of Diosmin Tablets, equivalent to 50 mg of diosmin according to the labeled amount, add 10 mL of 0.1 mol/L methanolic sodium hydroxide solution, warm on a steam bath to dissolve, and use the filtrate as the test solution. Weigh a50 mg of diosmin RS, dissolve in 10 mL of 0.1 mol/L methanolic

sodium hydroxide solution, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography, develop the plate with a mixture of ethyl acetate, methylethylacetone, water and formic acid (5 : 3 : 1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f value and the color of the spots obtained from the test and the standard solution are same.

Disintegration Meets the requirements. However, the disintegration time is 15 minutes.

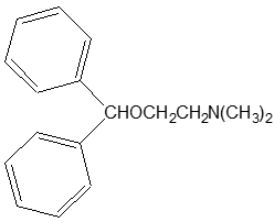
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Diosmin Tablets and powder. Weigh accurately an amount equivalent to 10 mg of diosmin ($C_{28}H_{32}O_{15}$), add 70 mL of 0.1 mol/L methanolic sodium hydroxide solution, warm on a steam bath to dissolve, cool, and add 0.1 mol/L methanolic sodium hydroxide solution to make exactly 100 mL. Filter this solution, pipet 10 mL of the filtrate, add 0.1 mol/L methanolic sodium hydroxide solution to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of diosmin RS, calculated on the dried basis, proceed in the same manner as in the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using 0.1 mol/L methanolic sodium hydroxide solution as the control solution, and determine the absorbances, A_T and A_S at a wavelength of 374 nm.

Amount (mg) of diosmin ($C_{28}H_{32}O_{15}$)
= Amount (mg) of diosmin RS × (A_T / A_S)

Packaging and storage Preserve in well-closed containers.

Diphenhydramine
디펜히드라민



$C_{17}H_{21}NO$: 255.36
2-Benzhydryloxy-*N*,*N*-dimethylethanamine [*58-73-1*]

Diphenhydramine contains NLT 96.0% and NMT 101.0% of diphenhydramine ($C_{17}H_{21}NO$).

Description Diphenhydramine occurs as a clear, pale yellow to yellow liquid with a characteristic odor, and has a tongue-burning taste at first, followed by slight sensation of numbness on the tongue.
It is miscible with ethanol(95), acetic acid(100), acetic anhydride or ether.
It is very slightly soluble in water.
Boiling point—About 162 ℃ (0.67 kPa).
Refractive index n_D^{20}: About 1.55.
It is gradually affected by light.

Identification Determine the infrared spectra of Diphenhydramine and Diphenhydramine RS as directed under the ART method under the mid-infrared absorption spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Specific gravity d_{20}^{20}: Between 1.013 and 1.020.

Purity (1) ***β-Dimethylaminoethanol***—Dissolve 1.0 g of Diphenhydramine in 20 mL of ether, shake well with 10 mL each of water to mix, and extract twice. Combine the water extracts, and add 2 drops of phenolphthalein TS and 1.0 mL of 0.05 mol/L sulfuric acid; the resulting solution does not exhibit a red color.

(2) ***Benzhydrol***—Put 1.0 g of Diphenhydramine into a separatory funnel, dissolve in 20 mL of ether, shake well with 25 mL each of diluted hydrochloric acid (1 in 15) to mix, and extract twice. Separate the ether layer to take, evaporate gradually on a steam bath, and dry the residue in vacuum in a desiccator (silica gel); the amount is NMT 20 mg.

(3) ***Heavy metals***—Proceed with 1.0 g of Diphenhydramine as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

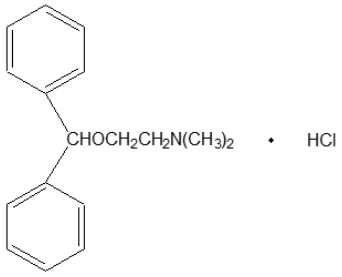
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Diphenhydramine, dissolve in 50 mL of a mixture of acetic acid(100) and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 25.536 mg of $C_{17}H_{21}NO$

Packaging and storage Preserve in almost well-filled and light-resistant, tight containers.

Diphenhydramine Hydrochloride
디펜히드라민염산염



$C_{17}H_{21}NO \cdot HCl$: 291.82
2-Benzhydryloxy-*N*,*N*-dimethyl-ethanamine hydrochloride [*147-24-0*]

Diphenhydramine Hydrochloride, when dried, contains NLT 98.0% and NMT 101.0% of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$).

Description Diphenhydramine Hydrochloride occurs as white crystals or a crystalline powder. It is odorless, has a bitter taste, and paralyzes the tongue.
It is very soluble in methanol or acetic acid(100), freely soluble in water or ethanol(95), sparingly soluble acetic anhydride and practically insoluble in ether.
It is gradually affected by light.

Identification (1) Determine the absorption spectra of solutions of Diphenhydramine Hydrochloride and Diphenhydramine hydrochloride RS in methanol (1 in 2000) as directed under the Ultraviolet-visible Spectroscopy; both exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Diphenhydramine Hydrochloride and Diphenhydramine Hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Diphenhydramine Hydrochloride (1 in 50) responds to the Qualitative Analysis for chloride.

Melting point Between 166 and 170 ℃.

pH Dissolve 1 g of Diphenhydramine Hydrochloride in 10 mL of water; the pH of this solution is between 4.0 and 5.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Diphenhydramine Hydrochloride in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Diphenhydramine Hydrochloride according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve 0.20 g of Diphenhydramine Hydrochloride in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with the upper layer of a mixture of hexane, ethyl acetate, methanol and ammonia water(28) (10 : 4 : 2 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly iodine TS on the plate; the spots other than the principal spot and the spot at the starting point from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (2 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Diphenhydramine Hydrochloride, previously dried, dissolve by adding 50 mL of a mixture of acetic anhydride and acetic acid (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 29.182 mg of $C_{17}H_{21}NO \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Diphenhydramine Hydrochloride Capsules
디펜히드라민염산염 캡슐

Diphenhydramine Hydrochloride Capsules contain NLT 90.0% and NMT 110.0% the labeled amount of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$: 291.82).

Method of preparation Prepare as directed under Capsules, with Diphenhydramine Hydrochloride.

Identification (1) Weigh an amount equivalent to 50 mg of Diphenhydramine Hydrochloride according to the labeled amount and perform the test as directed under the Identification under Diphenhydramine Hydrochloride.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Dissolution Perform the test with 1 capsule of Diphenhydramine Hydrochloride Capsules at 100 revolutions per minute according to Method 1, using 500 mL of

water as the dissolution medium. Take the dissolved solution 30 minutes after starting the test, and filter. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh an appropriate amount of Diphenhydramine Hydrochloride RS, previously dried at 105 ℃ for 3 hours, and dissolve in water to obtain a solution with the same concentration as the test solution. Use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Assay under Diphenhydramine Hydrochloride Injection. Meets the requirements if the dissolution rate of Diphenhydramine Hydrochloride Capsules in 30 minutes is NLT 80%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the contents of NLT 20 capsules of Diphenhydramine Hydrochloride Capsules. Weigh accurately an amount equivalent to 50 mg of Diphenhydramine Hydrochloride ($C_{17}H_{21}NO \cdot HCl$), dissolve in water, add water to make exactly 100 mL, and filter. Perform the test as directed under the Assay under Diphenhydramine Hydrochloride Injection.

$$\text{Amount (mg) of diphenhydramine hydrochloride } (C_{17}H_{21}NO \cdot HCl) = \text{Amount (mg) of diphenhydramine hydrochloride RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers.

Diphenhydramine Hydrochloride Injection
디펜히드라민염산염 주사액

Diphenhydramine Hydrochloride Injection is an aqueous solution for injection. Diphenhydramine Hydrochloride Injection contains NLT 90.0% and NMT 110.0% of the labeled amount of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$: 291.82).

Method of preparation Prepare Diphenhydramine Hydrochloride Injection as directed under Injections, with Diphenhydramine Hydrochloride.

Description Diphenhydramine Hydrochloride Injection occurs as a clear, colorless liquid.

Identification (1) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

(2) Weigh an amount of Diphenhydramine Hydrochloride Injection, equivalent to 50 mg of diphenhydramine hydrochloride, according to the labeled amount, and add 0.03 mol/L sulfuric acid to make 25 mL. Filter this solution, if necessary, and use it as the test solution. Separately, dissolve 50 mg of diphenhydramine hydrochloride RS in 0.01 mol/L hydrochloric acid to make 25 mL, and use this solution as the standard solution. Pipet 2 mL each of the test solution and the standard solution, add 2 mL of 1 mol/L sodium hydroxide and 4 mL of carbon disulfide, and shake well to mix for 2 minutes. If necessary, centrifuge, filter, and determine as directed under the solution method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

pH Between 4.0 and 6.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 3.4 EU per mg of Diphenhydramine Hydrochloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Accurately take an amount, equivalent to 50 mg of Diphenhydramine Hydrochloride ($C_{17}H_{21}NO \cdot HCl$), according to the labeled amount, add water to make exactly 100 mL and use this solution as the test solution. Separately, weigh accurately 50 mg of Diphenhydramine Hydrochloride RS, previously dried at 105 ℃, add water to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of Diphenhydramine, respectively.

$$\text{Amount (mg) of Diphenhydramine Hydrochloride } (C_{17}H_{21}NO \cdot HCl) = \text{Amount (mg) of Diphenhydramine Hydrochloride RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with nitrile silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Mobile phase: Adjust the pH to 6.5 with a mixture of water, acetonitrile and triethylamine (50 : 50 : 0.5) with acetic acid(100). Adjustments can be made if necessary.

Flow rate: 1 mL/min

System suitability

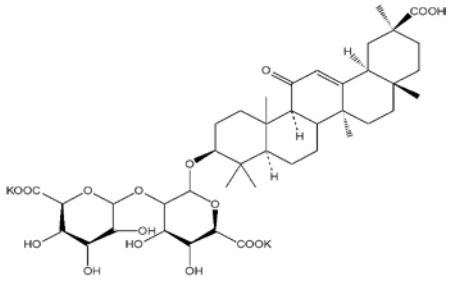
System performance: Dissolve 5 mg of benzophe-

none in 5 mL of acetonitrile, and add water to make 500 mL. To 1.0 mL of this solution, add 5 mg of Diphenhydramine Hydrochloride RS, and add water to make 10 mL. Proceed with 10 mL of this solution according to the above conditions; benzophenone and Diphenhydramine are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times according to the above conditions with 10 µL each of the standard solution; the relative standard deviation of the peak area is NMT 2.0%

Packaging and storage Preserve in light-resistant, hermetic containers.

Dipotassium Glycyrrhizinate
글리시리진산이칼륨



$C_{42}H_{60}K_2O_{16}$: 899.13

(3β,20β)-20-Carboxy-11-oxo-30-norolean-12-en-3-yl-2-*O*-β-*D*-glucopyranuronosyl-α-*D*-glucopyranosiduronic acid potassium salt (1:2), [68797-35-3]

Dipotassium Glycyrrhizinate ($C_{42}H_{60}K_2O_{16}$) contains NLT 95.0% and NMT 101.0% of dipotassium glycyrrhizinate, calculated on the anhydrous basis.

Description Dipotassium Glycyrrhizinate occurs as a white to light yellow powder with no odor and has a sweet taste.

It is freely soluble in dilute ethanol and slightly soluble in ethanol, and practically insoluble in chloroform or ether.

Identification (1) The residue obtained after the ignition of Dipotassium Glycyrrhizinate responds to the Qualitative Analysis for potassium salt.

(2) Add 10 mL of 1 mol/L hydrochloric acid TS10 mL to 0.5 g of Dipotassium Glycyrrhizinate and boil for 10 minutes. After cooling, filter the precipitate, wash it with water, and dry it at 105 °C for 1 hour. Add 0.5 mL of 2,6-di-tert-butyl-p-cresol TS and 1 mL of sodium hydroxide solution (1 in 5) to 1 mL of the dried in ethanol solution (1 in 1000). Then, heat the mixture on a steam bath for 90 minutes; a reddish purple to purple precipitate forms suspension.

(3) Weigh 10 mg of Dipotassium Glycyrrhizinate, dissolve in 10 mL of methanol, and use this solution as the test solution. Separately, weigh about 10 mg of dipotassium glycyrrhizinate RS, dissolve in 10 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 µL each of the test solution and standard solution on a plate of silica gel with a fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of methanol, toluene and acetic acid(100) (7 : 2 : 1) to about 15 cm, and air-dry the plate. Expose it to ultraviolet light (main wavelength: 254 nm); the color and R_f value of the spots obtained from the test solution and the standard solution are the same.

pH Between 5.0 and 6.0 (1% aqueous solution).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Dipotassium Glycyrrhizinate in 20 mL of water; the solution is colorless to light yellow in color and clear.

(2) ***Chloride***—Add 6 mL of dilute nitric acid and 10 mL of water to 0.5 g of Dipotassium Glycyrrhizinate, boil the mixture for 10 minutes, then filter it. Wash the residue with a small amount of water twice, and combine the washings with the filtrate. If the filtrate is colored, add 1 mL of hydrogen peroxide and heat on a steam bath for 10 minutes. After cooling, filter the precipitate and wash the residue twice with a small amount of water. Combine the washings with the filtrate, and add water to make 50 mL. Use this as the test solution and perform the test according to the Chloride. Prepare the control solution by adding 6 mL of dilute nitric acid and water to 0.20 mL of 0.01 mol/L hydrochloric acid solution to make 50 mL (NMT 0.014%).

(3) ***Sulfate***—To 0.5 g of Dipotassium Glycyrrhizinate, add 5 mL of dilute nitric acid and 10 mL of water, dissolve for 10 minutes, and filter it. Wash the residue with a small amount of water twice, combine the washings with the filtrate, and neutralize it with ammonia TS. If the filtrate is colored, add 1 mL of hydrogen peroxide and heat on a steam bath for 10 minutes. After cooling, if necessary, filter it and wash the residue twice with a small amount of water. Collect the washings and the filtrate and add water to make 50 mL. Use this solution as the test solution, perform the test according to the Sulfate. Prepare the control solution with 0.30 mL of 0.005 mol/L sulfuric acid and 1 mL of dilute hydrochloric acid and add water to make 50 mL (NMT 0.029%).

(4) ***Heavy metals***—Dissolve the residue obtained from Residue on Ignition test in 2 mL of dilute Acetic Acid and add water, and filter it if necessary, to make a volume of 50 mL. Use this as the test solution and perform the test according to the Heavy Metals. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Arsenic***—Proceed with 0.5 g of Dipotassium Glycyrrhizinate, and perform the test according to Method 3 (NMT 4 ppm).

Water NMT 8.0% (0.1 g, volumetric titration, direct titration).

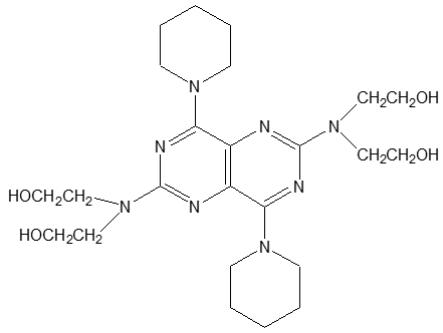
Residue on ignition Between 18.0% and 21.0% (2.0 g, calculated on the anhydrous basis).

Assay Weigh accurately about 0.1 g of Dipotassium Glycyrrhizinate and add water to make 500 mL. Take 10.0 mL of Dipotassium Glycyrrhizinate and add 50 mL of water. Use this solution as the test solution. After separately drying ncotinamide RS in a desiccator (in vacuum, silica gel) for 4 hours, weigh accurately about 20 mg of the nicotinamide RS and add water to make 200 mL. Take 10.0 mL of this solution, add water to make 50 mL, and use this solution as the standard solution. Perform the test according to the Ultraviolet-visible Spectroscopy, measure the absorbance A_T of the test solution at the absorption maximum wavelength around 257 nm and the absorbance A_S of the standard solution at the absorption maximum wavelength around 261 nm, respectively.

$$\text{Content (\%) of dipotassium glycyrrhizinate } (C_{42}H_{60}K_2O_{16}) = \frac{2A_T}{A_S \times 1.053} \times \left(\frac{Amount\ of\ nicotinamide\ RS\ taken\ (mg)}{\text{Amount of sample taken (mg)} - \text{water (mg)}} \right) \times 2.5 \times 100$$

Packaging and storage Preserve in tight containers.

Dipyridamole
디피리다몰



$C_{24}H_{40}N_8O_4$: 504.63

2-[[2-[*bis*(2-Hydroxyethyl)amino]-4,8-di(piperidin-1-yl)pyrimido[5,4-d]pyrimidin-6-yl]-(2-hydroxyethyl)amino]ethanol [*58-32-2*]

Dipyridamole, when dried, contains NLT 98.5% and NMT 101.0% of dipyridamole ($C_{24}H_{40}N_8O_4$).

Description Dipyridamole occurs as yellow crystals or a crystalline powder. It is odorless and has a slightly bitter taste.

It is freely soluble in chloroform, sparingly soluble in methanol or ethanol(99.5) and practically insoluble in water or ether.

Identification (1) Dissolve 5 mg of Dipyridamole in 2 mL of sulfuric acid, add 2 drops of nitric acid, and mix by shaking; the resulting solution exhibits a dark purple color.

(2) Determine the absorption spectra of solutions of Dipyridamole and Dipyridamole RS in a mixture of methanol and hydrochloric acid (99 : 1) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Dipyridamole and Dipyridamole RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 165 and 169 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Dipyridamole in 10 mL of chloroform; the solution is clear and yellow.

(2) ***Chloride***—Dissolve 0.5 g of Dipyridamole in 5 mL of ethanol(95) and 2 mL of 2 mol/L nitric acid, and add 1 mL of silver nitrate TS; neither turbidity nor precipitate develops.

(3) ***Heavy metals***—Proceed with 2.0 g of Dipyridamole according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Proceed with 1.0 g of Dipyridamole according to Method 3 and perform the test (NMT 2 ppm).

(5) ***Related substances***—Dissolve 50 mg of Dipyridamole in 50 mL of mobile phase and use this solution as the test solution. Pipet 0.5 mL of this solution, add the mobile phase to it make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of each solution as directed in the automatic integration method; the total area of the peak other than that of Dipyridamole from the test solution is not greater than the peak area of Dipyridamole from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm to 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 0.2 g of potassium dihydrogen phosphate in 200 mL of water and add 800 mL of methanol.

Flow rate: Adjust the flow rate so that the retention

time of dipyridamole is about 4 minutes.

System suitability

Detection sensitivity: Adjust the detection sensitivity so that the peak height of dipyridamole obtained from 20 μL of the standard solution is between 2 mm and 6 mm.

System performance: Weigh 7 mg of Dipyridamole and 3 mg of terphenyl, and dissolve in 50 mL of methanol. Proceed with 20 μL of this solution according to the above conditions; dipyridamole and terphenyl are eluted in this order with the resolution being NLT 5.

Time span of measurement: About 5 times the retention time of dipyridamole.

Loss on drying NMT 0.2% (1 g, 105 ℃, 3 hours).

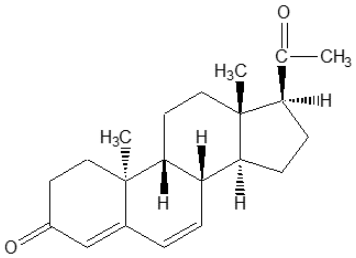
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.6 g of Dipyridamole, previously dried, dissolve in 70 mL of methanol, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 50.46 mg of $C_{24}H_{40}N_8O_4$

Packaging and storage Preserve in light-resistant, well-closed containers.

Dirithromycin
디리트로마이신



$C_{42}H_{78}N_2O_{14}$: 835.09

(1*S*,2*R*,4*R*,5*R*,6*S*,7*S*,8*R*,11*R*,12*R*,15*R*,17*S*)-5-[(2*S*,3*R*,4*S*,6*R*)-4-(Dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy-11-ethyl-4,12-dihydroxy-7-[(2*R*,4*R*,5*S*,6*S*)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-15-(2-methoxyethoxymethyl)-2,4,6,8,12,17-hexamethyl-10,14-dioxa-16-azabicyclo[11.3.1]heptadecan-9-one [*62013-04-1*]

Dirithromycin contains NLT 96.0% and NMT 102.0% per mg of dirithromycin and epidirithromyciin ($C_{42}H_{78}N_2O_{14}$), calculated on the anhydrous basis.

Description Dirithromycin occurs as a white or pale gray crystalline powder. It is freely soluble in chloroform, soluble in methanol, slightly soluble in propanol or acetonitrile, and very slightly soluble in water or cyclohexane.

Identification (1) Determine the infrared spectra of Dirithromycin and dirithromycin RS, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Crystallinity Meets the requirements.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Dirithromycin according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances*—**Weigh accurately 0.1 g of Dirithromycin, dissolve in a mixture of acetonitrile and methanol (70 : 30) to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately a suitable amount of dirithromycin RS, dissolve in a mixture of acetonitrile and methanol (70 : 30) to make a solution containing 0.2 mg per mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions. Determine each peak area in each solution by the automatic integration method and calculate the content (%) of each related substance according to the following equation; the content of 9-(S)-erythromycilamine is NMT 1.5%, the content of any other related substance is NMT 1.0%, and the total content of related substances is NMT 4.0%. However, dirithromycin 16S-epimer is not regarded as a related substance for calculation.

Content (%) of 9-(S)-erythromycilamine or other related substances (%)
$$= \frac{C}{W} \times \frac{A_i}{A_S} \times 1000$$

C: Concentration (mg /mL) of dirithromycin in the standard solution.

W: Amount (mg) of Dirithromycin taken.

A_i: Peak area of each related substance obtained from the test solution.

A_S: Peak area of dirithromycin (16R-epimer) obtained from the standard solution.

Operating conditions

For the detector, column and mobile phase, proceed as directed under the Assay.

Time span of measurement: About 3 times the retention time of dirithromycin (16R-epimer).

(3) ***Dirithromycin 16s-epimer*—**Determine the con-

tent (%) of dirithromycin 16S-epimer in Dirithromycin using the chromatogram obtained from the related substances test, according to the following equation (NMT 1.5%).

$$\text{Content (\%) of dirithromycin 16S-epimer} = \frac{C}{W} \times \frac{A_E}{A_S} \times 1000$$

A_E: Peak area of dirithromycin 16S-epimer in the test solution.

C: Concentration (mg /mL) of dirithromycin in the standard solution.

W: Amount (mg) of Dirithromycin taken.

A_S: Peak area of dirithromycin (16R-epimer) obtained from the standard solution.

Water NMT 1.0% (1.0 g, volumetric titration, direct titration).

Assay Weigh accurately about 20 mg each of Dirithromycin and dirithromycin RS, dissolve each in a mixture of acetonitrile and methanol (70 : 30) to make exactly 10 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of dirithromycin (16R-epimer).

$$\text{Content (\%) of dirithromycin } (C_{42}H_{78}N_2O_{14}) = 1000 \times \frac{C}{W} \times \frac{A_T}{A_S} + P_E$$

CS: Concentration (mg/mL) of dirithromycin in the standard solution.

W: Amount (mg) of Dirithromycin taken.

P_E: Content (%) of dirithromycin 16S-epimer calculated in (3) under Purity above.

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 205 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of acetonitrile, phosphate buffer solution (pH 7.5) and ethanol (44 : 37 : 19).

Flow rate: 2 mL/min

System suitability

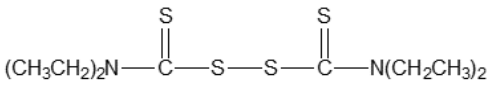
System performance: Proceed with 10 μL of the system suitability solution under the above operating conditions; the relative retention times of 9-(S)-erythromycilamine, dirithromycin (16R-epimer) and dirithromycin 16S-epimer are 0.7, 1.0 and 1.12, respectively. The resolution between the peaks of dirithromycin (16R-epimer) and dirithromycin 16S-epimer is NLT 2.0, the resolution between the peaks of dirithromycin (16R-epimer) and 9-(S)-erythromycilamine is NLT 5.0, and the symmetry factor of the dirithromycin (16R-epimer) peak is NMT 2.

System repeatability: Repeat the test 5 times with 10 μL of the system suitability solution under the above operating conditions; the relative standard deviation of the peak areas of dirithromycin (16R-epimer) is NMT 1.0%.

System suitability solution—Weigh accurately a suitable amount of dirithromycin RS and dissolve in the mobile phase to make a solution containing 2.5 mg per mL. Keep this solution at room temperature for 24 hours. The solution is an equilibrium mixture of dirithromycin (16R-epimer), dirithromycin 16S-epimer and 9-(S)-erythromycilamine, and may be used for 1 month at room temperature.

Packaging and storage Preserve in well-closed containers.

Disulfiram
디설피람



$C_{10}H_{20}N_2S_4$: 296.54

Diethylcarbamothioylsulfanyl-*N*,*N*-diethylcarbamo dithioate [*97-77-8*]

Disulfiram, when dried, contains NLT 99.0% and NMT 101.0% of disulfiramm ($C_{10}H_{20}N_2S_4$).

Description Disulfiram occurs as white to yellow crystals or a crystalline powder.

It is freely soluble in acetone or toluene, slightly soluble in methanol or ethanol(95) and practically insoluble in water.

Identification (1) Determine the absorption spectra of Disulfiram and disulfiram RS in ethanol(95) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Disulfiram and disulfiram RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 70 and 73 ℃.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Disulfiram according to Method 2 and perform the test. Prepare

the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Disulfiram according to Method 4 and perform the test (NMT 2 ppm).

(3) ***Diethyldithiocarbamic acid***—Dissolve 0.10 g of Disulfiram in 10 mL of toluene, add 10 mL of diluted sodium carbonate TS (1 in 20), and shake to mix. Take the water layer separately, wash with 10 mL of toluene, and add 5 drops of copper sulfate (1 in 250) and 2 mL of toluene. Shake to mix and allow to stand; the toluene layer does not exhibit a pale yellow color.

(4) ***Related substances***—Dissolve 50 mg of Disulfiram in 40 mL of ethanol, add water to make 50 mL, and use this solution as the test solution. Pipet 1 mL of the test solution, add the mobile phase to make exactly 200 mL, and use this solution as the standard solution. Pipet 10 μL each of the test solution and the standard solution and perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution according to the automatic integration method; the total area of the peaks other than disulfiram obtained from the test solution is not larger than the peak area of disulfiram from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 5 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of methanol and water (7:3).

Flow rate: Adjust the flow rate so that the retention time of disulfiram is about 8 minutes.

Selection of column: Dissolve 50 mg each of Disulfiram and benzophenone in 40 mL of methanol, and add water to make 50 mL. Pipet 1 mL of this solution add the mobile phase to make 200 mL. Proceed with 10 μL each of this solution according to the above operating conditions, and calculate the resolution. Use a column giving elution of benzophenone and disulfiram in this order with the resolution between these peaks being NLT 4.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of disulfiram obtained from 10 μL of the standard solution is 15 to 30 mm.

Time span of measurement: About 3.5 times of the retention time of disulfiram.

Loss on drying NMT 0.2% (2 g, silica gel, 24 hours).

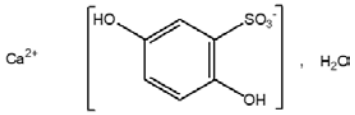
Residue on ignition NMT 0.1% (2 g).

Assay Weigh accurately about 0.2 g of Disulfiram, previously dried, in an iodine bottle, dissolve in 20 mL of acetone, add 1.5 mL of water and 1.0 g of potassium iodide, and dissolve by shaking thoroughly. To this solution, add 3.0 mL of hydrochloric acid, stopper the bottle tightly, shake to mix, and allow to stand in a dark place for 3 minutes. Add 70 mL of water and titrate with 0.1 mol/L sodium thiosulfate VS (potentiometric titration under the Titrimetry). Perform a blank test and make any necessary correction.

Each mL of 0.1 mol/L sodium thiosulfate VS
= 14.83 mg of $C_{10}H_{20}N_2S_4$

Packaging and storage Preserve in tight containers.

Dobesilate Calcium Hydrate
도베실산칼슘수화물



$C_{12}H_{10}O_{10}S_2Ca \cdot H_2O$: 436.43

Calcium di(2,5-dihydroxybenzenesulfonate) monohydrate, [*20123-80-2*]

Dobesilate Calcium Hydrate contains NLT 99.0% and NMT 101.0% of dobesilate calcium ($C_{12}H_{10}O_{10}S_2Ca$: 418.40), calculated on the anhydrous basis.

Description Dobesilate Calcium Hydrate occurs as a white crystalline powder. It is odorless.
It is freely soluble in water or ethanol and practically insoluble in ether and chloroform.

Melting point—About 300 °C (with decomposition).

Identification (1) A solution of Dobesilate Calcium Hydrate responds to the Qualitative Analysis for calcium hydrate.

(2) Determine the absorption spectrum of the solution (2.5 in 1000000) of Dobesilate Calcium Hydrate as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 218 nm and 222 nm and between 298 nm and 302 nm.

pH Between 4.3 and 5.1 (12% solution).

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Dobesilate Calcium Hydrate according to the Method 1, and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 15 ppm).

(2) ***Arsenic*—**Proceed with 0.4 g of Dobesilate Calcium Hydrate according to the Method 1 and perform the test (NMT 5 ppm).

(3) ***Sulfate***—Proceed with 0.5 g of Dobesilate Calcium Hydrate and perform the test. Prepare the control solution with 0.1 mL of 0.005 mol/L sulfuric acid (NMT 0.01%).

(4) ***Iron*—**Weigh accurately 10.0 g of Dobesilate

Calcium Hydrate and add 100 mL of water not containing carbon dioxide. Take 10 mL of this solution and add 2 mL of 200 g/L citric acid and 0.1 mL of thioglycolic acid. Alkalify the solution with 10.6 mol/L ammonia water, add 20 mL of water and shake, and use this solution as the test solution. Separately, take 1 mL of iron standard solution and prepare the control solution in the same way as the test solution. After allowing it to stand for 5 minutes, compare the colors of the test solution and the control solution against a pink background; the color of the test solution is not more intense than that of the control solution (NMT 10 ppm).

(5) ***Hydroquinone***—Weigh 1.0 g of Dobesilate Calcium Hydrate, dissolve in 10 mL of water, and use this solution as the test solution. Separately, weigh 10 mg of hydroquinone RS, dissolve in water to make 100 mL, and use this solution as the standard solution. With these solutions, spot 5 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel (with a fluorescence indicator) for thin-layer chromatography, develop the plate with a mixture of n-butanol, acetic acid and water (72 : 10 : 18), and air-dry the plate. Expose the plate to ultraviolet irradiation (254 nm) or spray a mixture of 1% ferric chloride, 1% potassium ferricyanide and nitric acid (50 : 50 : 5) on the plate; the spots other than the principal spot from the test solution are not more intense than the blue principal spot from the standard solution (NMT 0.1%).

Water NMT 6.0% (0.2 g, volumetric titration, direct titration).

Assay Weigh accurately about 0.9 g of Dobesilate Calcium Hydrate, previously dried, dissolve in 80 mL of water, add 2 mL of 8 mol/L potassium hydroxide TS and 0.1 g of N,N indicator, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS. The endpoint of titration is when the reddish purple color of solution turns into the blue color. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 20.920 mg of $C_{12}H_{10}O_{10}S_2Ca$

Packaging and storage Preserve in tight containers.

Dobesilate Calcium Tablets
도베실산칼슘 정

Dobesilate Calcium Tablets contains NLT 95.0% and NMT 105.0% equivalent to the labeled amount of dobesilate calcium hydrate ($C_{12}H_{10}O_{10}S_2Ca \cdot H_2O$: 436.43).

Method of preparation Prepare as directed under Tablets, with Dobesilate Calcium Hydrate.

Identification (1) Take equivalent to about 40 mg of Dobesilate Calcium Hydrate according to the labeled amount of Dobesilate Calcium Tablets, add water to make 100 mL, and filter. Take 10 mL of the filtrate, and add water to make 100 mL. Determine the absorption spectra of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima around 220 ± 2 nm and 300 ± 2 nm wavenumbers.

(2) Weigh a portion of powdered Dobesilate Calcium Tablets, equivalent to 0.1 g of Dobesilate Calcium according to labeled amount, add 10 mL of water, filter, and use this filtrate as the test solution. Separately, weigh about 0.1 g of dobesilate calcium hydrate RS, dissolve in 10 mL of water, and use this solution as the standard solution. Spot 5 μL each of the test solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer-chromatography. Develop the plate with the upper layer of a mixture of n-butanol, water and acetic acid (36 : 9 : 5) to a distance of about 17 cm and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm). The R_f values of the spots from the test solution and the standard solutions are the same.

Purity ***Hydroquinone***—Weigh the amount of Dobesilate Calcium Tablets, previously powdered, equivalent to 1.0 g of Dobesilate Calcium Hydrate, add 10 mL of water, shake to mix, centrifugate, and use the clear liquid at the top layer as the test solution. Separately, take 10 mg of hydroquinone RS, dissolve in water to make 100 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Thin Layer Chromatography according to the conditions of the Identification 2) and observe the solutions under ultraviolet light; spots other than the principal spot from the test solution is not more intense than the purple spots from the standard solution (NMT 0.1%).

Dissolution Perform the test with 1 tablet of Dobesilate Calcium Tablets at 50 revolutions per minute according to the Method 2 under the Dissolution Test, using 900 mL of water as the dissolution medium. Take the dissolved solution 30 minutes after starting the test, and filter. Pipet 5 mL of this solution, add water to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately about 70 mg of dobesilate calcium hydrate RS and dissolve in water to make 100 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of Dobesilate Calcium Hydrate from each solution, A_T and A_S, respectively.
It meets the requirements when the dissolution rate of Dobesilate Calcium Tablets in 30 minutes should be NLT 85%.

Dissolution rate (%) of dobesilate calcium hydrate ($C_{12}H_{10}S_2Ca \cdot H_2O$)
$= W_S \times (A_T/A_S) \times (1/C) \times 360$

W_S: Amount (mg) of dobesilate calcium hydrate RS.
C: Labeled amount (mg) of dobesilate calcium hydrate ($C_{12}H_{10}O_{10}S_2Ca \cdot H_2O$) per tablet.

Operating conditions

Detector: An ultraviolet-visible spectrophotometer (wavelength: 301 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of 0.1% phosphoric acid and methanol (9 : 1).

Flow rate: 1.0 mL/minute

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above operating conditions, the relative standard deviation of the peak areas of Dobesilate Calcium Hydrate is NMT 2.0%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately and powder NLT 20 Dobesilate Calcium Tablets. Weigh accurately equivalent to about 100 mg of dobesilate calcium hydrate ($C_{12}H_{10}O_{10}S_2Ca \cdot H_2O$), add 100 mL of water. Pipet 10 mL of the test solution, add the mobile phase to make exactly 100 mL and use this solution as the test solution. Separately, weigh accurately about 100 mg of dobesilate calcium hydrate RS, add water to make exactly 100 mL, take 10 mL of this solution, add water to make 100 mL, and use it as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine, A_T and A_S, of the peak areas of Dobesilate Calcium.

Amount (mg) of dobesilate calcium hydrate ($C_{12}H_{10}O_{10}S_2Ca \cdot H_2O$)
= Amount (mg) of dobesilate calcium hydrate RS
$\times (A_T / A_S)$

Operating conditions

Detector: An ultraviolet-visible spectrophotometer (wavelength: 301 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of 0.1% phosphoric acid and methanol (9 : 1).

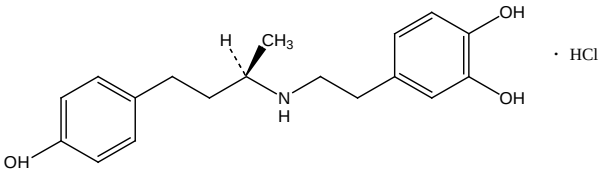
Flow rate: 1.0 mL/minute

System suitability

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak areas is NMT 2.0.

Packaging and storage Preserve in light-resistant, tight containers.

Dobutamine Hydrochloride
도부타민염산염



and enantiomer

$C_{18}H_{23}NO_3 \cdot HCl$: 337.84

(*RS*)-4-[2-[4-(4-Hydroxyphenyl)butan-2-ylamino]ethyl]benzene-1,2-diol hydrochloride [*49745-95-1*]

Dobutamine Hydrochloride, when dried, contains NLT 98.0% and NMT 101.0% of dobutaime hydrochloride ($C_{18}H_{23}NO_3 \cdot HCl$).

Description Dobutamine Hydrochloride occurs as a white to very pale orange crystalline powder or grain.
It is freely soluble in methanol, sparingly soluble in water or ethanol(95), and practically insoluble in ether.
A solution of Dobutamine Hydrochloride (1 in 100) shows no optical rotation.

Identification (1) Determine the infrared spectra of Dobutamine Hydrochloride and dobutamine hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) A solution of Dobutamine Hydrochloride (1 in 50) responds to the Qualitative Analysis (2) for chloride.

Melting point Between 188 and 191 ℃.

pH Dissolve 1 g of Dopamine Hydrochloride in 100 mL of water; the pH of this solution is between 4.0 and 5.5.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Dopamine Hydrochloride in 30 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Dissolve 1.0 g of Dopamine Hydrochloride in 40 mL of water by warming, cool down, and add 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and

perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve 0.10 g of Dopamine Hydrochloride in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of chloroform, methanol and formic acid (78 : 22 : 5) to a distance of about 12 cm, and air-dry the plate. Allow the plate to stand for 5 minutes in iodine vapor; spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.3% (1 g, 105 °C, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.1 g of Dobutamine Hydrochloride and dobutamine hydrochloride RS, previously dried, dissolve in exactly 10 mL of the internal standard solution, add diluted methanol (1 in 2) to make 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of Dobutamine Hydrochloride to the internal standard, respectively.

$$\text{Amount (mg) of dobutamine hydrochloride } (C_{18}H_{23}NO_3.HCl) = \text{Amount (mg) of dobutamine hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of salicylamide in diluted methanol (1 in 2) (1 in 125).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (7 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of tartaric acid buffer solution, pH 3.0 and methanol (7 : 3).

Flow rate: Adjust the flow rate so that the retention time of dobutamine is about 7 minutes.

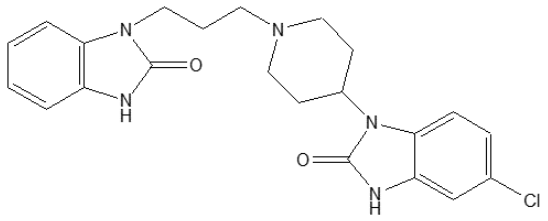
System suitability

System performance: Proceed with 5 μL of the standard solution under the above conditions; dobutamine and the internal standard are eluted in this order with the resolution being NLT 5.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution as directed under the above conditions, the relative standard deviation of peak area ratios of dobutamine to the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Domperidone
돔페리돈



$C_{22}H_{24}ClN_5O_2$: 425.91

5-Chloro-1-(1-(3-(2-oxo-2,3-dihydro-1*H*-benzo[d]imidazol-1-yl)propyl)piperidin-4-yl)-1*H*-benzo[d]imidazol-2(3*H*)-one [*57808-66-9*]

Domperidone, when dried, contains NLT 99.0% and NMT 101.0% of domperidone ($C_{22}H_{24}ClN_5O_2$).

Description Domperidone occurs as a white to pale yellow crystalline powder.

It is soluble in *N*,*N*-dimethylformamide, slightly soluble in methanol and ethanol(95), and practically insoluble in water.

Identification Determine the infrared spectra of Domperidone and domperidone RS, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 218 and 248 ºC.

Purity (1) ***Clarity and color of solution***—Dissolve 0.2 g of Domperidone in 20 mL of *N*,*N*-dimethylformamide; the solution is colorless and clear.

(2) ***Heavy metals***—Proceed with about 2.0 g of Domperidone according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Prepare the solutions for the test immediately before use. Dissolve 0.1 g of Domperidone in 10 mL of *N*,*N*-dimethylformamide, and use this solution as the test solution. Pipet 1 mL of the test solution, and add *N*,*N*-dimethylformamide to make exactly 100 mL. Pipet 5 mL of this solution, add *N*,*N*-dimethylformamide to make exactly 20 mL, and use this solution as the standard solution (1). Perform the test with 10 μL each of *N*,*N*-dimethylformamide (as a blank test solution), the test solution and the standard solution (1) as

directed under the Liquid Chromatography according to the following conditions. Determine each peak area from each solution by the automatic integration method and calculate the amount of related substances in the test solution; none of the domperidone related substance I {5-chloro-1(piperidin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one} having a relative retention time of about 0.4, the domperidone related substance II {4-(5-chloro-2-oxo2,3-dihydro-1*H*-benzimidazol-1-yl)-1-formylpiperidine} having a relative retention time of about 0.65, the domperidone related substance III {*cis*-4-(5-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-[3-(2-oxo2,3-dihydro-1*H*-benzimidazol-1-yl)propyl]piperidine1-oxide} having a relative retention time of about 0.7, the domperidone related substance IV {5-chloro-3-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)propyl]-1-[1-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)propyl]piperidin-4-yl]-1,3-dihydro-2-benzimidazol-2-one} having a relative retention time of about 1.15, the domperidone related substance V {1-[3-[4-(5-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]propyl]-3-[3-(2-oxo-2,3-dihydro-1Hbenzimidazol-1-yl)propyl]-1,3-dihydro-2*H*-benzimidazol-2-one} having a relative retention time of about 1.2 and the domperidone related substance VI {1,3-bis[3-[4-(5-chloro2-oxo-2,3-diihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]propyl]-1,3-dihydro-2*H*-benzimidazol-2-one} having a relative retention time of about 1.3, with respect to domperidone, is greater than the peak area of domperidone from the standard solution (1) (0.25%). Each peak area of other related substances is not greater than 0.4 times the peak area of domperidone from the standard solution (1) (0.1%). The sum of the peak areas of the related substances is not greater than 2 times the peak area of domperidone from the standard solution (1) (0.5%). Disregard any peak in the chromatogram obtained with the blank test solution and any peak with an area less than 0.2 times the area of the peak of Domperidone from the standard solution (1).

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 280 nm).

A stainless steel column, 4.6 mm in internal diameter and about 10 cm in length, packed with base-deactivated octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Mobile phase: Apply a mixture of ammonium acetate (5 in 1000) and methanol (70 : 30) to the column at a flow rate of 1.5 mL per minute, then increase the ratio of methanol sequentially over 10 min, followed by elution with methanol for 2 minutes.

Flow rate: 1.5 mL/min. Apply methanol to the column for at least 30 min to reach an equilibrium, and then equilibrate it again with the initial mobile phase composition (a mixture of ammonium acetate (5 in 1000) and methanol (70 : 30) for at least 5 minutes.

Selection of column: Dissolve 10 mg of domperidone RS and 15 mg of droperidol RS in 100 mL of *N*,*N*-dimethylformamide, and use this solution as the standard solution (2). Proceed with 10 μL of the standard solution (2) under the above operating conditions. At this time, use a column from which the retention times for domperidone and droperidol is 6.5 minutes and 7 minutes, respectively, with the resolution between these peaks being NLT 2.0. If necessary, adjust the concentration of methanol in the mobile phase or control it through the gradient elution.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of domperidone obtained from 10 μL of the standard solution (1) is NLT 50.0% of the full scale.

Loss on drying NMT 0.5% (1 g, 100 - 105 ºC, constant mass).

Ignition residue NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Domperidone, previously dried, dissolve in a mixture of 2-butanone and acetic acid(100) (7 : 1) to make 50 mL, and titrate with 0.1 mol/L perchloric acid VS (indictor: 0.2 mL of 1-naphtholbenzein TS). However, the endpoint of the titration is when the color changes from orange to green.

Each mL of 0.1 mol/L perchloric acid VS
= 42.59 mg of $C_{22}H_{24}ClN_5O_2$

Packaging and storage Preserve in light-resistant, well-closed containers.

Domperidone Oral Suspension
돔페리돈 현탁액

Domperidone Oral Suspension contains NLT 95.0% and NMT 105.0% of the labeled amount of domperidone ($C_{22}H_{24}ClN_5O_2$: 425.91).

Method of preparation Prepare as directed under Suspensions, with domperidone.

Identification Take 10 mL of Domperidone Oral Suspension, put in a 125-mL separatory funnel, add 10 mL of water and 2.5 mL of ammonia TS, and extract 3 times with 20 mL of ethyl acetate each time. Filter the extracts and evaporate to dryness. Dissolve the dried material in 5 mL of methanol, and use this solution as the test solution. Separately, dissolve 20 mg of domperidone RS in 10 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescence indicator for thin-layer chromatography, develop the plate with a mixture of ethyl acetate, methanol and acetate buffer solution (pH 4.7) (100 : 15 : 5) as the developing solvent to a distance of about 17 cm, and air-dry

the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm) or spray Dragendorff's TS onto the plate; the R_f values and color of the spots obtained from the test solution and the standard solution are the same.

pH Between 5.2 and 7.2.

Assay Take exactly an amount of Domperidone Oral Suspension, equivalent to about 10 mg of domperidone ($C_{22}H_{24}ClN_5O_2$), put in a 100-mL volumetric flask, add 1 mL of 0.1 mol/L hydrochloric acid TS and 50 mL of methanol, and sonicate for 20 minutes. Then, add methanol to make exactly 100 mL. Centrifuge this solution, and use the supernatant as the test solution. Separately, weigh accurately about 10 mg of domperidone RS, add 1 mL of 0.1 mol/L hydrochloric acid TS and 50 mL of methanol, and sonicate for 20 minutes. Add methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography and determine the peak areas, A_T and A_S of domperidone in each solution.

$$\text{Amount (mg) of domperidone } (C_{22}H_{24}ClN_5O_2) = \text{Amount (mg) of domperidone RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of 0.5% ammonium acetate solution and methanol (4 : 6).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in light-resistant, tight containers.

Domperidone Tablets
돔페리돈 정

Domperidone Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of Domperidone ($C_{22}H_{24}ClN_5O_2$: 425.91).

Method of preparation Prepare as directed under Tablets, with Domperidone.

Identification Weigh a portion of powdered Domperidone Tablets, equivalent to 20 mg of Domperidone, dissolve in 10 mL of a mixture of ethyl acetate - methanol (1 : 1), and filter. Use the filtrate as the test solution. Separately, weigh about 20 mg of domperidone RS, dissolve in 10 mL of a mixture of ethyl acetate-methanol (1 : 1), and use the filtrate as the standard solution. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of methanol-acetone -acetate (pH 3.9) (50 : 40 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 tablet of Domperidone Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of the first solution as the dissolution medium. Take the dissolved solution after 30 minutes from the start of the test, and filter. Discard the first 10 mL of the filtrate, pipet V mL of the subsequent filtrate, add the dissolution medium so that Each mL of the solution contains 11 μg of Domperidone according to the labeled amount. Make it exactly V' mL and use this solution as the test solution. Separately, weigh accurately about 11 mg of domperidone RS and dissolve in 50% methanol to make 100 mL. Pipet 10 mL of this solution, add the dissolution medium to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of domperidone from each solution. Meets the requirements if the dissolution rate of Domperidone Tablets in 30 minutes is NLT 75%.

$$\text{Dissolution rate (\%) of the labeled amount of domperidone } (C_{22}H_{24}ClN_5O_2) = W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 90$$

Ws: Amount (mg) of domperidone RS.

C: The labeled amount (mg) of domperidone ($C_{22}H_{24}ClN_5O_2$) in 1 tablet.

Operating conditions

Detector: An ultraviolet-visible spectrometer (wavelength: 285 nm).

Column: A stainless-steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of 0.02 mol/L potassium dihydrogen phosphate-methanol (1 : 1) (pH 3.5).

Flow rate: 1.0 mL/minute

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tables of

Domperidone Tablets and powder. Weigh accurately an amount equivalent to about 25 mg of Domperidone ($C_{22}H_{24}ClN_5O_2$), dissolve in 50% methanol, and make exactly 250 mL. Pipet 10 mL of the solution, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately 10 mg of domperidone RS and dissolve in 50% methanol to make exactly 100 mL. Pipet 10 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, AT and AS, for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of domperidone } (C_{22}H_{24}ClN_5O_2) = \text{Amount (mg) of domperidone RS} \times \frac{A_T}{A_S} \times 2.5$$

Operating conditions

Detector: An ultraviolet-visible spectrometer (wavelength: 285 nm).

Column: A stainless-steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of 0.02 mol/L potassium dihydrogen phosphate-methanol (1 : 1) (pH 3.5).

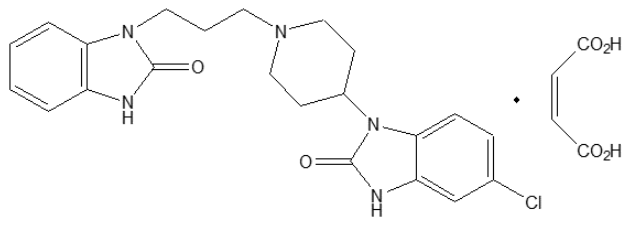
Flow rate: 1.0 mL/minute

System suitability

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above conditions; the relative standard deviation of the peak areas of Domperidone is NMT 1.5%.

Packaging and storage Preserve in tight containers.

Domperidone Maleate
돔페리돈말레산염



$C_{22}H_{24}ClN_5O_2 \cdot C_4H_4O_4$: 541.98

(*Z*)-But-2-enedioic acid; 5-chloro-1-(1-(3-(2-oxo-2,3-dihydro-1*H*-benzo[d]imidazol-1-yl) propyl)piperidin-4-yl)-1*H*-benzo[d]imidazol-2(3*H*)-one [*83898-65-1*]

Domperidone Maleate, when dried, contains NLT 99.0% and NMT 101.0% of domperidone maleate ($C_{22}H_{24}ClN_5O_2 \cdot C_4H_4O_4$).

Description Domperidone Maleate occurs as a white powder.

It is sparingly soluble in *N*,*N*-dimethylformamide, slightly soluble in methanol, and very slightly soluble in water or ethanol(95).

It shows polymorphism.

Identification (1) Triturate 0.1 g of Domperidone Maleate with a mixture of 1 mL of 10 mol/L sodium hydroxide solution and 3 mL of water, followed by extraction three times each with 5 mL of ether. Add 0.1 mL of the aqueous layer to 3 mL of resorcinol solution in sulfuric acid (1 in 300) and heat on a steam bath for 15 min; no color appears. To the remainder of the aqueous layer, add 2 mL of bromine TS, heat on a steam bath for 15 min, and then heat further to boiling. After cooling, add 0.1 mL of this solution to 3 mL of resorcinol solution in sulfuric acid (1 in 300) and heat on a steam bath for 15 min; a reddish purple color appears.

(2) Determine the infrared spectra of Domperidone Maleate and domperidone maleate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If there is any difference between the spectra, dissolve Domperidone Maleate and domperidone maleate RS each in as little volume of 2-propanol as possible, evaporate to dryness on a steam bath, and perform the test with the residues in the same way above.

(3) Dissolve 20 mg of Domperidone Maleate in 10 mL of methanol, and use this solution as the test solution. Separately, dissolve 20 mg of domperidone maleate RS in 10 mL of methanol, and use this solution as the standard solution (1). Also, dissolve 20 mg of domperidone maleate RS and 20 mg of droperidole RS in 10 mL of methanol, and use this solution as the standard solution (2). Perform the test with these solutions as directed under the Thin-layer chromatography. Spot 5 μL each of the test solution, standard solution (1) and standard solution (2) on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate using a mixture of methanol, acetonitrile and ammonium acetate TS (40 : 40 : 20) as a developing solvent to a distance of about 15 cm, and air-dry the plate. Expose the plate with iodine vapor until spots appear and examine in day-light; the spot in the chromatogram obtained with the test solution corresponds in the size and the R_f value to that with the standard solution (1), and the two spots in the chromatogram obtained with the standard solution (2) are clearly separated with each other.

Purity (1) ***Clarity and color of solution***—Dissolve 0.2 g of Domperidone Maleate in 20 mL of *N*,*N*-dimethylformamide; the solution is clear and not darker than a solution made by mixing 5 mL of the mixed solution of 1 w/v% hydrochloric acid, iron(III) chloride hexahydrate colorimetric stock solution and cobalt(II) chloride

hexahydrate colorimetric stock solution (70 : 24 : 6) and 95 mL of 1 w/v% hydrochloric acid.

(2) ***Heavy metals***—Proceed with 1.0 g of Domperidone Maleate according to Method 4, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Prepare the solutions for the test immediately before use. Dissolve 0.1 g of Domperidone Maleate in 10 mL of *N*,*N*-dimethylformamide, and use this solution as the test solution. Pipet 1 mL of the test solution, and add *N*,*N*-dimethylformamide to make exactly 100 mL. Pipet 5 mL of this solution, add *N*,*N*-dimethylformamide to make exactly 20 mL, and use this solution as the standard solution (1). Perform the test with 10 μL each of *N*,*N*-dimethylformamide (as a blank test solution), the test solution and the standard solution (1) as directed under the Liquid Chromatography according to the following conditions. Determine each peak area from each solution by the automatic integration method; none of the peak areas, other than the peak area of domperidone maleate, obtained from the test solution is larger than the peak area of domperidone maleate obtained from the standard solution (1) (0.25%), and the sum of the areas of all peaks other than the peak of domperidone maleate from the test solution is not larger than 2 times the peak area of domperidone maleate from the standard solution (1) (0.5%). Disregard any peak in the chromatogram obtained with the blank test solution and any peak with an area less than 0.2 times the area of the peak of domperidone maleate from the standard solution (1).

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 280 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 10 cm in length, packed with base-deactivated octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Mobile phase: Apply a mixture of ammonium acetate (5 in 1000) and methanol (70 : 30) to the column at a flow rate of 1.5 mL per minute, then increase the ratio of methanol sequentially to 100% over 10 min, followed by elution with methanol for 2 minutes.

Flow rate: 1.5 mL/min. Apply methanol to the column for at least 30 min to reach an equilibrium, and then equilibrate it again with the initial mobile phase composition (a mixture of ammonium acetate (5 in 1000) and methanol (70 : 30) for at least 5 minutes.

System suitability

Detection sensitivity: Adjust the detection sensitivity so that the peak height of domperidone maleate obtained from 10 μL of the standard solution (1) is NLT 50.0% of that obtained from the water bath.

System performance: Dissolve 10 mg of domperidone maleate RS and 15 mg of droperidol RS in 100 mL of *N*,*N*-dimethylformamide, and use this solution as the standard solution (2). Proceed with 10 μL of this solution, as directed under the above operating conditions; domperidone maleate and droperidol are eluted in this order with the resolution between their peaks being NLT 2.

Loss on drying NMT 0.5% (1 g, 105 ºC, constant mass).

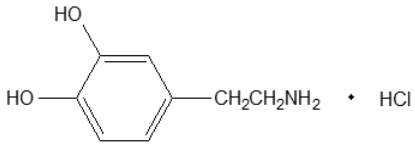
Ignition residue NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Domperidone Maleate, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 0.2 mL of 1-naphtholbenzein TS). However, the endpoint of the titration is when the color changes from orange to green.

Each mL of 0.1 mol/L perchloric acid VS
= 54.20 mg of $C_{26}H_{28}ClN_5O_6$

Packaging and storage Preserve in light-resistant, well-closed containers.

Dopamine Hydrochloride
도파민염산염



$C_8H_{11}NO_2 \cdot HCl$: 189.64
4-(2-Aminoethyl)benzene-1,2-diol hydrochloride [*62-31-7*]

Dobutamine Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of dobutaime hydrochloride ($C_8H_{11}NO_2 \cdot HCl$).

Description Dobutamine Hydrochloride occurs as white crystals or a crystalline powder.
It is freely soluble in water or formic acid and sparingly soluble in ethanol(95).

Melting point—About 248 °C (with decomposition).

Identification (1) Determine the absorption spectra of solutions of Dopamine Hydrochloride and dopamine hydrochloride RS in 0.1 mol/L hydrochloric acid TS (1 in 25000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Dopamine Hydrochloride and dopamine hydrochloride RS, previously dried, as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Dopamine Hydrochloride (1 in 50) responds to the Qualitative Analysis (1) for

chloride.

pH Dissolve 1 g of Dopamine Hydrochloride in 50 mL of water; the pH of this solution is between 4.0 and 5.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Dopamine Hydrochloride in 10 mL of water; the solution is clear and colorless.

(2) ***Sulfate***—Prepare the test solution with 0.8 g of Dopamine Hydrochloride and perform the test. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid (NMT 0.021%).

(3) ***Heavy metal***—Proceed with 1.0 g of Dopamine Hydrochloride according to the Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic***—Proceed with 1.0 g of Dopamine Hydrochloride according to the Method 1 and perform the test (NMT 2 ppm).

(5) ***Related substances***—Dissolve 0.10 g of Dopamine Hydrochloride in 10 mL of water and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 250 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of *1*-butanol, water and acetic acid(100) (16 : 8 : 1) to a distance of about 10 cm, and air-dry the plate. Spray evenly a solution of ninhydrin in acetone (1 in 50) on the plate and heat at 90 °C for 10 minutes; spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 °C, 3 hours).

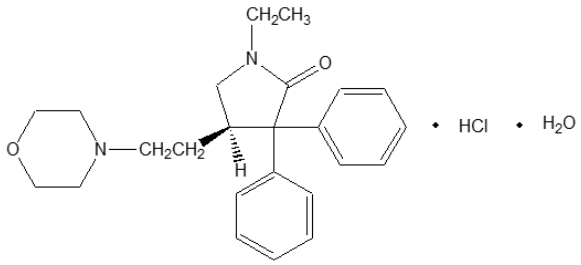
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Dopamine Hydrochloride, previously dried, dissolve in 5 mL of formic acid, add exactly 15 mL of 0.1 mol/L perchloric acid, and heat on a steam bath for 15 minutes. After cooling, add 50 mL of acetic acid(100) and titrate the exceeding amount of perchloric acid with 0.1 mol/L sodium acetate VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 18.964 mg of $C_8H_{11}NO_2 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Doxapram Hydrochloride Hydrate
독사프람염산염수화물



and enantiomer

Doxapram Hydrochloride

$C_{24}H_{30}N_2O_2 \cdot HCl \cdot H_2O$: 432.98

(*RS*)-1-Ethyl-4-(2-morpholin-4-ylethyl)-3,3-diphenylpyrrolidin-2-one hydrate hydrochloride [*7081-53-0*]

Doxapram Hydrochloride Hydrate contains NLT 98.0% and NMT 101.0% of doxapram hydrochloride (C24H30N2O2·HCl : 414.97), calculated on an anhydrous basis.

Description Doxapram Hydrochloride Hydrate occurs as white crystals or a crystalline powder.
It is freely soluble in methanol or acetic acid(100), sparingly soluble in water, ethanol(95), or acetic anhydride, and practically insoluble in ether.

Identification (1) Determine the absorption spectra of solutions of Doxapram Hydrochloride Hydrate and doxapram hydrochloride hydrate RS (1 in 2500) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectrum of Doxapram Hydrochloride Hydrate and doxapram hydrochloride hydrate RS as directed in the potassium bromide disk method under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) A solution of Doxapram Hydrochloride Hydrate (1 in 50) responds to the Qualitative Analysis for chloride.

Melting point Between 218 and 222 ºC.

pH Dissolve about 1.0 g of Doxapram Hydrochloride Hydrate in 50 mL of water; the pH of this solution is between 3.5 and 5.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Doxapram Hydrochloride Hydrate in 50 mL of water; the solution is clear and colorless

(2) ***Sulfate***—Proceed with about 1.0 g of Doxapram Hydrochloride Hydrate and perform the test. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid (NMT 0.024%).

(3) ***Heavy metals***—Proceed with 1.0 g of Doxapram Hydrochloride Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Proceed with 1.0 g of Doxapram Hydrochloride Hydrate according to Method 3 and perform the test (NMT 2 ppm).

(5) ***Related substances***—Dissolve 0.5 g of Doxapram Hydrochloride Hydrate in 10 mL of methanol and use this solution as the test solution. Pipet 3 mL of this solution and add methanol to make exactly 100 mL. Pipet 5 mL of this solution, add methanol to make exactly 50 mL, and use it as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 6 μL each of the test solution and the standard solution on a plate made of silica gel for the thin layer chromatography. Next, develop the plate with a mixture of chloroform, formic acid, ethyl formate and methanol (8 : 3 : 3 : 2) to a distance of about 10 cm, and air-dry the plate. Allow the plate to stand in iodine vapor; the spots other than the principal spot from the test solution are not more intense than that from the standard solution.

Water Between 3.5% and 4.5% (0.5 g, volumetric titration, direct titration).

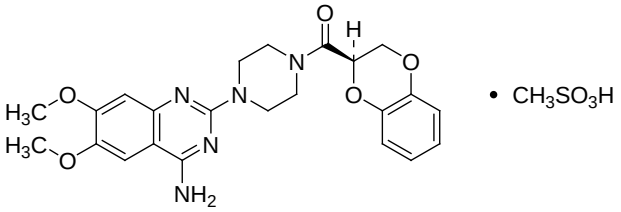
Residue on ignition NMT 0.3% (1 g).

Assay Weigh accurately about 0.8 g of Doxapram Hydrochloride Hydrate, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 41.50mg of $C_{24}H_{30}N_2O_2 \cdot HCl$

Packaging and storage Preserve in tight containers.

Doxazosin Mesilate
독사조신메실산염



and enantiomer

$C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$: 547.58

(*RS*)-[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl]-(2,3-dihydro-1,4-benzo-dioxin-3-yl)methanone; methanesulfonic acid [*77883-43-3*]

Doxazosin Mesilate contains NLT 98.0% and NMT 102.0% of doxazosin mesilate ($C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$), calculated on the dried basis.

Method of preparation If there is a possibility that alkyl (such as methyl, ethyl, and isopropyl) methanesulfonate esters are included as impurities during the manufacturing process of Doxazosin Mesilate, precautions must be taken in controlling the starting materials, manufacturing process, and intermediates in order to minimize the residue amounts of these impurities considering the results of risk assessment. If necessary, the validity of the manufacturing process can be demonstrated using test data that prove the absence of quality risk in the final drug substance.

Description Doxazosin Mesilate occurs as a white to pale yellow crystalline powder.
It is freely soluble in dimethylsulfoxide, slightly soluble in water or methanol, and very slightly soluble in ethanol(99.5).
A solution (1 in 20) of Doxazosin Mesilate in dimethylsulfoxide exhibits no optical rotation.

Melting point—About 272 ℃ (with decomposition).

Identification (1) Determine the absorption spectra of solutions of Doxazosin Mesilate and doxazosin mesilate RS in 0.01 mol/L hydrochloric acid-methanol TS (1 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Doxazosin Mesilate and doxazosin mesilate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy ; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Doxazosin Mesilate responds to the Qualitative Analysis (2) for phosphate.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Doxazosin Mesilate and perform the test according to Method 2. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 20 mg of Doxazosin Mesilate in 5 mL of a mixture of methanol and acetic acid(100) (1 : 1), and use this solution as the test solution. Pipet 10 mL of this solution, add a mixture of methanol and acetic acid(100) (1 : 1) to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescence indicator). Next, develop the plate with a mixture of 4-methyl-2-pentanone, water and acetic acid(100) (2 : 1 : 1) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spot with an R_f value of about 0.15 obtained from the test solution

is not intense than the one obtained from the standard solution. Also, no spots other than the principal spot and a spot with an R_f value of about 0.15 are observed in the test solution.

Loss on drying NMT 1.0% (1 g, 105 ℃, 4 h.).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 25 mg each of Doxazosin Mesilate and doxazosin mesilate RS, previously dried, dissolve separately in methanol to make exactly 50 mL. Pipet 3 mL of these solutions, add the mobile phase to make them exactly 100 mL, and use them as the test solution and the standard solution, respectively. Proceed with 10 μL each of the test solution and the standard solution, and perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of doxazosin in the test solution and the standard solution.

$$\text{Amount (mg) of doxazosin mesilate } (C_{23}H_{25}N_5O_5\cdot CH_4O_3S) = \text{Amount (mg) of doxazosin mesilate RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 246 nm).

Column: A stainless steel column with about 3.9 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (4 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of 0.05 mol/L potassium dihydrogen phosphate TS (pH 3.0), methanol and acetonitrile (12 : 8 : 3).

Flow rate: Adjust the flow rate so that the retention time of doxazosin is about 5 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the number of theoretical plates of the doxazosin peak is NLT 2,000 plates with the symmetry factor being NMT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of doxazosin is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Doxazosin Mesilate Tablets
독사조신메실산염 정

Doxazosin Mesilate Tablets contain NMT 95.0% and NLT 105.0% of the labeled amount of doxazosin ($C_{23}H_{25}N_5O_5$: 451.48).

Method of preparation Prepare Doxazosin Mesilate Tablets as directed under Tablets, with Doxazosin Mesilate.

Identification Weigh an amount of Doxazosin Mesilate Tablets, previously powdered, equivalent to about 5 mg of doxazosin according to the labeled amount, put into 100 mL of 0.01 mol/L hydrochloric acid-methanol TS, shake to mix, and centrifuge. Pipet 4 mL of the clear supernatant, add 0.01 mol/L hydrochloric acid-methanol TS to make 50 mL, and determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy; it exhibits an absorption maximum at wavelengths between 244 nm and 248 nm.

Dissolution Take 1 tablet of Doxazosin Mesilate Tablets and perform the test at 75 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of 0.05 mol/L acetic acid-sodium acetate buffer solution, pH 4.0 as the dissolution medium. Take NLT 20 mL of the medium 15 minutes after starting the test, filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, and add the dissolution medium to make exactly *V′ mL* so that the solution contains about 0.56 μg of doxazosin ($C_{23}H_{25}N_5O_5$) per mL according to the labeled amount. Pipet 5 mL of this solution, add 5 mL of methanol, and use it as the test solution. Separately, weigh accurately about 21 mg of doxazosin mesilate RS, previously dried at 105 °C for 4 hours, and dissolve in methanol to make exactly 50 mL. Pipet 2 mL of this solution and add methanol to make exactly 50 mL. Pipet 5 mL of this solution, add 5 mL of the dissolution medium, and use it as the standard solution. Proceed with 20 μL each of the test solution and the standard solution, respectively, and perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of doxazosin in the test solution and the standard solution. NLT 75% of the labeled amount of doxazosin ($C_{23}H_{25}N_5O_5$) is dissolved in 15 minutes.

$$\text{The dissolution rate (\%) of the labeled amount of doxazosin } (C_{23}H_{25}N_5O_5) = \text{Amount (mg) of doxazosin mesilate RS} \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times \frac{72}{25} \times 0.825$$

C: Labeled amount (mg) of doxazosin ($C_{23}H_{25}N_5O_5$). in 1 tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 246 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with

octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of methanol and buffer (55 : 45).

Buffer solution—Dissolve 3.4 g of potassium dihydrogen phosphate in 500 mL of water and adjust pH to 3.0 with diluted phosphoric acid (1 in 10).

Flow rate: Adjust the flow rate so that the retention time of doxazosin is about 5 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the number of theoretical plates of the doxazosin peak is NLT 1000 plates with the symmetry factor being NMT 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of doxazosin is NMT 2.0%.

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following procedure. Take 1 tablet of Doxazosin Mesilate Tablets, add 1 mL of water, shake to mix, and then add 0.01 mol/L hydrochloride-methanol TS to make exactly 100 mL, and shake to mix for 30 minutes. Centrifuge this solution, pipet V mL of clear supernatant, and add 0.01 mol/L hydrochloride-methanol TS to make exactly V′ mL so that the solution contains about 5 μg of doxazosin mesilate per mL, and use it as test solution. Separately, weigh accurately about 30 mg of doxazosin mesilate RS, previously dried at 105 °C for 4 hours, and dissolve it in 0.01 mol/L hydrochloric acid-methanol TS to make exactly 100 mL. Pipet 2 mL of this solution, add 0.01 mol/L hydrochloric acid-methanol TS to make exactly 100 mL, and use it as the standard solution. Perform the test as directed under the Assay described below.

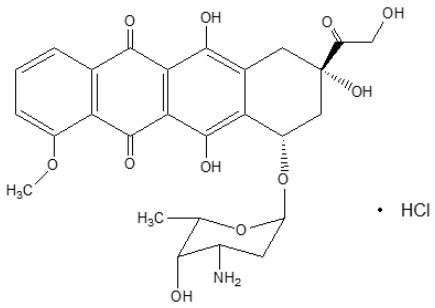
$$\text{Amount (mg) of doxazosin } (C_{23}H_{25}N_5O_5) = \text{Amount (mg) of doxazosin mesilate RS} \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{50} \times 0.825$$

Assay Weigh accurately the mass of NLT 20 Doxazosin Mesilate Tablets, and power. Weigh accurately an amount, equivalent to about 5 mg of doxazosin ($C_{23}H_{25}N_5O_5$) and dissolve in 5 mL of 0.01 mol/L hydrochloric acid-methanol TS to make 100 mL, and shake to mix for 30 minutes. Centrifuge this solution, pipet 4 mL of the clear supernatant, add 0.01 mol/L hydrochloric acid-methanol TS to make exactly 50 mL, and use it as the test solution. Separately, weigh accurately about 24 mg of doxazosin mesilate RS, previously dried at 105 °C for 4 hours, and dissolve in 0.01 mol/L hydrochloric acid-methanol TS to make exactly 100 mL. Pipet 2 mL of this solution, add 0.01 mol/L hydrochloric acid-methanol TS to make exactly 100 mL, and use it as the standard solution. Using the test solution and the standard solution with 0.01 mol/L hydrochloric acid-methanol TS as a control solution, perform the test as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbances, A_T and A_S, at 246 nm.

$$\text{Amount (mg) of doxazosin } (C_{23}H_{25}N_5O_5) = \text{Amount (mg) of doxazosin mesilate RS} \times \frac{A_T}{A_S} \times \frac{1}{4} \times 0.825$$

Packaging and storage Preserve in tight containers.

Doxorubicin Hydrochloride
독소루비신염산염



$C_{27}H_{29}NO_{11}\cdot HCl$: 579.98

(7*S*,9*S*)-7-[(2*R*,4*S*,5*S*,6*S*)-4-Amino-5-hydroxy-6-methyloxan-2-yl]oxy-6,9,11-trihydroxy-9-(2-hydroxyacetyl)-4-methoxy-8,10-dihydro-7*H*-tetracene-5,12-dione hydrochloride [*25316-40-9*]

Doxorubicin Hydrochloride is the hydrochloride of a derivative of daunorubicin.

Doxorubicin hydrochloride, when dried, contains NLT 980 μg and NMT 1080 μg (potency) of doxorubicin hydrochloride (C27H29NO11·HCl), calculated on the anhydrous basis.

Description Doxorubicin Hydrochloride occurs as an orange crystalline powder.

It is sparingly soluble in water, slightly soluble in methanol, very slightly soluble in ethanol(99.5), and practically insoluble in acetonitrile.

Identification (1) Determine the absorption spectra of solutions of Doxorubicin Hydrochloride and doxorubicin hydrochloride RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Doxorubicin Hydrochloride and doxorubicin hydrochloride RS as directed in the potassium chloride disk method under the

Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous of Doxorubicin Hydrochloride (1 in 200) responds to the Qualitative Analysis (1) for chloride.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between +240° and +290° (20 mg calculated on the anhydrous basis, methanol, 20 mL, 100 mm).

pH Dissolve 50 mg of Doxorubicin Hydrochloride in 10 mL of water; the pH of this solution is between 4.0 and 5.5.

Absorbance $E_{1cm}^{1\%}$ (495 nm): Between 200 and 230 (10 mg calculated on the anhydrous basis, methanol, 500 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 50 mg of Doxorubicin Hydrochloride in 10 mL of water; the solution is clear and red.

(2) ***Related substances***—Dissolve 25 mg of Doxorubicin Hydrochloride in 100 mL of the mobile phase and use this solution as the test solution. Pipet 2 mL of this solution, add the mobile phase to make exactly 100 mL, and use it as the standard solution. Pipet 20 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography under the following operating conditions, measure the peak areas of each peak of the solutions using the automatic integration method, and determine the peak areas of each solution; each peak area of the peaks other than that of doxorubicin in the test solution is not greater than one-fourth of the peak area of doxorubicin in the standard solution. Additionally, the sum of peak areas other than that of doxorubicin in the test solution is not greater than the peak area of doxorubicin in the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for the liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of a solution of phosphoric acid diluted in 3 g of sodium lauryl sulfate and acetonitrile (1 : 1).

Flow rate: Adjust the flow rate so that the retention time of doxorubicin is about 8 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution and add the mobile phase to make exactly 20 mL. Confirm that the peak area of doxorubicin obtained from 20 μL of this solution is in the range of 3.5% to 6.5% of the peak area of doxorubicin in the standard solution.

System performance: Dissolve 5 mg of Doxorubicin Hydrochloride in 20 mL of water, add 1.5 mL of phosphoric acid, and allow it to stand at room temperature for 30 minutes. Adjust the pH of this solution to 2.5 with 2 mol/L sodium hydroxide TS. Proceed with 20 μL of this solution under the above operating conditions; doxorubicinone, in which the relative retention time is about 0.6 with respect to doxorubicin, and doxorubicin are eluted in this order with the resolution between these peaks being NLT 5.

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area for doxorubicin is NMT 2.0%.

Time span of measurement: About 3 times the retention time of doxorubicin.

Water NMT 3.0% (0.3 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in a sterile preparation.

Bacterial endotoxins Less than 2.50 EU/mg of doxorubicin hydrochloride when used in a sterile preparation.

Histamine It meets the requirements when used in a sterile preparation. Proceed with an appropriate amount of Doxorubicin Hydrochloride to prepare a solution containing 2.0 mg (potency) per mL**.** Use the solution as the test solution. Use 0.5 mL of the solution for the test.

Assay Take exactly an amount of Doxorubicin Hydrochloride, equivalent to about 2.0 mg (potency) according to the labeled potency, dilute it with the mobile phase to make the concentration 0.1 mg (potency) per mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg (potency) of doxorubicin hydrochloride RS, dilute it with the mobile phase to make the concentration 0.1 mg (potency) per mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak areas, A_T and A_S, of doxorubicin hydrochloride in the test solution and in the standard solution.

$$\text{Potency (μg) of doxorubicin hydrochloride } (C_{27}H_{29}NO_{11}\cdot HCl) = \text{Potency (μg) of doxorubicin hydrochloride RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with trimethylsilanized silica gel for liquid chromatography (5

μm to 10 μm in particle diameter).

Mobile phase: Dissolve 1 g of sodium lauryl sulfate in a mixture of water, acetonitrile, ethanol(95) and phosphoric acid (540 : 290 : 170 : 2), and adjust pH to 3.6 ± 0.1 with 2 mol/L sodium hydroxide TS.

Flow rate: About 1.5 mL/minute.

System suitability

System performance: Proceed with 20 μL of the resolution test solution under the above operating conditions; the relative retention time of doxorubicinone with respect to doxorubicin is about 0.6 with the resolution between these peaks being NLT 5.5, and the relative retention time of doxorubicinone to doxorubicin is about 0.6, and the resolution is NLT 5.5. The number of theoretical plates and the symmetric factor for the peak of doxorubicin are NLT 2250 and between 0.7 and 1.2, respectively.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions under the above operating conditions; the relative standard deviation of the peak area of doxorubicin is NMT 1.0%.

Resolution test solution—Dissolve about 10 mg (potency) of Doxorubicin Hydrochloride in 5 mL of water, add 5 mL of phosphoric acid, and allow it to stand for about 30 minutes. Adjust pH to 2.6 ± 0.1 with 2 mol/L sodium hydroxide TS (about 37 mL), add 15 mL of acetonitrile and 10 mL of methanol, mix, filter, and use this solution as the resolution test solution. Store some of this solution in a freezer, and unfreeze and mix before use.

Packaging and storage Preserve in tight containers.

Doxorubicin Hydrochloride Injection
독소루비신염산염 주사액

Doxorubicin Hydrochloride Injection contains NLT 90.0% and NMT 120.0% of the labeled amount of doxorubicin hydrochloride ($C_{27}H_{29}NO_{11}$·HCl : 579.98).

Method of preparation Prepare as directed under Injections, with Doxorubicin Hydrochloride.

Description Doxorubicin Hydrochloride Injection occurs as an orange liquid.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

pH Between 2.5 and 3.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 2.2 EU per mg (potency) of doxorubicin hydrochloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet the amount of Doxorubicin Hydrochloride Injection, equivalent to about 2.0 mg (potency) according to the labeled potency, dilute with the mobile phase to make a solution containing 0.1 mg (potency) per mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg (potency) of doxorubicin hydrochloride RS, dilute with the mobile phase to make a solution containing 0.1 mg (potency) per mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of doxorubicin in the test solution and the standard solution.

$$\text{Potency (μg) of doxorubicin hydrochloride } (C_{27}H_{29}NO_{11}\cdot HCl) = \text{Potency (μg) of doxorubicin hydrochloride RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with trimethylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Dissolve 1 g of sodium lauryl sulfate in a mixture of water, acetonitrile, ethanol(95) and phosphoric acid (540 : 290 : 170 : 2) and adjust pH to 3.6 ± 0.1 with 2 mol/L sodium hydroxide TS.

Flow rate: About 1.5 mL/minute.

System suitability

System performance: Proceed with 20 μL of the resolution test solution under the above operating conditions; the relative retention time of doxorubicinone with respect to doxorubicin is about 0.6 with the resolution between these peaks being NLT 5.5. The number of theoretical plates of doxorubicin is 2250 and the symmetry factor is between 0.7 and 1.2.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions; the relative standard deviation of the peak area of doxorubicin is NMT 1.0%.

Resolution test solution—Dissolve about 10 mg (potency) of Doxorubicin Hydrochloride in 5 mL of water, add 5 mL of phosphoric acid, and allow it to stand for about 30 minutes. Adjust pH to 2.6 ± 0.1 with 2 mol/L sodium hydroxide TS (about 37 mL), add 15 mL of acetonitrile and 10 mL of methanol, filter, and use this solu-

tion as the resolution test solution. Store some of this solution in a freezer and unfreeze before use.

Packaging and storage Preserve in hermetic containers.

Doxorubicin Hydrochloride for Injection
주사용 독소루비신염산염

Doxorubicin Hydrochloride for Injection is a preparation for injection, which is dissolved before use. Doxorubicin Hydrochloride for Injection contains NLT 90.0% and NMT 110.0% of the labeled amount of doxorubicin hydrochloride ($C_{27}H_{29}NO_{11}\cdot HCl$: 579.98).

Method of preparation Prepare as directed under Injections, with Doxorubicin Hydrochloride for Injection.

Description Doxorubicin Hydrochloride for Injection occurs as an orange powder or a mass.

Identification (1) Dissolve an amount of Doxorubicin Hydrochloride for Injection, equivalent to 10 mg (potency) of doxorubicin hydrochloride according to the labeled amount, in methanol to make 100 mL. To 5 mL of this solution, add methanol to make 50 mL, and determine the absorption spectrum of the solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits absorption maxima at wavelengths of between 231 and 235 nm, between 250 and 254 nm, between 477 and 481 nm, between 493 and 497 nm, and between 528 and 538 nm.

(2) Both the test solution and the standard solution exhibit the same retention times in the chromatograms obtained by the test under the Assay.

pH Dissolve 50 mg of Doxorubicin Hydrochloride for Injection in 10 mL of water; the pH of this solution is between 5.0 and 6.0.

Purity ***Clarity and color of solution***—Take exactly an amount of Doxorubicin Hydrochloride for Injection, equivalent to about 50 mg of doxorubicin hydrochloride according to the labeled amount, and dissolve in 10 mL of water; the solution is clear and red.

Water NMT 4.0% (0.2 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 2.50 EU per mg (potency) of Doxorubicin Hydrochloride for Injection.

Uniformity of dosage units Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Assay Weigh accurately the mass of the contents of NLT 10 vials of Doxorubicin Hydrochloride for Injection. Weigh accurately the amount equivalent to 10 mg (potency) of Doxorubicin Hydrochloride, add exactly 5 mL of the internal standard solution, dissolve in the mobile phase to make 100 mL. Use this solution as the test solution. Separately, weigh accurately an amount of doxorubicin hydrochloride RS, equivalent to 10 mg (potency), add exactly 5 mL of the internal standard solution, dissolve in the mobile phase to make 100 mL, and use this solution as the standard solution.
Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and determine the peak area ratios of doxorubicin, Q_T and Q_S, to the internal standard solution in each solution.

$$\text{Potency (μg) of doxorubicin hydrochloride } (C_{27}H_{29}NO_{11}\cdot HCl) = \text{Potency (μg) of doxorubicin hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of parahydroxybenzoic acid in the mobile phase (1 in 10000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve the diluted phosphoric acid (7 in 5000) in 3 g of sodium lauryl sulfate. To this solution, add 1000 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of doxorubicin is about 8 minutes.

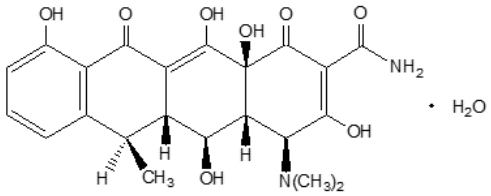
System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; doxorubicin and the internal standard solution are eluted in this order with the resolution being NLT 5, and the symmetry factor for the doxorubicin peak is between 0.8 and 1.2.

System repeatability: Repeat the test 6 times with 10 μL of the standard solutions under the above operating conditions; the relative standard deviation of the ratio of the peak area of doxorubicin to that of the internal standard solution is NMT 1.0%.

Packaging and storage Preserve in hermetic containers.

Doxycycline Hydrate
독시사이클린수화물



$C_{22}H_{24}N_2O_8 \cdot H_2O$: 462.45

(4*S*,4a*R*,5*S*,5a*R*,6*R*,12a*S*)-4-(Dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide hydrate [*17086-28-1*]

Doxycycline Hydrate contains NLT 880 μg and NMT 980 μg (potency) per mg of doxycycline ($C_{22}H_{24}N_2O_8$: 444.44), calculated on the anhydrous basis.

Description Doxycycline Hydrate occurs as a yellow crystalline powder.
It is sparingly soluble in ethanol(95), very slightly soluble in water and practically insoluble in chloroform or ether.
It dissolves in dilute acid or alkaline solutions.

Identification Determine the infrared spectra of Doxycycline Hydrate and doxycycline RS, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Crystallinity Meets the requirements.

pH The pH of a suspension obtained by suspending 0.1 g of Doxycycline Hydrate in 10 mL of water is between 5.0 and 6.5.

Purity (1) ***Heavy metals*—**Weigh 0.5 g of Doxycycline Hydrate, mix with 4 mL of a solution of magnesium sulfate heptahydrate in dilute sulfuric acid (1 in 4), heat until a liquid is obtained, and then evaporate to dryness on a steam bath. Ignite the residue at below 800 °C to incinerate. Allow to cool and moisten the residue with a small amount of dilute sulfuric acid. Evaporate to dryness, incinerate for NMT 2 hours, and allow to cool. Extract the residue twice each with 5 mL of 2 mol/L hydrochloric acid TS, add 0.1 mL of phenolphthalein TS, and add ammonia water(28) until the solution turns pale red. Allow to cool, add acetic acid(100) until the color disappears, and add another 0.5 mL. Filter and wash, if necessary. Add water to make 20 mL and use this solution as the test solution. Separately, proceed in the same manner as the preparation of the test solution using 2.5 mL of lead standard solution instead of Doxycycline Hydrate. To 10 mL of this solution, add 2 mL of the test solution and use this solution as the control solution. Separately, add 2 mL of the test solution to 10 mL of water and use this solution as the blank test solution. To 12 mL each of the test solution, the standard solution and the blank test solution, add 2 mL of acetate buffer (pH 3.5), mix, add 1.2 mL of thioacetamide TS, mix immediately, and allow to stand for 2 minutes. The brown color of the test solution is not more intense than that of the control solution.

System suitability: The control solution shows a faint brown color compared to the blank test solution. Add 2.5 mL of lead standard solution to the test solution. To 10 mL of this solution, add 2 mL of the test solution, and use this solution as the system suitability solution. The system suitability solution is more intense than or has the same intensity as the control solution.

(2) ***Related substances*—**Weigh accurately about 55 mg of Doxycycline Hydrate, dissolve in 12 mL of 0.1 mol/L hydrochloric acid, add 0.01 mol/L hydrochloric acid to make exactly 50 mL, and use this solution as the test solution. Weigh accurately an appropriate amount of methacycline hydrochloride RS, dissolve in 0.01 mol/L hydrochloric acid to make a solution containing 1.2 mg per mL, and use this solution as the methacycline standard stock solution. Separately, weigh accurately about 12 mg of doxycycline RS, dissolve in 0.01 mol/L hydrochloric acid to make exactly 10 mL, and use this solution as the standard solution (1). Pipet 2.0 mL of standard solution (1) and 2.0 mL of the methacycline standard stock solution, add 0.01 mol/L hydrochloric acid to make exactly 100 mL, and use this solution as the standard solution (2). Perform the test with 20 μL each of the test solution and standard solution (2) as directed under the Liquid Chromatography according to the following operating conditions, and then determine the peak areas of methacycline A_M and A_U, obtained from standard solution (2) and the test solution, respectively. Likewise, determine the peak area of doxycycline A_S, obtained from standard solution (2) and the peak areas of each related substance other than methacycline A_i from the test solution. The content of methacycline is NMT 2.0%, the content of related substances eluted before methacycline is NMT 0.5%, the content of 6-epidoxycycline is NMT 2.0%, and the content of related substances eluted after the doxycycline peak is NMT 0.5%.

$$\text{Content (\%) of methacycline} = \frac{C_M}{W} \times \frac{A_U}{A_M} \times 5000$$

$$\text{Content (\%) of each related substance other than methacycline} = \frac{C_S}{W} \times \frac{A_i}{A_S} \times 5000$$

C_M: Concentration (mg/mL) of methacycline hydrochloride in standard solution (2)

W: Weight (mg) of Doxycycline Hydrate taken

C_S: Concentration (mg/mL) of doxycycline in standard solution (2)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with spherical styrene-divinylbenzene copolymer for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 60 ℃.

Mobile phase: Dissolve 2.72 g of potassium dihydrogen phosphate, 0.74 g of sodium hydroxide, 0.50 g of tetrabutyl ammonium hydrogen sulfate and 0.40 g of disodium dihydrogen ethylenediaminetetraacetate in 850 mL of water. To this solution, add 60 g of *t*-butyl alcohol, add water to make exactly 1000 mL, and adjust the pH to 7.0 - 9.0 with 1 mol/L sodium hydroxide solution.

Flow rate: 1 mL/min

System suitability

System performance: Proceed with 20 μL of the system suitability solution under the above operating conditions; the relative retention times of 4-epidoxycycline, methacycline, 6-epidoxycycline and doxycycline are 0.4, 0.6, 0.7 and 1.0, respectively, and the resolution between the peaks of 4-epidoxycycline and doxycycline is NLT 3.0 with the symmetry factor of the peaks being NMT 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of standard solution (1) under the above operating conditions; the relative standard deviation of the peak area of doxycycline is NMT 2.0%.

Time span of measurement: About 1.7 times the retention time of doxycycline.

System suitability solution—Dissolve doxycycline RS in 0.01 mol/L hydrochloric acid to make a solution containing 6 mg per mL. Pipet 5 mL of this solution, warm on a steam bath for 60 minutes, and evaporate to dryness on a hot plate while taking care not to burn the residue. Dissolve the residue in 0.01 mol/L hydrochloric acid to make exactly 25 mL and use this solution as the system suitability solution. This solution contains 4-epidoxycycline, 6-epidoxycycline and doxycycline. Keep this solution in a refrigerator and use it within 14 days.

Water Between 3.6% and 4.6% (0.2 g, volumetric titration, direct titration).

Assay Weigh accurately an appropriate amount of Doxycycline Hydrate, equivalent to about 55 mg (potency), dissolve in 12 mL of 0.1 mol/L hydrochloric acid by shaking, add 0.01 mol/L hydrochloric acid to make exactly 50 mL, and filter through a filter with pore size of NMT 0.5 μm. Use the filtrate as the test solution. Separately, weigh accurately about 11 mg (potency) of doxycycline RS, add 6 mL of 0.01 mol/L hydrochloric acid, sonicate for 5 minutes to dissolve, and make exactly 10 mL. Use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and determine the peak areas, A_T and A_S of doxycycline in each solution.

$$\text{Potency (μg) of doxycycline } (C_{22}H_{24}N_2O_8) = \text{Potency (μg) of doxycycline RS} \times \frac{A_T}{A_S} \times 5$$

Operating conditions

Proceed as directed under the Assay under Doxycycline Hyclate Hydrate.

Packaging and storage Preserve in light-resistant, tight containers.

Doxycycline Capsules
독시사이클린 캡슐

Doxycycline Capsules contain NLT 90.0% and NMT 120.0% of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$: 444.44).

Method of preparation Prepare as directed under Capsules, with Doxycycline Hydrate.

Identification (1) Weigh about 0.1 g (potency) each of Doxycycline Capsules and doxycycline RS, add 100 mL of methanol, shake well to mix, filter, and use the clear supernatant as the test solution and the standard solution, respectively. Perform the test with these solutions as directed under the Thin Layer Chromatography. Heat a plate coated with octylsilanized silica gel for liquid chromatography, 0.25 mm in thickness, at 130 °C for 20 minutes and allow to cool. Spot the test solution and the standard solution on the plate while the plate is still warm, develop the plate with a mixture of 0.5 mol/L oxalic acid (previously adjusted to pH 2.0 with ammonium hydroxide), methanol and acetonitrile (80 : 20 : 20) as a developing solvent. After air-drying the plate, expose it to ammonia vapor for 5 minutes and examine it under ultraviolet light (main wavelength: 254 nm); the spot obtained from the test solution shows the same R_f value as that obtained from the standard solution.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Loss on drying NMT 5.0% (0.1 g, 60 ℃, 2 hours).

Dissolution Perform the test with 1 tablet of Doxycycline Capsules at 75 revolutions per minute according to Method 2 under the Dissolution using 900 mL of 0.01 mol/L hydrochloric acid TS as the dissolution medium. Take the dissolved solution after 60 minutes from the start of the test and filter. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add the dissolution medium to make exactly *V*'mL, and use this solution as the test solution. Separately, weigh accurately

an appropriate amount of doxycycline RS, dissolve it in the dissolution medium to make it the same concentration as the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength of about 268 nm as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as the control solution. Doxycycline Capsules meet the requirement when the dissolution rate at 60 minutes is NLT 85% (Q).

Dissolution rate (%) with respect to the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$)

$$= C_S \times \frac{V'}{V} \times \frac{1}{C} \times 90000$$

Cs: Concentration [mg (potency)/mL] of the standard solution

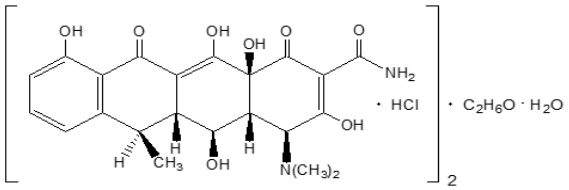
C: Labeled amount [mg (potency)] of doxycycline ($C_{22}H_{24}N_2O_8$) in 1 capsule

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay under Doxycycline Hyclate Hydrate. In this case, weigh accurately the contents of NLT 20 Doxycycline Capsules. Weigh accurately an appropriate amount of the combined contents, equivalent to about 100 mg (potency), according to the labeled potency of Doxycycline Capsules, add 20 mL of 0.1 mol/L hydrochloric acid, sonicate for 5 minutes, shake for 15 minutes to dissolve, and add 0.01 mol/L hydrochloric acid to make exactly 100 mL. Filter this solution through a membrane filter with a pore size of NMT 0.5 μm and use the filtrate as the test solution. Separately, weigh accurately about 10 mg (potency) of doxycycline RS, add 6 mL of 0.01 mol/L hydrochloric acid, sonicate for 5 minutes to dissolve, make exactly 10 mL, and use this solution as the standard solution.

Packaging and storage Preserve in light-resistant, tight containers.

Doxycycline Hyclate Hydrate
독시사이클린하이클레이트수화물



Doxycycline Hyclate
$(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6O \cdot H_2O$: 1025.89
(4*S*,4a*R*,5*S*,5a*R*,6*R*,12a*S*)-4-(Dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide; ethanol; hydrate; dihydrochloride [*24390-14-5*]

Doxycycline Hyclate Hydrate is the hydrochloride of a derivative of oxytetracycline.

Doxycycline Hyclate Hydrate contains NLT 800 μg and NMT 920 μg (potency) per mg of doxycycline ($C_{22}H_{24}N_2O_8$: 444.43), calculated on the anhydrous basis and corrected by the amount of ethanol.

Description Doxycycline Hyclate Hydrate occurs as yellow to dark yellow crystals or a crystalline powder.
It is freely soluble in water and in methanol, and slightly soluble in ethanol(99.5).

Identification (1) Determine the infrared spectra of Doxycycline Hyclate Hydrate and doxycycline hyclate hydrate RS, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Doxycycline Hyclate Hydrate (1 in 20) responds to the Qualitative Analysis for chlorides.

Crystallinity Meets the requirements.

Specific optical rotation $[\alpha]_D^{20}$: Between -105° and -120° (0.25 g calculated on the anhydrous basis and corrected by the amount of alcohol, 0.01 mol/L hydrochloric acid-methanol TS, 25 mL, 100 mm). Determine within 5 minutes after the test solution is prepared.

pH Dissolve 1.0 g of Doxycycline Hyclate Hydrate in 10 mL of water; the pH of this solution is between 2.0 and 3.0.

Absorbance $E_{1cm}^{1\%}$(249 nm): Between 285 and 315 (10 mg, 0.01 mol/L hydrochloric acid-methanol, 500 mL).

Purity (1) ***Ethanol***—Weigh accurately about 1.0 g of Doxycycline Hyclate Hydrate, dissolve in exactly 5 mL of the internal standard solution, add water to make exactly 25 mL, and use this solution as the test solution. Separately, pipet 2 mL of ethanol(99.5), add water to make exactly 100 mL., and use this solution as the standard stock solution. Pipet 0.25 mL of this standard stock solution, add exactly 5 mL of the internal standard solution, add water to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and determine the ratio of the peak area of ethanol to that of the internal standard, Q_T and Q_S. The amount of ethanol is between 4.3% and 6.0%.

Content (%) of ethanol per g of Doxycycline Hyclate Hydrate

$$= 1 / W_T \times Q_T / Q_S \times 0.5 \times 0.79$$

W_T: Weight (g) of Doxycycline Hyclate Hydrate

taken

0.79: Density (g/mL) of ethanol at 20 ℃

Internal standard solution—1-propanol solution (1 in 1000).

Operating conditions

Detector: A flame-ionization detector

Column: A fused silica capillary column, 0.53 mm in internal diameter and 30 m in length, of which the inner surface is coated with 6% cyanopropylphenyl-94% polydimethylsiloxane for gas chromatography to a thickness of 3.0 μm.

Column temperature: Maintain at 50 °C for 5 minutes, then raise to 200 °C by 50 °C per minute, and keep at 200 °C for 5 minutes.

Sample injection port temperature: 210 ℃

Detector temperature: 280 °C

Split ratio: 1 : 5

Carrier gas: Nitrogen

Flow rate: 5 mL/min

System suitability

System performance: Proceed with 1 μL of the standard solution under the above operating conditions; ethanol and the internal standard are eluted in this order.

System reproducibility: Repeat the test 5 times with 1 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area of ethanol with respect to that of the internal standard is NMT 2.0%.

(2) ***Heavy metal***—Proceed with 1.0 g of Doxycycline Hyclate Hydrate according to Method 2 and perform the test. Prepare the control solution with 5.0 mL of lead standard solution (NMT 50 ppm).

(3) ***Related substances***—Weigh accurately about 120 mg (potency) each of Doxycycline Hyclate Hydrate and doxycycline RS, dissolve them each in 0.01 mol/L hydrochloric acid TS to make exactly 100 mL, and use these solutions as the test solution and standard solution (1). Separately, weigh an appropriate amount of methacycline hydrochloride RS and dissolve in 0.01 mol/L hydrochloric acid TS to make a solution containing 1.2 mg per mL. Pipet 2.0 mL of this solution and 2.0 mL of standard solution (1), dissolve in 0.01 mol/L hydrochloric acid TS to make 100 mL of a solution containing 0.024 mg of doxycycline and methacycline hydrochloride per mL, and use this solution as standard solution (2). Perform the test with exactly 20 μL each of the test solution and standard solution (2) as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak area of methacycline obtained from standard solution (2), A_M, and that from the test solution, A_U. Likewise, determine the peak area of doxycycline obtained from standard solution (2), A_S, and the peak areas of each related substance other than methacycline obtained from the test solution, A_i; the content of methacycline is NMT 2.0%, the content of each related substance eluted before the methacycline peak is NMT 0.5%, the content of 6-epidoxycycline is NMT 2.0%, and the content of each related substance eluted after the doxycycline peak is NMT 0.5%.

$$\text{Content (\%) of methacycline} = \frac{C_M}{W} \times \frac{A_U}{A_M} \times 10000$$

$$\text{Content (\%) of each related substance other than methacycline (\%)} = \frac{C_S}{W} \times \frac{A_i}{A_S} \times 10000$$

C_M: Concentration (mg/mL) of methacycline hydrochloride in standard solution (2)

W: Weight [mg (potency)] of Doxycycline Hyclate Hydrate taken

C_S: Concentration [mg (potency)/mL] of doxycycline in standard solution (2)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with spherical styrene-divinylbenzene copolymer for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 60 ℃.

Mobile phase: Dissolve 2.72 g of potassium dihydrogen phosphate, 0.74 g of sodium hydroxide, 0.50 g of tetrabutylammonium hydrogen sulfate and 0.40 g of disodium dihydrogen ethylenediaminetetraacetate in 850 mL of water. To this solution, add 60 g of *t*-butyl alcohol, add water to make 1000 mL, and adjust the pH to 8.0 with 1 mol/L sodium hydroxide. If necessary, increase the resolution between the peaks of related substances and doxycycline and the retention time of doxycycline by reducing the proportion of *t*-butyl alcohol.

Flow rate: About 1.0 mL/min.

System suitability

System performance: Proceed with 20 μL of the system suitability solution under the above operating conditions; the relative retention times of 4-epidoxycycline, 6-epidoxycycline and doxycycline are about 0.4, 0.7 and 1.0, respectively, and the resolution between the peaks of 4-epidoxycycline and doxycycline is NLT 3.0 with the symmetry factor of doxycycline being NMT 2.0.

System repeatability: Repeat the test 6 times with a solution prepared by dissolving 12 mg of doxycycline RS in 10 mL of 0.01 mol/L hydrochloric acid; the relative standard deviation is NMT 2.0%.

Time span of measurement: About 1.7 times the retention time of doxycycline.

System suitability solution—Weigh an appropriate amount of doxycycline RS and dissolve in 0.01 mol/L hydrochloric acid to make a solution containing 6 mg of

doxycycline per mL. Take 5 mL of this solution, heat over a steam bath for 60 minutes, and evaporate to dryness on a hot plate while taking care not to burn the residue. Dissolve the residue in 0.01 mol/L hydrochloric acid to make exactly 25 mL, filter through a membrane filter with a pore size of NMT 0.5 μm, and use this solution as the system suitability solution. Keep this solution in a refrigerator and use it within 14 days.

Water Between 1.4% and 2.8% (0.3 g, volumetric titration, direct titration).

Residue on ignition NMT 0.3% (1 g).

Assay Weigh accurately about 0.120 g (potency) of Doxycycline Hyclate Hydrate, dissolve in 0.01 mol/L hydrochloric acid to make exactly 100 mL, filter through a membrane filter with a pore size of NMT 0.5 μm, and use the filtrate as the test solution. Separately, weigh accurately about 12 mg (potency) of doxycycline RS, add 6 mL of 0.01 mol/L hydrochloric acid, sonicate for 5 minutes to dissolve, make exactly 10 mL, and use this solution as the standard solution. Perform the test with 20 mL each of the test solution and the standard solution as directed under the Liquid Chromatography, and determine the peak areas A_T and A_S of doxycycline in each solution.

$$\text{Potency (μg) of doxycycline } (C_{22}H_{24}N_2O_8) = \text{Potency (μg) of doxycycline RS} \times \frac{A_T}{A_S} \times 10$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with spherical styrene-divinylbenzene copolymer for liquid chromatography (5 μm - 10 μm in particle diameter).

Column temperature: A constant temperature of about 60 °C.

Mobile phase: Dissolve 2.72 g of potassium dihydrogen phosphate, 0.74 g of sodium hydroxide, 0.50 g of tetrabutylammonium hydrogen sulfate and 0.40 g of disodium dihydrogen ethylenediaminetetraacetate in 850 mL of water. To this solution, add 60 g of *t*-butyl alcohol, add water to make 1000 mL, and adjust the pH to 8.0 ± 0.1 with 1 mol/L sodium hydroxide. If necessary, increase the resolution between the peaks of related substances and doxycycline and the retention time of doxycycline by reducing the proportion of *t*-butyl alcohol.

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 20 μL of the system suitability solution under the above operating conditions; the relative retention times of 4-epidoxycycline, 6-epidoxycycline and doxycycline are about 0.4, 0.7 and 1.0, respectively, and the resolution between the peaks of 4-epidoxycycline and doxycycline is NLT 3.0 with the symmetry factor of the doxycycline peak being NMT 2.0.

System repeatability: Repeat the test 5 times with 20 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area of doxycycline is NMT 2.0%.

System suitability solution—Weigh an appropriate amount of doxycycline RS and dissolve in 0.01 mol/L hydrochloric acid to make a solution containing 6 mg of doxycycline per mL. Take 5 mL of this solution, heat over a steam bath for 60 minutes, and evaporate to dryness on a hot plate while taking care not to burn the residue. Dissolve the residue in 0.01 mol/L hydrochloric acid to make exactly 25 mL, filter through a membrane filter with a pore size of NMT 0.5 μm, and use this solution as the system suitability solution. Keep this solution in a refrigerator and use it within 14 days.

Packaging and storage Preserve in light-resistant, tight containers.

Doxycycline Hyclate Capsules
독시사이클린하이클레이트 캡슐

Doxycycline Hyclate Capsules contain NLT 90.0% and NMT 120.0% of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$: 444.44).

Method of preparation Prepare as directed under Capsules, with Doxycycline Hyclate Hydrate.

Identification (1) Take the contents of 1 capsule of Doxycycline Hyclate Capsules and add 3 drops of sulfuric acid to the powdered contents; a yellow color is observed.

(2) Weigh about 10 mg (potency) of powdered Doxycycline Hyclate Capsules, dissolve in 20 mL of water, and add silver nitrate TS; the solution becomes turbid in white.

(3) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Water NMT 5.0% (0.2 g, volumetric titration, direct titration).

Dissolution Perform the test with 1 capsule of Doxycycline Hyclate Capsules at 75 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium, with the distance between the bottom edge of the stirring blade and the inside bottom of the flask being maintained at 4.5 ± 0.5 cm during the test. Take the dissolved solution after 30 minutes from the start of the test and filter. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent

filtrate, add the dissolution medium to make exactly V' mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of doxycycline RS, dissolve it in the dissolution medium to make it the same concentration as the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength of about 276 nm as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as the control solution. Doxycycline Hyclate Capsules meet the requirement when the dissolution rate at 30 minutes is NLT 80% (Q).

Dissolution rate (%) with respect to the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$)

$$= C_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 90000$$

Cs: Concentration [mg (potency)/mL] of the standard solution

C: Labeled amount [mg (potency)] of doxycycline ($C_{22}H_{24}N_2O_8$) in 1 capsule

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay under Doxycycline Hyclate Hydrate. In this case, weigh accurately the contents of NLT 20 Doxycycline Hyclate Capsules. Weigh accurately an appropriate amount of the combined contents of Doxycycline Hyclate Capsules, equivalent to about 100 mg (potency) according to the labeled potency of this drug, add 75 mL of 0.01 mol/L hydrochloric acid, sonicate for 5 minutes, shake for 15 minutes to dissolve, and add 0.01 mol/L hydrochloric acid to make exactly 100 mL. Filter this solution through a membrane filter with a pore size of NMT 0.5 μm and use the filtrate as the test solution. Separately, weigh accurately about 10 mg (potency) of doxycycline RS, add 6 mL of 0.01 mol/L hydrochloric acid, sonicate for 5 minutes to dissolve, make exactly 10 mL, and use this solution as the standard solution.

Packaging and storage Preserve in light-resistant, tight containers.

Doxycycline Hyclate Tablets
독시사이클린하이클레이트 정

Doxycycline Hyclate Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$: 444.44).

Method of preparation Prepare as directed under Tablets, with Doxycycline Hyclate Hydrate.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Water NMT 5.0% (0.2 g, volumetric titration, direct titration).

Dissolution Perform the test with 1 tablet of Doxycycline Hyclate Tablets at 75 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium, with the distance between the bottom edge of the stirring blade and the inside bottom of the flask being maintained at 4.5 ± 0.5 cm during the test. Take the dissolved solution after 90 minutes from the start of the test and filter. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add the dissolution medium to make exactly V' mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of doxycycline RS, dissolve it in the dissolution medium to make it the same concentration as the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength of about 276 nm as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as the control solution. Doxycycline Hyclate Tablets meet the requirement when the dissolution rate at 90 minutes is NLT 85% (Q).

Dissolution rate (%) with respect to the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$)

$$= C_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 90000$$

Cs: Concentration [mg (potency)/mL] of the standard solution

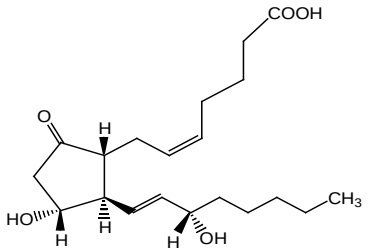
C: Labeled amount [mg (potency)] of doxycycline ($C_{22}H_{24}N_2O_8$) in 1 tablet

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay under Doxycycline Hyclate Hydrate. Take NLT 20 Doxycycline Hyclate Tablets and powder them. Then, weigh accurately an appropriate amount of the powder, equivalent to about 100 mg (potency), according to the labeled potency of Doxycycline Hyclate Tablets, add 75 mL of 0.01 mol/L hydrochloric acid, sonicate for 5 minutes, shake for 15 minutes to dissolve, and add 0.01 mol/L hydrochloric acid to make exactly 100 mL. Filter this solution through a membrane filter with a pore size of NMT 0.5 μm and use the filtrate as the test solution. Separately, weigh accurately about 10 mg (potency) of doxycycline RS, add 6 mL of 0.01 mol/L hydrochloric acid, sonicate for 5 minutes to dissolve, make exactly 10 mL, and use this solution as the standard solution.

Packaging and storage Preserve in light-resistant, tight containers.

Dydrogesterone
디드로게스테론



$C_{21}H_{28}O_2$: 312.45

(8*S*,9*R*,10*S*,13*S*,14*S*,17*S*)-17-Acetyl-10,13-dimethyl-1,2,8,9,11,12,14,15,16,17-decahydrocyclopenta[a]phenanthren-3-one [*152-62-5*]

Dydrogesterone, when dried, contains NLT 98.0% and NMT 102.0% of dydrogesterone ($C_{21}H_{28}O_2$).

Description Dydrogesterone occurs as white or pale yellow crystals or a crystalline powder and is odorless.
It is freely soluble in chloroform, soluble in acetonitrile, sparingly soluble in methanol or in ethanol(95), slightly soluble in ether and practically insoluble in water.

Identification (1) To 5 mg of Dydrogesterone, add 5 mL of 4-methoxybenzaldehyde-acetic acid TS and 2 to 3 drops of sulfuric acid, and heat on a steam bath for 2 minutes; an orange color appears.

(2) Determine the absorption spectra of solutions of Dydrogesterone and dydrogesterone RS in methanol (1 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Dydrogesterone and dydrogesterone RS, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -47° and -50° (after drying 0.1 g, chloroform, 10 mL, 100 mm).

Melting point Between 167 and 171 ºC.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Dydrogesterone according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 10 mg of Dydrogesterone in 200 mL of the mobile phase, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of these solutions by the automatic integration method; the sum of the peak areas, other than the peak of dydrogesterone, obtained from the test solution, is not larger than the peak area of dydrogesterone obtained from the standard solution.

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 280 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: A mixture of water, ethanol(95) and acetonitrile (53 : 26 : 21).

Flow rate: Adjust the flow rate so that the retention time of dydrogesterone is about 12 minutes.

System suitability

Detection sensitivity: Adjust the detection sensitivity so that the peak height of dydrogesterone obtained from 10 μL of the standard solution is between 5 mm and 10 mm.

Selection of column: Dissolve 1 mg each of Dydrogesterone and progesterone in 20 mL of the mobile phase. Proceed with 10 μL of this solution under the above operating conditions. At this time, use a column from which dydrogesterone and progesterone are eluted in this order with the resolution between these peaks being NLT 8. In this case, use the wavelength of 265 nm for measurement.

Time span of measurement: About twice the retention time of dydrogesterone after the solvent peak.

Loss on drying NMT 0.5% (0.5 g, in vacuum, P_2O_5, 24 hours).

Ignition residue NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg of Dydrogesterone, previously dried, and dissolve in methanol to make exactly 100 mL. Pipet 1 mL of this solution and add methanol to make exactly 100 mL. Determine the absorbance *A* of this solution at the absorbance maximum wavelength around 286 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of dydrogesterone } (C_{21}H_{28}O_2) = \frac{A}{845} \times 100000$$

Packaging and storage Preserve in tight containers.

Dydrogesterone Tablets
디드로게스테론 정

Dydrogesterone Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of dydrogesterone ($C_{21}H_{28}O_2$: 312.45).

Method of preparation Prepare Dydrogesterone Tablets as directed under Tablets, with Dydrogesterone.

Identification (1) Take a portion of powdered Dydrogesterone Tablets, equivalent to 50 mg of dydrogesterone, add 50 mL of methanol, shake well to mix, and filter. Evaporate 5 mL of the filtrate to dryness on a steam bath. Perform the test as directed under the Identification (1) of Dydrogesterone with the residue.

(2) Take 1 mL of the filtrate and add methanol to make 200 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible spectrophotometry; it exhibits a maximum at the wavelengths between 284 nm and 288 nm.

Dissolution Perform the test with 1 tablet of Dydrogesterone Tablets. Perform the test with 1 tablet of Dydrogesterone Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the test solution. Take NLT 20 mL of the dissolved solution 30 minutes after starting the test, filter, and discard 10 mL of the first filtrate. Pipet *V* mL of the subsequent filtrate and add water to make *V′ mL* so that each mL contains about 50 μg of dydrogesterone according to the labeled amount. Use this solution as the test solution. Separately, dry dydrogesterone RS in a desiccator (in vacuum, phosphorus pentoxide) for 24 hours, weigh accurately 50 mg of dydrogesterone RS, dissolve in methanol to make exactly 100 mL. Pipet 1 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Measure the absorbances, A_T and A_S, of the test solution and the standard solution at the wavelength of 296 nm as directed under the Ultraviolet-visible Spectroscopy. Meets the requirements if the dissolution rate of Dydrogesterone Tablets in 30 minutes is NLT 80%.

$$\text{Dissolution rate (\%) of the labeled amount of dydrogesterone } (C_{21}H_{28}O_2) = W_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 9$$

W_S: Amount (mg) of dydrogesterone RS

C: Labeled amount (mg) of dydrogesterone ($C_{21}H_{28}O_2$) in 1 tablet

Uniformity of dosage units It meets the requirements when tested according to the following procedure. Powder 1 tablet of Dydrogesterone Tablets and add methanol to make exactly 100 mL. Shake well to mix until the tablet is fully disintegrated and filter through a membrane filter with a pore diameter of NMT 0.45 μm. Discard 20 mL of the first filtrate, pipet *V* mL of the subsequent filtrate, and add methanol to make exactly V′ mL so that each mL contains about 5 μg of dydrogesterone. Use this solution as the test solution. Perform the test as directed under the Assay below.

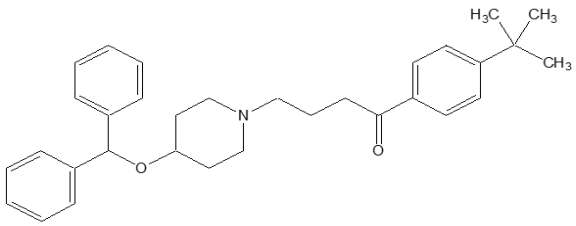
$$\text{Amount (mg) of dydrogesterone } (C_{21}H_{28}O_2) = \text{Amount (mg) of dydrogesterone RS} \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{20}$$

Assay Weigh accurately the mass of NLT 20 Dydrogesterone Tablets and powder. Weigh accurately a portion of the powder, equivalent to about 10 mg of dydrogesterone ($C_{21}H_{28}O_2$), add 50 mL of methanol, shake well to mix, and add methanol to make exactly 100 mL. Filter this solution, discard the first 20 mL of the filtrate, take 5 mL of the subsequent filtrate, and add methanol to make exactly 100 mL. Use this solution as the test solution. Separately, dry dydrogesterone RS in a desiccator (in vacuum, phosphorus pentoxide) for 24 hours, weigh accurately 10 mg of dydrogesterone RS, and proceed in the same manner as in the preparation of the test solution. Use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at 286 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of dydrogesterone } (C_{21}H_{28}O_2) = \text{Amount (mg) of dydrogesterone RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers.

Ebastine
에바스틴



Ebastine $C_{32}H_{39}NO_2$: 469.66

4-(4-Benzhydryloxypiperidin-1-yl)-1-(4-*tert*-butylphenyl)butan-1-one [*90729-43-4*]

Ebastine contains NLT 99.0% and NMT 101.0% of ebastine ($C_{32}H_{39}NO_2$), calculated on the anhydrous basis.

Description Ebastine occurs as white crystals or a crystalline powder.

It is very soluble in dichloromethane, slightly soluble in methanol, and practically insoluble in water.

Melting point—About 86 °C.

Identification Determine the infrared spectra of Ebastine and ebastine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Sulfate***—Weigh 2.5 g of Ebastine and add 25 mL of dilute nitric acid and shake. Reflux with a reflux condenser for 10 minutes, cool and filter. Rinse the filter paper and the residue with a suitable amount of water, combine with the filtrate all together, dilute with water to make 50 mL, and use this solution as the test solution. Prepare the control solution with 0.53 mL of 0.005 mol/L sulfuric acid and 25 mL of dilute nitric acid to make 50 mL (NMT 0.01%).

(2) ***Related substances***—Keep the test solution and the standard solution of this test protected from light. Dissolve about 0.125 g of Ebastine in the mobile phase to make 50.0 mL, and use this solution as the test solution. Dissolve 5.0 mg of ebastine related substance III [4-(Diphenylmethoxy)piperidine] RS and 5.0 mg of ebastine related substance IV {1-[4-(1,1-Dimethylethyl) phenyl]-4-(4-hydroxypiperidine-1-yl)butan-1-one] RS in the mobile phase to make exactly 20 mL, pipet 1.0 mL of this solution, add the mobile phase to make exactly 100 mL and use this solution as the standard solution (1). Pipet 1.0 mL of the test solution, and add the mobile phase to make exactly 100 mL. Pipet 1.0 mL of this solution, add the mobile phase to make exactly 10 mL, and use this solution as the standard solution (2). Perform the test with 10 μL each of the test solution and the standard solution (2) as directed under the Liquid Chromatography according to the following conditions. Determine each peak area by the automatic integration method; any peak area of related substances I, II, III, IV, V, VI, and VII in the automatic integration method obtained with the test solution is NMT the area of the major peak with the standard solution (2) (0.1%), the peak area of the other related substances are NMT that of the major peak from the standard solution (2) (0.1%). The total area of all related substances is not greater than 4 times the area of the major peak area from the standard solution (2) (0.4%). Exclude any peak being NMT 0.5 times the area of the major peak with the standard solution (2).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25cm in length, packed with nitrile silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of phosphate buffer and acetonitrile (65 : 35). Adjust the percentage of acetonitrile so that the retention time of ebastine is about 110 minutes.

Flow rate: 1 mL/min

System suitability

System performance: Proceed with 10 μL of the test solution under the above operating conditions; the relative retention time of related substances I, II, III, IV, V, VI, and VII with reference to ebastine are 0.04, 0.05, 0.20, 0.22, 0.42, 0.57 and 1.14, respectively. Proceed with 10 μL of the standard solution (1) under the above operating conditions; the resolution between the peaks of related substance IV and related substance III is NLT 2.0.

Time span of measurement: About 1.4 times the retention time of ebastine.

Phosphate buffer—Adjust pH of 0.06 w/v% phosphoric acid with 4 w/v% sodium hydroxide to pH 5.0.

Water NMT 0.5% (0.5 g, volumetric titration, direct titration).

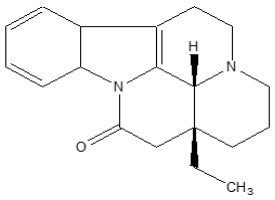
Residue on ignition 0.1% (1.0 g).

Assay Weigh accurately about 0.35 g of Ebastine, dissolve it in 50 mL of acetic acid(100) and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 46.97 mg of $C_{32}H_{39}NO_2$

Packaging and storage Preserve in light-resistant, well-closed containers.

(-)Eburnamonine
(-)에버나모닌



$C_{19}H_{22}N_2O$: 294.39

(-)-Eburnamonin-14(15*H*)-one, [*474-00-0*]

(-)Eburnamonine, when dried, contains NLT 99.0% and NMT 101.0% of (-)eburnamonine ($C_{19}H_{22}N_2O$: 294.39).

Description (-)Eburnamonine occurs as a white crystalline powder. It is practically insoluble or insoluble in water, soluble in ethanol, and very soluble in chloroform, but slightly soluble in ether. It dissolves in inorganic acid.

Melting point— Between 172 and 174 °C.

Identification (1) To a solution of (-)Eburnamonine in ether, add dehydrated ethanol solution containing phosphoric acid to form a white precipitate of eburnamonine phosphate. Filter this precipitate and recrystallize this

with ethanol and measure the melting point; the melting point is between 255 and 258 ℃.

(2) Pass a hydrogen chloride gas through the solution of (-)Eburnamonine in ether to form a white precipitate.

(3) Weigh about 25 mg each of (-)Eburnamonine and (-)eburnamonine RS, dissolve each in 5 mL of ethyl acetate, and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL of each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography (previously sprayed with 0.1 mol/L sodium hydroxide solution and dried for 20 minutes at 105 ℃). Next, develop the plate with a mixture of acetone and methanol (1 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm) or spray sulfuric acid and heat it, the colors (blue) and R_f values of the spots obtained from the test solution and the standard solution are the same.

(4) Determine the absorption maxima at wavelengths of 299 to 301 nm, 292 to 294 nm, 263 nm, 239 to 241 nm, and 202 to 206 nm under a solution of (-)Eburnamonine in 0.01 mol/L hydrochloric acid (1 in 100000).

Optical rotation $[a]_D^{20}$: Between -88° and -104° (after drying, 1 g, chloroform, 100 mL).

Purity ***Heavy metals***—Weigh about 1.0 g of (-)Eburnamonine and perform the test according to Method 2. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

Loss on drying NMT 0.5% (1.0 g, 100 ℃, constant mass).

Residue on ignition NMT 0.1% (1.0 g).

Assay Weigh accurately about 0.1 g of (-)Eburnamonine, previously dried, and put it in a 100-mL volumetric flask. Dissolve in 0.1 mol/L hydrochloric acid-ethanol solution to make 100 mL. Take 1.0 mL of this solution and dilute it with 0.1 mol/L hydrochloric acid-ethanol solution to make 100 mL. Perform the test according to the Ultraviolet-visible Spectroscopy and measure the absorbance *A* at the wavelength of 240 nm.

$$\text{Amount (mg) of (-)eburnamonine } (C_{19}H_{22}N_2O) = \frac{A}{725} \times 100000$$

Packaging and storage Preserve in tight containers.

Econazole Nitrate and Triamcinolone Acetonide Ointment
에코나졸질산염·트리암시놀론아세토니드 연고

Econazole Nitrate and Triamcinolone Acetonide Ointment contains NLT 90.0% and NMT 110.0% of the labeled amounts of econazole nitrate ($C_{18}H_{15}Cl_3N_2O \cdot HNO_3$: 444.70) and triamcinolone acetonide ($C_{24}H_{31}FO_6$: 434.49).

Method of preparation Prepare as directed under Ointments, with Econazole Nitrate and Triamcinolone Acetonide.

Identification Weigh an amount of Econazole Nitrate and Triamcinolone Acetonide Ointment, equivalent to 10 mg of econazole nitrate (1 mg of triamcinolone acetonide), dissolve in 10 mL of methanol, and use this solution as the test solution. Separately, use a 0.1% methanol solution of econazole nitrate and a 0.01% methanol solution of triamcinolone acetonide as the standard solutions. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 1 μL each of the test solution and the standard solution onto a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of toluene, ethanol, ethyl acetate and 85% formic acid (50 : 20 : 20 : 5) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light (principal wavelength: 254 nm) or spray evenly with platinic acid iodide-potassium iodide TS; the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

Assay (1) ***Econazole nitrate—***Weigh accurately an amount of Econazole Nitrate and Triamcinolone Acetonide Ointment equivalent to about 40 mg of econazole nitrate ($C_{18}H_{15}Cl_3N_2O \cdot HNO_3$) according to the labeled amount, add a mixture of methanol and water (40 : 60) to make 100 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 40 mg of econazole nitrate RS, add a mixture of methanol and water (40 : 60) to make 100 mL, and use this solution as the econazole nitrate standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of econazole nitrate, A_T and A_S, for each solution.

$$\text{Amount (mg) of econazole nitrate } (C_{18}H_{15}Cl_3N_2O \cdot HNO_3) = \text{Amount (mg) of econazole nitrate RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: Dissolve 0.77 g of ammonium acetate in water to make 1000 mL. Add 200 mL of methanol to 800 mL of this solution.

Mobile phase B: A mixture of acetonitrile and methanol (60 : 40).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 ~ 25	60 → 10	40 → 90
25 ~ 27	10	90
27 ~ 27.1	10 → 60	90 → 40
27.1 ~ 30	60	40

Flow rate: 1.5 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the symmetry factor is NMT 1.5.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of Piroxicam is NMT 0.73%.

(2) ***Triamcinolone acetonide*—**Weigh accurately an amount of Econazole Nitrate and Triamcinolone Acetonide Ointment equivalent to about 5 mg of triamcinolone acetonide ($C_{24}H_{31}FO_6$) according to the labeled amount, add methanol to make 100 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 50 mg of triamcinolone acetonide RS and add methanol to make 100 mL. Take 10.0 mL of this solution, add methanol to make 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas of triamcinolone acetonide, A_T and A_S, for each solution.

$$\text{Amount (mg) of triamcinolone acetonide } (C_{24}H_{31}FO_6) = \text{Amount (mg) of triamcinolone acetonide RS} \times \frac{A_T}{A_S} \times \frac{1}{10}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 to 10 μm in particle diameter).

Mobile phase: A mixture of water, acetonitrile and acetic acid(100) (59 : 40 : 1).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Econazole Nitrate, Triamcinolone Acetonide and Gentamicin Sulfate Cream
에코나졸질산염·트리암시놀론아세토니드·겐타마이신황산염 크림

Econazole Nitrate, Triamcinolone Acetonide and Gentamicin Sulfate Cream contains NLT 90.0% and NMT 110.0% of the labeled amounts of econazole nitrate ($C_{18}H_{15}Cl_3N_2O \cdot HNO_3$: 444.70) and triamcinolone acetonide ($C_{24}H_{31}FO_6$: 434.50), and NMT 90.0% and NLT 120.0% of the labeled amount of gentamicin sulfate.

Method of preparation Prepare as directed under Creams, with Econazole Nitrate, Triamcinolone Acetonide and Gentamicin Sulfate.

Identification (1) ***Econazole nitrate and triamcinolone acetonide*—**Weigh an amount of Econazole Nitrate, Triamcinolone Acetonide and Gentamicin Sulfate Cream equivalent to 10 mg of econazole nitrate, dissolve in 10 mL of methanol, and use this solution as the test solution. Separately, use a 0.1% methanol solution of econazole nitrate RS and a 0.01% methanol solution of triamcinolone acetonide RS as the standard solutions. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solutions onto a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of toluene, ethanol, ethyl acetate and 85% formic acid (55 : 20 : 20 : 5) as the developing solvent, and air-dry the plate. Spray evenly hexachloroplatinic (IV) acid-potassium iodide TS on the plate and examine under ultraviolet light; the R_f values and the colors of the spots obtained from the test solution and the standard solution are the same.

(2) ***Gentamicin sulfate***—(1) Dissolve 5 g of Econazole Nitrate, Triamcinolone Acetonide and Gentamicin Sulfate Cream in 10 mL of water, then add 2 mL of α-naphtholethanol solution (1 in 500). Gently superimpose the solution onto 1 mL of sulfuric acid; a purplish blue color develops at the boundary layer.

(3) Weigh an amount of Econazole Nitrate, Triamcinolone Acetonide and Gentamicin Sulfate Cream equivalent to 0.1 g of gentamicin sulfate, add 0.1 mol/L of phosphate buffer solution (pH 8.0) to make 100 mL, and use this solution as the test solution. Separately, weigh 10 mg of gentamicin sulfate RS, add 0.1 mol/L

phosphate buffer solution (pH 8.0) to make 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 50 μL each of the test solution and the standard solution onto a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop with a mixture of chloroform, methanol and strong ammonia water (2 : 1 : 1) as the developing solvent, and air-dry the plate. Place the plate in an appropriate container containing between 2 g and 4 g of iodine crystals, close the lid, and let stand for 3 to 5 minutes; the spots obtained from the test solution and the standard solution have the same R_f value and color.

Assay (1) ***Econazole nitrate*—**Weigh accurately an amount of Econazole Nitrate, Triamcinolone Acetonide and Gentamicin Sulfate Cream equivalent to about 40 mg of econazole nitrate ($C_{18}H_{15}Cl_3N_2O \cdot HNO_3$) according to the labeled amount, add a mixture of methanol and water (40 : 60) to make 100 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 40 mg of econazole nitrate RS, add a mixture of methanol and water (40 : 60) to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of econazole nitrate from each solution, A_T and A_S, respectively.

Amount (mg) of econazole nitrate ($C_{18}H_{15}Cl_3N_2O \cdot HNO_3$)
= Amount (mg) of econazole nitrate RS $\times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: Dissolve 0.77 g of ammonium acetate in water to make 1000 mL. Add 200 mL of methanol to 800 mL of this solution.

Mobile phase B: A mixture of acetonitrile and methanol (60 : 40).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 ~ 25	60 → 10	40 → 90
25 ~ 27	10	90
27 ~ 27.1	10 → 60	90 → 40
27.1 ~ 30	60	40

Flow rate: 1.5 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the symmetry factor is NMT 1.5.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of Piroxicam is NMT 0.73%.

(2) ***Triamcinolone acetonide*—**Weigh accurately an amount of Econazole Nitrate, Triamcinolone Acetonide and Gentamicin Sulfate Cream equivalent to about 5 mg of triamcinolone acetonide ($C_{24}H_{31}FO_6$), add methanol to make 100 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 50 mg of triamcinolone acetonide RS and add methanol to make 100 mL. Take 10.0 mL of this solution, add methanol to make 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of triamcinolone acetonide, A_T and A_S, in each solution.

Amount (mg) of triamcinolone acetonide ($C_{24}H_{31}FO_6$)
= Amount (mg) of triamcinolone acetonide RS $\times \frac{A_T}{A_S} \times \frac{1}{10}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 to 10 μm in particle diameter).

Mobile phase: A mixture of water, acetonitrile and acetic acid(100) (59 : 40 : 1).

Flow rate: 1.0 mL/min

(3) ***Gentamicin sulfate*—**(1) (A) Cylinder plate method ① Medium (a) Medium for seed and base layer

Peptone	6.0 g
Glucose	1.0 g
Yeast extract	3.0 g
Sodium chloride	10.0 g
Meat extract	1.5 g
Agar	13.0 ~ 20.0 g

Weigh the above ingredients, add purified water to make 1000 mL, and adjust the pH after sterilization of the solution so that it will be 7.8 to 8.0.

(b) Agar medium for transferring test organism: Use the medium in (A)→② (b) (ii) ⓑ under the Microbial Assays for Antibiotics.

② Test organism: Use *Staphylococcus epidermidis*

ATCC 12228 as the test organism.

③ Standard solution: Weigh an appropriate amount of gentamicin RS, dry for 3 hours at 110 ℃ under vacuum (NMT 0.67 kPa), then weigh accurately an amount equivalent to 5 mg (potency) and dissolve in 0.1 mol/L phosphate buffer solution (pH 8.0) to prepare a standard stock solution containing 1 mg (potency) per mL. Pipet an appropriate amount of this standard stock solution, dilute with the above buffer solution to contain 4.0 μg and 1.0 μg (potency) per mL, and use these solutions as the standard solutions.

④ Test solution: Weigh accurately an amount of Econazole Nitrate, Triamcinolone Acetonide and Gentamicin Sulfate Cream equivalent to about 25 mg (potency), dissolve in 0.1 mol/L phosphate buffer solution (pH 8.0) to prepare a solution containing 1 mg (potency) per mL; pipet an appropriate amount of this solution and dilute with the above buffer solution to contain 4.0 μg and 1.0 μg (potency) per mL, and use these solutions as the test solutions.

(B) Standard curve method ① Medium: Prepare according to (A) ① under the Microbial assays for antiobiotics.

② Test organism: Follow (A) ② under Microbial assays for antiobiotics.

③ Standard solution: Pipet an appropriate amount of the standard stock solution of (A) ③ under Microbial Assays for Antibiotics, dilute to contain 0.064 μg (potency), 0.080 μg (potency), 0.100 μg (potency), 0.125 μg (potency) and 0.156 μg (potency) per mL with 0.1 mol/L phosphate buffer solution (pH 8.0), and use these solutions as the standard solutions. Prepare a solution containing 0.100 μg (potency) per mL and use this as the standard intermediate diluent.

④ Test solution: Pipet an appropriate amount of the solution from (A) ④ under Microbial Assays for Antibiotics, and dilute to contain 0.10 μg (potency) per mL with 0.01 mol/L phosphate buffer solution (pH 8.0), and use this solution as the test solution.

(2) Content of gentamicin C1, etc. (liquid chromatography) Weigh an appropriate amount of Econazole Nitrate, Triamcinolone Acetonide and Gentamicin Sulfate Cream and gentamicin RS and dissolve in water to prepare solutions containing 0.65 mg per mL; take 10.0 mL of the solution, add 5 mL of isopropanol and 4 mL of *o*-phthaldehyde, shake to mix, add isopropanol to make 25 mL, warm for 15 minutes on a steam bath at 60 ℃, cool, and use as the test solution and the standard solution, respectively. Using the test solution and the standard solution, perform the test as directed under the Liquid Chromatography under the following conditions, and measure the peak areas of gentamicin A_T, and A_S for each solution (Gentamicin C_1: 25 to 50%, Gentamicin C_{1a}: 10 to 35%, Gentamicin C_2 and C_{2a}: 25 to 55%).

Respective content (%) of Gentamicin C_1, Gentamicin C_{1a}, Gentamicin C_{2a} and Gentamicin C_2

$$= \frac{A_T}{A_S} \times 100$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 330 nm).

Column: A stainless steel column about 5 mm in internal diameter and about 10 cm in length, packed with octadecylsilanized porous silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Mobile phase: Add 250 mL of water and 50 mL of acetic acid(100) to 700 mL of methanol, shake to mix, and dissolve 5 mg of sodium 1-heptanesulfonate in this solution.

Flow rate: About 1.5 mL/min.

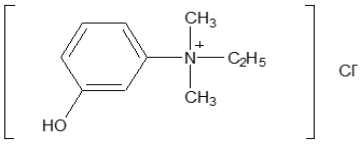
System suitability

System performance: K as determined from the Gentamicin C_1 peak is 2 to 7, the number of theoretical plates determined from the Gentamicin C_2 peak is NLT 1200, and the resolution R between the two peaks is NLT 1.25. Test according to the above conditions; Gentamicin C_1, Gentamicin C_{1a}, Gentamicin C_{2a} and Gentamicin C_2 are eluted in this order.

System repeatability: The relative standard deviation for repeatability is NMT 2.0.

Packaging and storage Preserve in tight containers.

Edrophonium Chloride
에드로포늄염화물



Edrophonium Chloride $C_{10}H_{16}ClNO$: 201.69
N-Ethyl-3-hydroxy-*N*,*N*-dimethylbenzenaminium chloride [*116-38-1*]

Edrophonium Chloride, when dried, contains NLT 98.0% and NMT 101.0% of edrophonium chloride ($C_{10}H_{16}ClN$).

Description Edrophonium Chloride occurs as white crystals or a crystalline powder and is odorless.
It is very soluble in water, freely soluble in ethanol(99.5) or acetic acid(100), and practically insoluble in acetic anhydride or ether.
It is hygroscopic.
It is gradually colored by light.

Identification (1) To 5 mL of an aqueous solution of Edrophonium Chloride (1 in 100), add one drop of

iron(III) chloride TS; the solution exhibits a pale purple color.

(2) Determine the absorption spectra of the solutions of Edrophonium Chloride and edrophonium chloride RS in 0.1 mol/L hydrochloric acid (1 in 20000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) An aqueous solution of Edrophonium Chloride (1 in 50) responds to the Qualitative Analysis for chloride.

Melting point Between 166 and 171 ℃ (with decomposition).

pH Dissolve 1.0 g of Edrophonium Chloride in 10 mL of water; the pH of this solution is between 3.5 and 5.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Edrophonium Chloride in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals*—**Proceed with 1.0 g of Edrophonium Chloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic*—**Proceed with 1.0 g of Edrophonium Chloride according to Method 1 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve about 0.50 g of Edrophonium Chloride in 10 mL of ethanol(95) and use this solution as the test solution. Pipet 1 mL of the test solution, and add ethanol(95) to make exactly 100 mL. Pipet 3 mL of this solution, add ethanol(95) to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of methanol, chloroform and ammonia water(28) (16 : 4 : 1) to a distance of about 10 cm, and air-dry the plate. Observe the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.2% (1 g, in vacuum, phosphorus pentoxide, 3 hours).

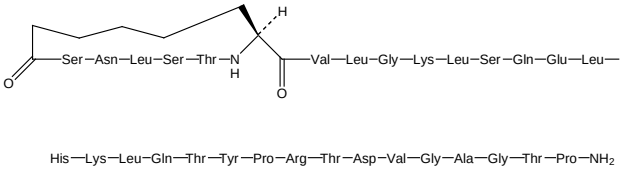
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Edrophonium Chloride, previously dried, dissolve in 100 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 20.169 mg of $C_{10}H_{16}ClNO$

Packaging and storage Preserve in light-resistant, tight containers.

Elcatonin
엘카토닌



Elcatonin $C_{148}H_{244}N_{42}O_{47}$: 3363.77
N-{[(3*S*,6*S*,9*S*,12*S*)-3-Amino-6-(2-amino-2-oxoethyl)-15-[(1*R*)-1-hydroxyethyl]-12-(hydroxymethyl)-9-isobutyl-4,7,10,13,16,24-hexaoxo-1-oxa-5,8,11,14,17-pentaazacyclotetracosan-18-yl]carbonyl}-L-valyl-L-le ucylglycyl-L-lysyl-L-leucyl-L-seryl-L-glutaminyl-L-α-glutamyl-L-leucyl-L-histidyl-L-lysyl-L-leucyl-L-glutaminyl-L-threonyl-L-tyrosyl-L-prolyl-L-arginyl-L-threonyl-L-α-aspartyl-L-valylglycyl-L-alanylglycyl-L-threonyl-L-prolinamide [*60731-46-6*]

Elcatonin contains NLT 5000 and not more 7000 of elcatonin units per mg of peptide, calculated on the anhydrous basis.

Description Elcatonin occurs as a white powder.
It is very soluble in water, freely soluble in ethanol(95), and practically insoluble in acetonitrile.
It is hygroscopic.
The pH of aqueous solution of Elcatonin (1 in 500) is between 4.5 and 7.0.

Identification Determine the absorption spectra of the solutions of 5 mg each of Elcatonin and elcatonin RS in 5 mL of water, respectively, as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Constituent amino acids Put about 1 mg of Elcatonin into a test tube for hydrolysis, dissolve in phenolic acid TS, replace the air inside with nitrogen, seal the tube in vacuum, and heat at 110±2 °C for 24 hours. After cooling, open the tube, evaporate the hydrolysate to dryness in vacuum, dissolve the residue in about 1 mL of 0.02 mol/L hydrochloric acid TS, and use this solution as the test solution. Separately weigh exactly 1.33 mg of L-aspartic acid, 1.19 mg of L-threonine, 1.05 mg of L-serine, 1.47 mg of L-glutamic acid, 1.15 mg of L-proline, 0.75 mg of glycine, 0.89 mg of L-alanine, 1.17 mg of L-valine, 1.89 mg of L-2-aminosuberic acid, 1.31 mg of L-leucine, 1.81 mg of L-tyrosine, 1.83 mg of L-lysine hy-

drochloride, 2.10 mg of L-histidine hydrochloride monohydrate and 2.11 mg of L-arginine hydrochloride, dissolve them in 0.02 mol/L hydrochloric acid TS to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions; 14 peaks of amino acids obtained from the test solution appear. Molar ratios of respective constituent amino acids to alanine are as follows: between 1.7 and 2.2 for aspartic acid, between 3.5 and 4.2 for threonine, between 2.4 to 3.0 for serine, between 2.7 and 3.2 for glutamic acid, between 1.7 and 2.2 for proline, between 2.7 and 3.2 for glycine, between 1.6 and 2.2 for valine, between 0.8 and 1.2 for 2-aminosuberic acid, between 4.5 and 5.2 for leucine, between 0.7 and 1.2 for tyrosine, between 1.7 and 2.2 for lysine, between 0.8 and 1.2 for histidine, and between 0.7 and 1.2 for arginine.

Operating conditions

Detector: Visible spectrophotometer (wavelengths: 440 nm and 570 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 8 cm in length, packed with strongly acidic ion exchange resin for liquid chromatography composed of a sulfonated styrene-divinylbenzene copolymer (3 μm in particle diameter).

Column temperature: Varied between 50 and 65 °C.

Chemical reaction vessel temperature: A constant temperature of about 130 °C.

Color developing time: About 1 minute.

Mobile phase: Buffer solutions A, B, C and D, with sodium ion concentrations of 0.10 mol/L, 0.135 mol/L, 1.26 mol/L and 0.20 mol/L, respectively; provided that the ion concentration is varied stepwise from 0.10 mol/L to 1.26 mol/L with the buffer solutions A, B, C and D.

Composition of buffer solutions (g)				
	A	B	C	D
Citric acid	8.85	7.72	6.10	-
Sodium citrate monohydrate	3.87	10.05	26.67	-
Sodium hydroxide dihydrate	-	-	2.50	8.00
Sodium chloride	3.54	1.87	54.35	-
Ethanol	60.0 mL	-	-	60.0 mL
Thiodiglycol	5.0 mL	5.0 mL	-	-
Purified water	A suitable amount	A suitable amount	A suitable amount	A suitable amount
Total volume	1000 mL	1000 mL	1000 mL	1000 mL

Reaction reagent: Mix 407 g of lithium acetate dihydrate, 245 mL of acetic acid(100) and 801 mL of 1-methoxy-2-propanol, add water to make 2000 mL, stir for about 20 minutes to mix while passing nitrogen, and use this solution as the solution A. Separately, add 77 g of ninhydrin and 0.134 g of sodium borohydride to 1957 mL of 1-methoxy-2-propanol, stir for 20 minutes to mix while passing nitrogen, and use this solution as the solution B. Mix the solution A and solution B before use.

Flow rate of mobile phase: Adjust so that the retention time of arginine is about 75 minutes.

Flow rate of reaction reagent: About 0.2 mL/min.

Selection of column: Proceed with 10 μL of the standard solution according to the above conditions; use a column from which aspartic acid, threonine, serine, glutamic acid, proline, glycine, alanine, valine, 2-aminosuberic acid, leucine, tyrosine, lysine, histidine and arginine are eluted in this order with complete separation of each peak.

Purity (1) ***Acetic acid***—Weigh accurately about 3 mg to 6 mg of Elcatonin quickly under conditions of 25±2 °C and 50±5% relative humidity, add exactly 1 mL of the internal standard solution to mix, and use this solution as the test solution. Separately, weigh accurately about 0.5 g of acetic acid(100), and add the internal standard solution to make exactly 100 mL. Pipet 5 mL of the resulting solution, add the internal standard solution to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of acetic acid to that of the internal standard; the amount of acetic acid is NMT 7.0%.

$$\text{Content (\%) of acetic acid } (CH_3COOH) = \frac{Q_T}{Q_S} \times \frac{W_{ST}}{W_{SA}} \times 50$$

W_{ST}: Amount (g) of acetic acid(100) taken
W_{SA}: Amount (mg) of sample taken

Internal standard solution—An aqueous solution of citric acid monohydrate (1 in 4000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and 6 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 13.2 g of monobasic ammonium phosphate in 900 mL of water, adjust the pH to 2.5 with phosphoric acid, and add water to make 1000

mL.

Flow rate: Adjust the flow rate so that the retention time of acetic acid is about 4 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; acetic acid and citric acid are eluted in this order with the resolution being NLT 2.0.

(2) ***Related substances***—Dissolve 1.0 mg of Elcatonin in 1 mL of a mixture of trichloroacetic acid and acetonitrile (2 : 1), and use this solution as the test solution. Pipet 0.3 mL of the resulting solution, add a mixture of trichloroacetic acid and acetonitrile (2 : 1) to make 10 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine each peak area as directed in the automatic integration method; the sum of the peak areas other than elcatonin in the test solution is not greater than the peak area of elcatonin in the standard solution, and each peak area other than elcatonin in the test solution is not greater than one-third of the peak area of elcatonin in the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of trifluoroacetic acid TS and acetonitrile (change the ratio from 85 : 15 to 55 : 45 in 30 minutes).

Flow rate: Adjust the flow rate so that the retention time of elcatonin is about 25 minutes.

System suitability

Detection sensitivity: Adjust the detection sensitivity so that the peak height of elcatonin obtained from 10 μL of the standard solution is between 50 mm and 200 mm.

System performance: Dissolve 2 mg of Elcatonin in 200 μL of trypsin TS for test of elcatonin. Warm this solution at 37 °C for 1 hour, and add one drop of acetic acid(100), and heat at 95 °C for 1 minute. To 10 μL of this solution, add 50 μL of the test solution, and mix it. Proceed with 10 μL of this solution according to the above operating conditions; the resolution between the peak of elcatonin and the peak which is eluted immediately before the peak of elcatonin is NLT 2.0, and the retention time of elcatonin is about 25 minutes.

Time span of measurement: A range in which the gradient elution appearing on the chromatogram is regularly changing after the solvent peak.

Water Weigh accurately about 1 to 3 mg of Elcatonin quickly and perform the test as directed under the coulometric titration under the Water; it is NMT 8.0%. It should be weighed under conditions of 25±2 °C and 50±5% relative humidity.

Nitrogen content Weigh accurately 15 to 20 mg of Elcatonin quickly under the conditions of 25±2 °C and 50±5% relative humidity, and perform the test as directed under the Nitrogen Determination; the amount of nitrogen (N: 14.01) is NLT 16.1% and NMT 18.7%, calculated on the anhydrous and residual acetic acid-free basis.

Assay (i) Animals: Select healthy male Sprague-Dawley rats each weighing between 90 g and 110 g. Keep the rats for NLT 3 days before use, providing an appropriate uniform diet and water.

(ii) Solution for elcatonin: Dissolve 2.72 g of sodium acetate trihydrate in water to make 200 mL, add 0.2 g of bovine serum albumin, and adjust the pH to 6.0 with acetic acid(100). Prepare before use.

(iii) Standard solution: Dissolve elcatonin RS in the solution for elcatonin to make two standard solutions: the high-dose standard solution, S_H, containing exactly 0.075 unit in each mL, and the low-dose standard solution, S_L, containing exactly 0.0375 unit in each mL.

(iv) Test solution: Weigh accurately 0.5 to 2.0 mg of Elcatonin quickly under conditions of 25±2 °C and 50±5% relative humidity, and dissolve in the solution for elcatonin to make two test solutions: the high-dose test solution, T_H, containing the units per mL equivalent to S_H and the low-dose test solution, T_L, containing the units per mL equivalent to S_L.

(v) Deproteinizing solution for elcatonin: Dissolve 160 g of trichloroacetic acid and 30.6 g of strontium chloride in water to make 3600 mL.

(vi) Procedure: Divide the animals into 4 equal groups of NLT 10 animals each. Withhold all food for 18 to 24 hours before the injections, and also withhold water during the assay until the final blood sample is taken. Handle the animals with care in order to avoid undue excitement.

Inject exactly 0.2 mL each of the standard solution and the test solution into the tail vein of each animal as indicated in the following regimen:

First Group	S_H	Third Group	T_H
Second Group	S_L	Fourth Group	T_L

At 1 hour after the injection, take a sufficient blood sample to perform the test from the carotid vein of each animal under ether anesthesia, centrifuge the blood samples to separate serum, and determine the serum calcium according to the following (G).

(vii) Serum calcium determination: Pipet 0.3 mL of the serum, add the deproteinizing solution for elcatonin to make exactly 3 mL, mix well, centrifuge, and use the clear supernatant as the test solution for calcium determination. Separately, pipet 1 mL of calcium standard solu-

tion for the Atomic Absorption Spectroscopy, and add a solution of sodium chloride (17 in 2000) to make exactly 50 mL. Use this solution as the standard solution for calcium determination. Determine the absorbances, A_T and A_S, of the test solution and standard solution as directed under the Atomic Absorption Spectroscopy according to the following conditions. Determine the absorbance, A_0, of a solution obtained in the same manner used for preparation of the standard solution, but with 1 mL of water.

Amount (mg) of calcium (Ca) in 100 mL of the serum

$$= 0.01\frac{A_T - A_0}{A_S - A_0} \times 10 \times 100$$

Gas: Air–acetylene
Lamp: Calcium hollow cathode lamp
Wavelength: 422.7 nm

(viii) Calculation: Amounts of calcium in 100 mL of the serum obtained with S_H, S_L, T_H and T_L in (G) are denoted by y_1, y_2, y_3 and y_4, respectively. Sum up y_1, y_2, y_3 and y_4 of each group to obtain Y_1, Y_2, Y_3 and Y_4, respectively.

Units per mg of peptide, calculated on the anhydrous and residual acetic acid-free basis.

= Anti log M × (units per mL of high-dose standard solution)$\times \frac{b}{a}$

$M = 0.3010 \times \frac{Y_a}{Y_b}$

$Y_a = -Y_1 - Y_2 + Y_3 + Y_4$

$Y_b = Y_1 - Y_2 + Y_3 - Y_4$

a: Amount (mg) of sample taken

$$\times \frac{100 - [Content\ (\%)\ of\ water + content\ (\%)\ of\ Acetic\ acid]}{100}$$

b: Total volume (mL) of the high-dose test solution prepared by dissolving the sample with solution for elcatonin

F' calculated by the following equation is smaller than F shown in the table against n with which s^2 is calculated. When calculate L (P = 0.95) according to the following equation, L is NMT 0.20. If F' exceeds F, or if L exceeds 0.20, repeat the test, increasing the number of animals or arranging the assay conditions so that F' is NMT F and L is NMT 0.20.

$$F' = \frac{(-Y_1 + Y_2 + Y_3 - Y_4)^2}{4fs^2}$$

f: Number of the animals of each group

$$s2 = \frac{\sum y^2 - \frac{Y}{f}}{n}$$

$\sum y^2$: The sum of squares of y_1, y_2, y_3 and y_4 in each group

$$Y = Y_1^2 + Y_2^2 + Y_3^2 + Y_4^2$$

$$n = 4(f\text{-}1)$$

$$L = 2\sqrt{(C-1)(CM^2 + 0.09062)}$$

$$C = \frac{Y_b^2}{Y_b^2 - 4fs^2t^2}$$

t^2: Value shown in the following table against n used to calculate s^2

n	$t^2 = F$	n	$t^2 = F$	n	$t^2 = F$
1	161.45	13	4.667	25	4.242
2	18.51	14	4.600	26	4.225
3	10.129	15	4.543	27	4.210
4	7.709	16	4.494	28	4.196
5	6.608	17	4.451	29	4.183
6	5.987	18	4.414	30	4.171
7	5.591	19	4.381	40	4.085
8	5.318	20	4.351	60	4.001
9	5.117	21	4.325	120	3.920
10	4.965	22	4.301	∞	3.841
11	4.844	23	4.279		
12	4.747	24	4.260		

Packaging and storage Preserve in tight containers and store at below 8 °C.

Elcatonin Injection
엘카토닌 주사액

Elcatonin Injection is an aqueous injection and contains NLT 80.0% and NMT 125.0% of the labeled amount of elcatonin units.

Method of preparation Prepare as directed under Injections, with Elcatonin.

Description Elcatonin Injection occurs as a clear, colorless liquid.

Identification (1) Take 12 mL of Elcatonin Injection, evaporate to dryness on a steam bath, dissolve in 3 mL of water, and use this solution as the test solution. Add 1 mL of alkaline copper TS to the test solution, shake to mix, and allow to stand for 10 minutes. To this solution, add 0.2 mL of diluted Folin TS (1 in 2) and heat on a steam bath for 3 minutes; the solution exhibits a pale blue color.

(2) Perform the test with Elcatonin Injection as directed under Assay; the test group exhibits NLT 20% serum calcium reduction compared to the control group. The test animals are divided into 2 groups with 5 animals, respectively: the test group and control group. For the test group, Prepare the test solution by pipetting 0.5 mL of Elcatonin Injection and diluting in solution for elcatonin to obtain a solution having known a concentration of 0.1 elcatonin unit per mL. Use a solution for elcatonin vehicle as a control solution. Inject 0.2 mL of each of these solutions into the tail vein.

pH Between 5.0 and 6.5.

Sterility Meets the requirements.

Pyrogen Meets the requirements. The amount tested is 2.0 mL per kg of the body weight of a test animal.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay (1) ***Animals*—**Select healthy male Sprague-Dawley rats each weighing 90 to 110 g. Keep the rats for NLT 3 days before use, providing an appropriate uniform diet and water.

(2) ***Solution for elcatonin*—**Dissolve 2.72 g of sodium acetate trihydrate in water to make 200 mL, add 0.2 g of bovine serum albumin, and adjust the pH to 6.0 with acetic acid(100). Prepare before use.

(3) ***Standard solution*—**Dissolve elcatonin RS in the solution for elcatonin to prepare solutions containing exactly 0.075 units and 0.0375 units per mL, respectively. Use these solutions as the high-concentration standard solution S_H and the low-concentration standard solution S_L, respectively.

(4) ***Test solution*—**Pipet 0.5 mL of Elcatonin Injection, add the solution for elcatonin to obtain solutions having known concentration of units equivalent to the high-concentration standard solution S_H and the low-concentration standard solution S_L, and use these solutions as the high-concentration test solution T_H and the low-concentration test solution T_L, respectively.

(5) ***Procedure*—**Divide the test animals into 4 groups of NLT 10 animals each (the same number of animals). Withhold all food for 18 to 24 hours before the injections, and also withhold water during the assay until the final blood sample is taken. Handle the animals with care in order to avoid undue excitement.
Inject exactly 0.2 mL each of the standard solutions and the test solutions into the tail vein of each animal as indicated in the following regimen:

Group 1 S_H	Group 3 T_H
Group 2 S_L	Group 3 T_L

At 1 hour after the injection, take a sufficient blood sample to perform the test from the carotid artery and vein of each animal under ether anesthesia, centrifuge the blood samples to separate serum, and determine the serum calcium according to the following (G).

(6) ***Serum calcium assay*—**Pipet 0.5 mL of serum, add the deproteinizing solution for elcatonin to make exactly 5 mL, shake to mix well, centrifuge, and use the clear supernatant as the test solution for calcium assay. Separately, pipet 1.0 mL of calcium standard solution for atomic absorption spectrophotometry, and add sodium chloride solution (0.85 in 100) to make 10 mL. Pipet 5.0 mL of this solution, add deproteinizing solution for elcatonin to make exactly 50 mL, and use this solution as the standard solution for calcium assay. Separately, take 1.0 mL of water, proceed in the same manner as in preparation of standard solution for calcium assay, and use this solution as the blank test solution. Determine the absorbances, A_T and A_S, of the test solution, standard solution and the blank test solution as directed under the Atomic Absorption Spectroscopy according to the following conditions.

Gas: Air–acetylen
Lamp: Calcium hollow cathode lamp
Wavelength: 422.7 nm

$$\text{Amount (mg) of calcium (Ca) in 100 mL of serum} = 0.01 \times \frac{A_T - A_0}{A_S - A_0} \times 10 \times 100$$

Deproteinizing solution for elcatonin—Dissolve 160 g of trichloroacetic acid and 30.6 g of strontium chloride in water to make 3600 mL.

(7) ***Calculation*—**The amounts of calcium in 100 mL of serum obtained from S_H, S_L, T_H and T_L in the serum calcium Assay shall be y_1, y_2, y_3 and y_4, respectively. For each group, add y_1, y_2, y_3 and y_4 to make Y_1, Y_2, Y_3 and Y_4, respectively.

$$\text{Number of elcatonin units per mL of Elcatonin Injection} = \text{antilog } M \times [\text{Number of elcatonin units in 1 mL of the high-concentration standard solution}] \times \frac{b}{a}$$

$$M = 0.3010 \times \frac{Y_a}{Y_b}$$

$$Y_a = -Y_1 - Y_2 + Y_3 + Y_4$$

$$Y_b = Y_1 - Y_2 + Y_3 - Y_4$$

a: Amount (mL) of sample taken
b: Total amount (mL) when elcatonin vehicle is

added to the sample to prepare the high-concentration test solution

F′ calculated according to the following equation is less than the F in the table for n when S^2 is calculated. Also, when L (P = 0.95) is calculated according to the following equation, L is NMT 0.2. If F' exceeds F, or if L exceeds 0.2, repeat the test, increasing the number of animals or arranging the assay conditions so that F' is NMT F and L is NMT 0.20.

$$F' = \frac{(-Y_1 + Y_2 + Y_3 - Y_4)^2}{4fS^2}$$

f = Number of test animals in each group

$$S^2 = \frac{\sum Y^2 - Y/f}{n}$$

Σy^2 = The sum of the squares of y_1, y_2, y_3 and y_4 of each group

$$Y = Y_1^2 + Y_2^2 + Y_3^2 + Y_4^2$$

$$n = 4(f - 1)$$

$$L = 2\sqrt{(C-1)(CM^2 + 0.09062)}$$

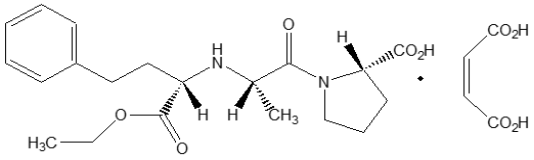
$$C = \frac{Y_b^2}{Y_b^2 - 4fs^2t^2}$$

t^2: The table corresponding to n in the following table when s^2 is calculated.

n	$t^2 = F$	*n*	$t^2 = F$	*n*	$t^2 = F$
1	161.45	13	4.667	25	4.242
2	18.51	14	4.600	26	4.225
3	10.129	15	4.543	27	4.210
4	7.709	16	4.494	28	4.196
5	6.608	17	4.451	29	4.183
6	5.987	18	4.414	30	4.171
7	5.591	19	4.381	40	4.085
8	5.318	20	4.351	60	4.001
9	5.117	21	4.325	120	3.920
10	4.965	22	4.301	∞	3.841
11	4.844	23	4.279		
12	4.747	24	4.260		

Packaging and storage Preserve in hermetic containers.

Enalapril Maleate
에날라프릴말레산염



$C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$: 492.52

(2*S*)-1-[(2*S*)-2-{[(2*S*)-1-Ethoxy-1-oxo-4-phenylbutan-2-yl]amino}propanoyl]pyrrolidine-2-carboxylic acid (*Z*)-but-2-enedioate [*76095-16-4*]

Enalapril Maleate contains NLT 98.0% and NMT 102.0% of enalapril maleate ($C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$), calculated on the dried basis.

Description Enalapril Maleate occurs as white crystals or a crystalline powder.
It is freely soluble in methanol, sparingly soluble in water or ethanol(99.5), and slightly soluble in acetonitrile.

Melting point—About 145 °C (with decomposition).

Identification (1) To 20 mg of Enalapril Maleate, add 1 mol/L hydrochloric acid TS, shake, add 5 mL of ether, and shake for 5 minutes. Take 3 mL of the upper layer, distill the ether on a steam bath, and add 5 mL of water to the residue while shaking. Add 1 drop of potassium permanganate TS; the red color of the solution disappears immediately.

(2) Determine the infrared spectra of Enalapril Maleate and enalapril maleate RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) The retention times of the major peaks obtained from the test solution and the standard solution in the Assay are the same.

Optical rotation $[\alpha]_D^{25}$: Between -41.0° and -43.5° (0.1 g after drying, methanol, 10 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Enalapril Maleate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Weigh accurately about 30 mg of Enalapril Maleate, dissolve in a mixture of phosphate buffer solution, pH 2.5, and acetonitrile (95 : 5) to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 30 mg of enalapril maleate RS, dissolve in a mixture of phosphate buffer solution, pH 2.5 and acetonitrile (95 : 5) to make exactly 100 mL. Pipet accurately 1 mL of this solution, add a mixture of phosphate buffer solution, pH 2.5 and acetonitrile (95 : 5) to make exactly 100 mL, and use this solution as the standard solution Perform the test with 50

μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of each solution by the automatic integration method, and calculate the content of each related substance; a peak among two peaks other than the major peak is NMT 1.0%, another peak is NMT 0.3%, and the total content of the related substances is NMT 2.0%.

$$\text{Content (\%) of each related substance} = 100 \times \left(\frac{C_S}{C_i} \times \frac{A_T}{A_S}\right)$$

C_S: Concentration (mg/mL) of the standard solution

C_i: Concentration (mg/mL) of Enalapril Maleate in the test solution

A_T: Peak area of each related substance in the test solution

A_S: Peak area of each related substance in the standard solution

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

Loss on drying NMT 1.0% (NMT 0.67 kPa, 60 ℃, 2 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 30 mg of Enalapril Maleate, dissolve in a mixture of phosphate buffer solution, pH 2.5, and acetonitrile (95 : 5) to make exactly 100 mL, and use this solution as the test solution. Separately, dissolve about 30 mg, accurately weighed, of enalapril maleate RS in a mixture of phosphate buffer solution, pH 2.5, and acetonitrile (95 : 5) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the major peak areas, A_T and A_S, from each solution.

$$\text{Amount (mg) of enalapril maleate } (C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4) = \text{Amount (mg) of enalapril maleate RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.1 mm in internal diameter and about 15 cm in length, packed with styrene-divinylbenzene copolymer for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: 70 °C

Flow rate: 1.5 mL/min

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: A mixture of phosphate buffer solution, pH 6.8 and acetonitrile (19 : 1).

Mobile phase B: A mixture of acetonitrile and phosphate buffer solution, pH 6.8 (33 : 17).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0	95	5
0 - 20	95 → 40	5 → 60
20 - 25	40	60
25 - 26	40 → 95	60 → 5
26 - 30	95	5

System suitability

System performance: Mix 1 mL of enalapril diketopiperazine solution and 50 mL of the standard solution. Proceed with 50 μL of this solution according to the above operating conditions; enalapril and enalapril diketopiperazine are eluted in this order with the resolution being NLT 3.5.

System repeatability: Repeat the test 6 times with 50 μL each of the standard solution according to the operating conditions under the Assay; the relative standard deviation of the peak areas is NMT 1.0%.

pH 6.8 phosphate buffer solution—Dissolve 2.8 g of sodium dihydrogen phosphate dihydrate in about 900 mL of water. Adjust with 9 mol/L of sodium hydroxide TS to a pH of 6.8, dilute with water to make 1000 mL.

pH 2.5 phosphate buffer solution—Dissolve 2.8 g of sodium dihydrogen phosphate dihydrate in about 900 mL of water. Adjust with phosphoric acid to a pH of 2.5, dilute with water to make 1000 mL.

Enalapril diketopiperazine solution—Place about 20 mg of enalapril maleate RS in a 100-mL beaker to form a mound on the bottom of the beaker, and place the beaker on a hotplate stirrer. Heat up to a temperature not to cause pyrolysis for about 5 to 10 minutes until the solid is melted. Immediately allow to cool, add 50 ml of acetonitrile, and sonicate for a few minutes. The solution typically contains, in each mL, between 0.2 mg and 0.4 mg of enalapril diketopiperazine.

Packaging and storage Preserve in well-closed containers.

Enalapril Maleate Tablets
에날라프릴말레산염 정

Enalapril Maleate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of enalapril maleate ($C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$: 492.52).

Method of preparation Prepare as directed under Tablets, with Enalapril Maleate.

Identification (1) Weigh an amount of previously powdered Enalapril Maleate Tablets equivalent to 50 mg of Enalapril Maleate according to the labeled amount, add 20 mL of methanol, and shake well. Centrifuge this solution, take the clear supernatant, and use this solution as the test solution. Separately, dissolve 25 mg of enalapril maleate RS in 10 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of water, acetone, 1-butanol and acetic acid(100) (1 : 1 : 1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the R_f values of the 2 spots obtained from the test solution and 2 spots obtained from the standard solution are the same.

(2) The retention times of the major peaks obtained from the test solution and the standard solution in the Assay are the same.

Purity ***Related substances***—Use the test solution and the standard solution prepared as directed under the Assay, the pH 2.2 phosphate buffer solution, and the enalapril diketopiperazine solution prepared as directed under the Assay of Enalapril Maleate. Take 1.0 mL of the standard solution, add phosphate buffer solution, pH 2.2, to make exactly 100 mL, and use this solution as the related substance standard solution. Perform the test with 50 μL each of the test solution, the standard solution, the related substance standard solution and the buffer solution as directed under the Liquid Chromatography according to the conditions of the Assay, determine the peak area of each solution by the automatic integration method, and calculate the content of related substances. Determine the peak areas of all peaks with peak areas NLT 0.1% of the enalapril peak area except for peaks appearing in the buffer solution in the chromatogram of the test solution.

$$\text{Content (\%) of anhydrous enalaprilate} = \frac{492.53}{348.39} \times \frac{CV}{N} \times \frac{A_T}{A_S} \times \frac{100}{L}$$

492.53: Molecular weight of enalapril maleate

348.39: Molecular weight of anhydrous enalaprilate

C: Concentration (μg/mL) of enalaprilate in the standard solution

V: Volume (mL) of the test solution

N: Number of tablets taken for the test

L: Labeled amount (mg) of enalapril maleate for tablets

A_T: Peak area of enalaprilate in the test solution

A_S: Peak area of enalaprilate in the standard solution

$$\text{Content (\%) of enalapril piperazine} = \frac{492.53}{358.44} \times \frac{C'V}{N} \times \frac{A_T}{1.25A_S} \times \frac{100}{L}$$

492.53: Molecular weight of enalapril maleate

358.44: Molecular weight of enalapril diketopiperazine

C': Concentration (mg/mL) of enalapril maleate RS in related substance standard solution

V: Volume (mL) of the test solution

N: Number of tablets taken for the test

1.25: Peak area of enalapril diketopiperazine to enalapril

L: Labeled amount (mg) of enalapril maleate for tablets

$$\text{Content (\%) of other related substances} = \frac{C'V}{N} \times \frac{A_T}{A_S} \times \frac{100}{L}$$

A_T: Peak area of other related substances

C', *V* and *N* are as above

The total amount of related substances, including enalaprilate and enalapril diketopiperazine, is NMT 5.0%.

Enalaprilate standard solution—Weigh accurately an appropriate amount of enalaprilate RS, and dissolve in water to make a solution containing 0.4 mg per mL.

Standard solution—Weigh accurately about 20 mg of enalapril maleate RS, add 0.5 mL of enalaprilate RS, add 50 mL of buffer solution, dissolve by mixing well, and add phosphate buffer solution, pH 2.2, to make exactly 100 mL.

Related substance standard solution—Pipet 1 mL of the standard solution accurately, and add phosphate buffer solution, pH 2.2, to make exactly 100 mL.

Dissolution Perform the test with 1 tablet of Enalapril Maleate Tablet at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of phosphate buffer solution, pH 6.8, as the dissolution medium. After 30 minutes from starting the dissolution test, take 20 mL of the dissolved solution, and filter through a membrane filter with a pore size NMT 0.8 μm. Discard the first 10 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately 10 mg of enalapril maleate RS, dissolve in phosphate buffer solution, pH 6.8, to make exactly 100 mL, and use this solution as the standard solution. Perform the test according to the operating conditions under the Assay of Enalapril Maleate.

It meets the requirements if the dissolution rate of Enalapril Maleate Tablets for 30 minutes is NLT 80%.

Uniformity of dosage units It meets the requirements of the Content Uniformity Test when the test is performed according to the following method. Take 1 tablet of Enalapril Maleate Tablet, add 50 mL of phosphate buffer solution, pH 2.2, sonicate for 15 minutes if necessary, shake for 30 minutes, add phosphate buffer solution, pH 2.2, to make exactly 100 mL, and use this solution as the test solution. Take a certain amount of this solution, and dilute exactly with the buffer solution to the concentration of 0.1 mg per mL. Separately, weigh accurately 10 mg of enalapril maleate RS, dissolve in phosphate buffer solution, pH 2.2, to make exactly 100 mL, and use this solution as the standard solution. Perform the test as directed under the Assay of Enalapril Maleate.

$$\text{Amount (mg) of enalapril maleate } (C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4) = T \times \frac{C}{D} \times \frac{A_T}{A_S}$$

T: Labeled amount (mg) of enalapril maleate in 1 tablet
C: Concentration (mg/mL) of the standard solution
D: Concentration (mg/mL) of enalapril maleate in the test solution
A_T: Peak area of enalapril maleate in the test solution
A_S: Peak area of enalapril maleate in the standard solution

pH 2.2 phosphate buffer solution—Dissolve 1.38 g of sodium dihydrogen phosphate dihydrate in about 800 mL of water, add phosphoric acid to adjust the pH to 2.2, and add water to make 1000 mL.

Assay Weigh accurately the mass of NLT 20 tablets of Enalapril Maleate Tablets, and powder. Weigh accurately a portion of this powder, equivalent to about 20 mg of enalapril maleate ($C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$), add 50 mL of phosphate buffer solution, pH 2.2, from the Uniformity of dosage units, sonicate for 15 minutes, and shake for 30 minutes. Then, add phosphate buffer solution, pH 2.2, to make 100 mL, sonicate for 15 minutes, filter through a membrane filter, and use this solution as the test solution. Separately, weigh accurately about 20 mg of enalapril maleate RS, add 0.5 mL of enalaprilate RS, dissolve in 50 mL of phosphate buffer solution, pH 2.2, and sonicate if necessary. Then, add phosphate buffer solution, pH 2.2, to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of each solution.

$$\text{Amount (mg) of enalapril maleate } (C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4) = \text{Amount (mg) of enalapril maleate RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with hydroxy propylsilyl silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: 50 °C

Mobile phase: A mixture of phosphate buffer solution, pH 2.2, and acetonitrile (75 : 25).

Flow rate: 2 mL/min

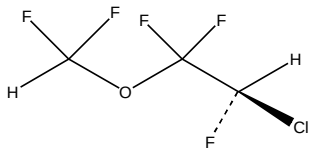
System suitability

System performance: Take 0.5 mL of enalapril diketopiperazine solution, and add the standard solution to make 25 mL. Proceed with 50 μL of this solution according to the above conditions; maleic acid, enalaprilate, enalapril and enalapril diketopiperazine are eluted in this order with the resolutions between maleic acid and enalaprilate, enalaprilate and enalapril, and enalapril and enalapril diketopiperazine being NLT 2.0, respectively.

System repeatability: Repeat the test 6 times with 50 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of enalapril is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Enflurane
엔플루란



and enantiomer

Enflurane $C_3H_2ClF_5O$: 184.49
2-Chloro-1-(difluoromethoxy)-1,1,2-trifluoroethane
[*13838-16-9*]

Description Enflurane occurs as a clear, colorless fluid.
It is slightly soluble in water.
It is miscible with ethanol(95) or ether.
It is a volatile, and not inflammable.
It shows no optical rotation.

Boiling point—Between 54 and 57°C.

Identification (1) Take 50 μL of Enflurane, and prepare the test solution as directed under the Oxygen Flask Combustion using 40 mL of water as the absorbent. The test solution responds to the Qualitative Analysis for chloride and fluoride.

(2) Determine the infrared spectra of Enflurane and enflurane RS as directed under the liquid film method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Refractive index n_D^{20}: Between 1.302 and 1.304.

Specific Gravity d_{20}^{20}: Between 1.520 and 1.540.

Purity (1) ***Acidity or alkalinity***—To 60 mL of Enflurane, add 60 mL of freshly boiled and cooled water, shake for 3 minutes to mix, take the water layer, and use this solution as the test solution. To 20 mL of the test solution, add 1 drop of bromocresol purple TS and 0.10 mL of 0.01 mol/L sodium hydroxide solution; a violet color develops. To 20 mL of the test solution, add 1 drop of bromocresol purple TS and 60 μL of 0.01 mol/L hydrochloric acid; a yellow color is produced.

(2) ***Chloride***—Weigh 20 g of Enflurane, add 20 mL of water, shake well to mix, and separate the water layer. Take 10 mL of the water layer, and add 6 mL of dilute nitric acid and water to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.001%).

(3) ***Related substances***—Perform the test with 5 μL of Enflurane as directed under the Gas Chromatography according to the following conditions. Introduce the sample, immediately determine each peak area other than the peak of air as directed in the automatic integration method, and calculate the amount of each peak by the percentage peak area method; the amount of the substances other than enflurane is NMT 0.10%.

Operating conditions

Detector: A thermal conductivity detector

Column: A stainless steel about 3 mm in inside diameter and about 3 m in length, packed with diatomaceous earth for gas chromatography, 180 to 250 μm in particle diameter, coated with diethylene glycol succinate ester for gas chromatography at the ratio of 20%.

Column temperature: A constant temperature of about 80 °C.

Carrier gas: Helium

Flow rate: Adjust the flow rate so that the retention time of enflurane is about 3 minutes.

System suitability

Test for required detectability: Take 1 mL of Enflurane, and add 2-propanol to make 100 mL. Take 2 mL of this solution, add 2-propanol to make 10 mL, and use this solution as the system suitability solution. Take 1.0 mL of this solution and add 2-propanol to make exactly 10 mL. Confirm that the peak area of enflurane obtained from 5 μL of this solution is equivalent to 7 to 13% of the peak area of enflurane from the system suitability solution.

System performance: Mix 5 mL of Enflurane with 5 mL of 2-propanol. Proceed with 5 μL of this solution according to the above operating conditions, enflurane and 2-propanol are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 5 μL of the system suitability solution according to the above operating conditions; the relative standard deviation of the ratios of the peak area of enflurane is NMT 2.0%.

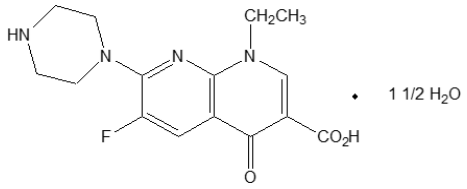
Time span of measurement: About 3 times the retention time of enflurane.

(4) ***Evaporation residue***—Pipet 65 mL of Enflurane, evaporate to dryness on a steam bath, and dry the residue at 105 ºC for 1 hour; the mass of the residue is NMT 1.0 mg.

Water NMT 0.1% (10 g, volumetric titration, direct titration).

Packaging and storage Preserve in tight containers and store at below 30 °C.

Enoxacin Hydrate
에녹사신수화물



Enoxacin $C_{15}H_{17}FN_4O_3 \cdot 1½H_2O$: 347.34
1-Ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid sesquihydrate
[*84294-96-2*]

Enoxacin Hydrate, when dried, contains NLT 98.5% and NMT 101.0% of enoxacin ($C_{15}H_{17}FN_4O_3$: 320.32).

Description Enoxacin Hydrate occurs as white to pale yellowish brown crystals or a crystalline powder.
It is freely soluble in acetic acid(100), slightly soluble in methanol, very slightly soluble in chloroform, and practically insoluble as water, ethanol(95) or ether.
It dissolves in dilute sodium hydroxide TS.
It is gradually colored by light.

Identification (1) Put 20 mg of Enoxacin Hydrate and 30 mg of sodium metal in a test tube, and heat gently with caution until glowing red. After cooling, add 0.5 mL of methanol and 5 mL of water, and heat to boiling. Add 2 mL of dilute acetic acid and filter; the filtrate responds to the Qualitative Analysis (2) for fluoride.

(2) Dissolve 50 mg each of Enoxacin Hydrate and enoxacin hydrate RS in dilute sodium hydroxide TS to make 100 mL. Pipet 1 mL each of these solutions and add water to make 100 mL. With these solutions, determine the absorption spectra as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Enoxacin Hydrate and enoxacin hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of ab-

sorption at the same wavenumbers.

Melting point Between 225 and 229 ℃ (after drying).

Purity (1) ***Sulfate***—Dissolve 1.0 g of Enoxacin Hydrate in 50 mL of dilute sodium hydroxide TS, add 10 mL of dilute hydrochloric acid, shake to mix, and centrifuge. Filter the clear supernatant, take 30 mL of the filtrate, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 0.50 mL of 0.005 mol/L sulfuric acid, 25 mL of dilute sodium hydroxide TS, 5 mL of dilute hydrochloric acid and water to make 50 mL (NMT 0.048%).

(2) ***Heavy metals***—Proceed with 1.0 g of Enoxacin Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Enoxacin Hydrate according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 50 mg of Enoxacin Hydrate in 25 mL of a mixture of methanol and chloroform (7 : 3), and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of methanol and chloroform (7 : 3) to make 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, water and acetic acid(100) (3 : 1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Observe the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying Between 7.0% and 9.0% (1 g, 105 ℃, 3 hours).

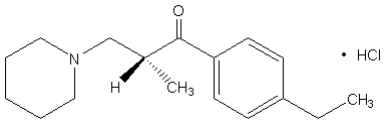
Residue on ignition NMT 0.1% (1 g, platinum crucible).

Assay Weigh accurately about 0.3 g of Enoxacin Hydrate, previously dried, dissolve in 30 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 32.03 mg of $C_{15}H_{17}FN_4O_3$

Packaging and storage Preserve in light-resistant, tight containers.

Eperisone Hydrochloride
에페리손염산염



and enantiomer

$C_{17}H_{25}NO \cdot HCl$: 295.85

1-(4-Ethylphenyl)-2-methyl-3-(piperidin-1-yl) propan-1-one hydrochloride [*56839-43-1*]

Eperisone Hydrochloride contains NLT 98.5% and NMT 101.0% of eperisone hydrochloride ($C_{17}H_{25}NO \cdot HCl$).

Description Eperisone Hydrochloride occurs as a white crystalline powder.
It is freely soluble in water, methanol or acetic acid(100), and soluble in ethanol(99.5).

Melting point—About 167 ℃ (with decomposition)
A solution of Eperisone Hydrochloride in methanol (1 in 100) shows no optical rotation.

Identification (1) Determine the absorption spectra of solutions of Eperisone Hydrochloride and eperisone hydrochloride RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Eperisone Hydrochloride and eperisone hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Eperisone Hydrochloride (1 in 50) responds to the Qualitative Analysis for chloride.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Eperisone Hydrochloride as directed under Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Piperidine hydrochloride***—Weigh 1.0 g of Eperisone Hydrochloride and dissolve in 20 mL of water, add 2.0 mL of diluted hydrochloric acid (1 in 2), 2.0 mL of copper(II) sulfate pentahydrate solution (1 in 20) and 1.5 mL of ammonia water(28), and use this solution as the test solution. Separately, to 2.0 mL of piperidine hydrochloride solution (1 in 1000), add 18 mL of water, 2.0 mL of diluted hydrochloric acid (1 in 2), 2.0 mL of copper(II) sulfate pentahydrate solution (1 in 20) and 1.5 mL of ammonia water(28), and use this solution as the standard solution. To each of the test solution and the standard solution, add 10 mL of a mixture of isopropyl ether and carbon disulfide (3 : 1), mix well for 30 seconds, allow them to stand for 2 minutes, and compare the color of two

supernatants; the color obtained from the test solution is not more intense than that obtained from the standard solution.

(3) ***Related substances***—Weigh 0.1 g of Eperisone Hydrochloride, dissolve it in 100 mL of the mobile phase, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine each peak area as directed in the automatic integration method; the total area of the peaks other than eperisone obtained from the test solution is not greater than 1/5 times the peak area of eperisone from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of methanol, 0.0375 mol/L sodium 1-decanesulfonate solution and perchloric acid (600 : 400 : 1).

Flow rate: Adjust so that the retention time of eperisone is about 17 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution and add the mobile phase to make exactly 10 mL. Confirm that the peak area of eperisone obtained from 10 μL of this solution is equivalent to 7 to 13% of that from the standard solution.

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; the number of theoretical plates and symmetry factor of the peak of eperisone are NLT 4000 and NMT 2.0, respectively.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of eperisone is NMT 3.0%.

Time span of measurement: About 2 times the retention time of eperisone.

Sodium 1-decanesulfonate solution, 0.0375 mol/L—Dissolve 3.665 g of sodium 1-decanesulfonate in 400 mL of water.

Water NMT 0.2% (0.1 g, coulometric titration).

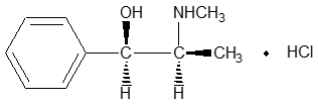
Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.6 g of Eperisone Hydrochloride, dissolve in 20 mL of acetic acid(100), add 80 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 29.59 mg of $C_{17}H_{25}NO{\cdot}HCl$

Packaging and storage Preserve in well-closed containers.

Ephedrine Hydrochloride
에페드린염산염



$C_{10}H_{15}NO{\cdot}HCl$: 201.69

(1*R*,2*S*)-2-(Methylamino)-1-phenylpropan-1-ol hydrochloride [*50-98-6*]

Ephedrine Hydrochloride, when dried, contains NLT 99.0% and NMT 101.0% of ephedrine hydrochloride ($C_{10}H_{15}NO{\cdot}HCl$).

Description Ephedrine Hydrochloride occurs as white crystals or a crystalline powder.
It is freely soluble in water, soluble in ethanol(95), slightly soluble in acetic acid(100), and practically insoluble in acetic anhydride or acetonitrile.

Identification (1) Determine the absorption spectra of aqueous solutions of Ephedrine Hydrochloride and ephedrine hydrochloride RS (1 in 2000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelength.

(2) Determine the infrared spectra of Ephedrine Hydrochloride and ephedrine hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Ephedrine Hydrochloride (1 in 15) responds to the Qualitative Analysis for chloride.

Optical rotation $[\alpha]_D^{20}$: Between -33.0° and -36.0° (after drying, 1 g, water, 20 mL, 100 mm).

Melting point Between 218 and 222 ℃.

pH Dissolve 1.0 g of Ephedrine Hydrochloride in 20 mL of water; the pH of this solution is between 4.5 and 6.5.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Ephedrine Hydrochloride in 10 mL of water; the solution is colorless and clear.

(2) ***Acidity and Alkalinity***—Weigh accurately 1.0 g

of Ephedrine Hydrochloride, dissolve in 20 mL of water, and add 1 drop of methyl red TS. Add 0.01 mol/L of sulfuric acid until the solution turns red if the solution exhibits a yellow color; the amount used of sulfuric acid is NMT 0.10 mL. Add 0.02 mol/L of sodium hydroxide solution until the solution turns yellow if the solution exhibits a pink color; the amount used of the sodium hydroxide solution is NMT 0.20 mL.

(3) ***Sulfate***—Dissolve 50 mg of Ephedrine Hydrochloride in 40 mL of water, add 1 mL of dilute hydrochloric acid and 1 mL of barium chloride TS and allow to stand for 10 minutes; the solution remains unchanged.

(4) ***Heavy metals***—Proceed with 1.0 g of Ephedrine Hydrochloride as directed under Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (10 ppm).

(5) ***Related substances***—Dissolve 50 mg of Ephedrine Hydrochloride in 50 mL of mobile phase and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to it make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area obtained from each solution as directed in the automatic integration method; the sum of peak areas other than the major peak area from the test solution is not greater than the major peak area from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 45 ℃.

Mobile phase: A mixture of sodium lauryl sulfate solution (1 in 128), acetonitrile and phosphoric acid (640 : 360 : 1).

Flow rate: Adjust so that the retention time of ephedrine is about 14 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution and add the mobile phase to make 20 mL. Confirm that the peak area of ephedrine obtained from 10 μL of this solution is equivalent to 4% to 6% of that of ephedrine from the standard solution.

System performance: Dissolve 1 mg of ephedrine hydrochloride RS and 4 mg of atropine sulfate in 100 mL of diluted methanol (1 in 2). Proceed with 10 μL of this solution according to the above operating conditions; ephedrine and atropine are eluted in this order with the resolution being NLT 1.5.

System repeatability: Repeat the test 6 times according to the above operating conditions with 10 μL each of the standard solution; the relative standard deviation of the peak areas of ephedrine is NMT 2.0%.

Time span of measurement: About 3 times the retention time of ephedrine after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Ephedrine Hydrochloride, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3) by warming. After cooling, titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 20.169 mg of $C_{10}H_{15}NO \cdot HCl$

Packaging and storage Preserve in well-closed containers.

Ephedrine Hydrochloride Injection
에페드린염산염 주사액

Ephedrine Hydrochloride Injection is an aqueous injection and contains NLT 95.0% and NMT 105.0% of the labeled amount of ephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$: 201.69).

Method of preparation Prepare as directed under Injections, with Ephedrine Hydrochloride.

Description Ephedrine Hydrochloride Injection occurs as a clear, colorless liquid.

pH—Between 4.5 and 6.5.

Identification Take an amount of Ephedrine Hydrochloride Injection equivalent to 509 mg of ephedrine hydrochloride according to the labeled amount, and add water to make 100 mL. Determine the absorption spectra of this solution as directed under Ultraviolet-visible Spectroscopy; it exhibits maxima between 249 nm and 253 nm, between 255 nm and 259 nm, and between 261 nm and 265 nm.

Sterility Meets the requirements.

Bacterial endotoxins Less than 7.5 EU per mg of ephedrine hydrochloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Ephedrine Hydrochloride Injection equivalent to about 40 mg of ephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$), add exactly 10 mL of the internal standard solution, then add water to make 200 mL, and use this solution as the test solution. Separately, weigh accurately about 40 mg of ephedrine hydrochloride RS, previously dried at 105 ℃ for 3 hours, dissolve in exactly 10 mL of the internal standard solution, then add water to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, of ephedrine to the peak area of the internal standard, respectively.

$$\text{Amount (mg) of ephedrine hydrochloride } (C_{10}H_{15}NO \cdot HCl) = \text{Amount (mg) of ephedrine hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Etilefrine hydrochloride solution (1 in 500).

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed under the operating conditions under the Purity (5) of Ephedrine Hydrochloride.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the internal standard and ephedrine are eluted in this order with the resolution being NLT 1.5.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak area ratios of ephedrine to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, hermetic containers.

10% Ephedrine Hydrochloride Powder
에페드린염산염 10 배산

Ephedrine Hydrochloride

10% Ephedrine Hydrochloride

10% Ephedrine Hydrochloride Powder contains NLT 9.3% and NMT 10.7% of ephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$: 201.69).

Method of preparation

Ephedrine hydrochloride	100 g
Starch, lactose hydrate or a mixture of these	A sufficient quantity
Total amount	1000 g

Prepare as directed under Powders, with the above.

Identification Take 0.5 g of 10% Ephedrine Hydrochloride Powder, add 100 mL of water, shake for 20 minutes and filter. Determine the absorption spectrum of the filtrate as directed under Ultraviolet-visible Spectrophotometry: it exhibits maxima between 249 nm and 253 nm, between 255 nm and 259 nm and between 261 nm and 265 nm. Determine the absorption spectrum of the filtrate as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 249 nm and 253 nm, between 255 nm and 259 nm, and between 261 nm and 265 nm.

Particle size distribution estimation by analytical sieving Meets the requirements.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Weigh accurately about 0.4 g of 10% Ephedrine Hydrochloride Powder, add 150 mL of water and extract with the aid of ultrasonicator for 10 minutes with occasional shaking. Shake more for 10 minutes, add exactly 10 mL of the internal standard solution and water to make 200 mL, centrifuge and use the supernatant as the test solution. Separately, weigh accurately about 40 mg of Ephedrine Hydrochloride RS, previously dried at 105 ºC for 3 hours, put exactly to 10 mL of internal standard solution to dissolve, add water to make 200 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test and the standard solution as directed under Liquid Chromatography according to the following condition and calculate the ratios, QT and QS, of the peak area of ephedrine to that of the internal standard of each solution.

$$\text{Amount (mg) of ephedrine hydrochloride } (C_{10}H_{15}NO \cdot HCl) = \text{Amount (mg) of ephedrine hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Etilefrine hydrochloride solution (1 in 500).

Operating conditions

Follow the operating conditions under the Purity (4) of Ephedrine Hydrochloride for the detector, column, column temperature, mobile phase and flow rate.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the internal standard and ephedrine are eluted in this order with the resolution being NLT 1.5.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area ratio of ephedrine to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Ephedrine Hydrochloride Tablets
에페드린염산염 정

Ephedrine Hydrochloride Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of ephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$: 201.69).

Method of preparation Prepare as directed under Tablets, with Ephedrine Hydrochloride.

Identification Weigh an amount of Ephedrine Hydrochloride Tablets, previously powdered, equivalent to 50 mg of ephedrine hydrochloride according to the labeled amount, add 100 mL of water, shake for 20 minutes to mix, and then filter. Determine the absorption spectrum of the filtrate as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 249 nm and 253 nm, between 255 nm and 259 nm, and between 261 nm and 265 nm.

Dissolution Perform the test with 1 tablet of Ephedrine Hydrochloride Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take 20 mL or more of the dissolved solution 30 minutes after starting the test, and filter through a membrane filter with a pore size of NMT 0.45 μm. Discard the first 10 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately about 28 mg of ephedrine hydrochloride RS, previously dried at 105 °C for 3 hours, and dissolve in water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of ephedrine, respectively. The acceptable dissolution criterion is NLT 80% of Ephedrine Hydrochloride Tablets dissolved in 30 minutes.

Dissolution rate (%) of the labeled amount of ephedrine ($C_{10}H_{15}NO \cdot HCl$)
= Amount (mg) of the ephedrine RS taken

$$\times \frac{A_T}{A_S} \times \frac{1}{C} \times 90$$

C: Labeled amount (mg) of ephedrine ($C_{10}H_{15}NO \cdot HCl$) in 1 tablet.

Operating conditions

Ephedrine Hydrochloride: Perform the test according to the operating conditions under the Purity (5) Related substances.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the number of theoretical plates and the symmetry factor of the peak of ephedrine are NLT 10000 and NMT 2.0, respectively.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above operating conditions; the relative standard deviation of the peak areas of ephedrine is NMT 2.0%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Ephedrine Hydrochloride Tablets, and powder. Weigh accurately an amount, equivalent to about 40 mg of ephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$), add 150 mL of water, sonicate for 10 minutes while occasionally shaking to mix, and shake for 10 minutes to mix. Then, add exactly 10 mL of the internal standard solution, and then add water to make 200 mL. Centrifuge this solution, and use the clear supernatant as the test solution. Separately, weigh accurately about 40 mg of ephedrine hydrochloride RS, previously dried at 105 °C for 3 hours, dissolve exactly 10 mL of the internal standard solution, then add water to make 200 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, of ephedrine to the peak area of the internal standard, respectively.

Amount (mg) of ephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$)
= Amount (mg) of ephedrine hydrochloride RS $\times \frac{Q_T}{Q_S}$

Internal standard solution—Etilefrine hydrochloride solution (1 in 500).

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed under the operating conditions in the Purity (4) under Ephedrine Hydrochloride.

System suitability

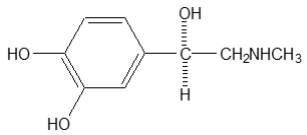
System performance: Proceed with 10 μL of the standard solution according to the above conditions; the internal standard and ephedrine are eluted in this order with the resolution being NLT 1.5.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak

area ratios of ephedrine to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Epinephrine
에피네프린



Adrenaline
Epirenamine $C_9H_{13}NO_3$: 183.20
4-[(1*R*)-1-Hydroxy-2-(methylamino)ethyl]benzene-1,2-diol [*51-43-4*]

Epinephrine, when dried, contains NLT 98.0% and NMT 101.0% of epinephrine ($C_9H_{13}NO_3$).

Description Epinephrine occurs as a white to grayish white crystalline powder and is odorless.
It is freely soluble in acetic acid(100), very slightly soluble in water, and practically insoluble in methanol, ethanol(95) or ether.
It dissolves in dilute hydrochloric acid.
It is gradually changed to brown by air or light.

Identification (1) Dissolve 10 mg of Epinephrine in 10 mL of diluted ethanol (1 in 500) and use this solution as the test solution. To 1 mL of the test solution, add 4 mL of water and 1 drop of iron(III) chloride TS; the resulting solution exhibits dark green and then slowly turns red.

(2) Take 1 mL each of the test solution in (1) in test tubes A and B, respectively, add 10 mL of potassium hydrogen phthalate buffer solution (pH 3.5) to the test tube A and add 10 mL of phosphate buffer solution (pH 6.5) to the test tube B, add 1 mL of iodine TS to the test tubes A and B, respectively, allow them to stand for 5 minutes, then add 2 mL of sodium thiosulfate TS to each test tube; the test tube A exhibits red and the test tube B develops deep red color.

Optical rotation $[\alpha]_D^{20}$: Between -50.0° and -53.5° (1 g, after drying, 1 mol/L hydrochloric acid TS, 25 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g of Epinephrine in 10 mL of dilute hydrochloric acid; the solution is clear and the color is not more intense than that of the Color Matching Fluid A.

(2) ***Adrenalone***—Dissolve 50 mg of Epinephrine in 0.05 mol/L hydrochloric acid TS to make exactly 25 mL, and perform the test as directed under the Ultraviolet-visible Spectroscopy; the absorbance at a wavelength of 310 nm is NMT 0.40.

(3) ***Norepinephrine***—Weigh 10.0 mg of Epinephrine, dissolve in 2.0 mL of a solution of L-tartaric acid in methanol (1 in 200). Pipet 1 mL of this solution, and add 3.0 mL of pyridine. Add 1.0 mL of freshly prepared sodium naphthoquinone sulfonate TS, allow to stand for 30 minutes in the dark, and add 5.0 mL of pyridine containing 50 mg of L-ascorbic acid to the resulting solution; the color of the solution is not more intense than that of the control solution.

Control solution—Dissolve 2.0 mg of norepinephrine tartrate RS and 90 mg of epinephrine tartrate RS in methanol to make exactly 10 mL. Pipet 1 mL of this solution, and proceed in the same manner.

Loss on drying NMT 1.0% (2 g, in vacuum, silica gel, 18 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Epinephrine, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of methylrosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 18.321 mg of $C_9H_{13}NO_3$

Packaging and storage Preserve in light-resistant, tight containers. Store at a cold place under nitrogen atmosphere.

Epinephrine Injection
에피네프린 주사액

Adrenaline Hydrochloride Injection
Epirenamine Hydrochloride Injection
Epinephrine Hydrochloride Injection

Epinephrine Injection is an aqueous solution for injection and contains NLT 0.085 w/v% and NMT 0.115 w/v% of epinephrine (C9H13NO3: 183.20).

Preparation Prepare as directed under Injections, with Epinephrine by dissolving in diluted hydrochloric acid (9 in 10000).

Description Epinephrine Injection occurs as a clear, colorless liquid.
It is gradually changed to pale red and then brown by air or light.

pH—Between 2.3 and 5.0.

Identification (1) Add 4 mL of water and 1 drop of iron(III) chloride TS to 1 mL of Epinephrine Injection; the solution turns dark green and slowly changes to red.

(2) Take 1 mL each of Epinephrine Injection in test tubes A and B and perform the test as directed under the Identification (2) under Epinephrine.

Sterility Meets the requirements.

Bacterial endotoxins Less than 357.0 EU per mg of epinephrine.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

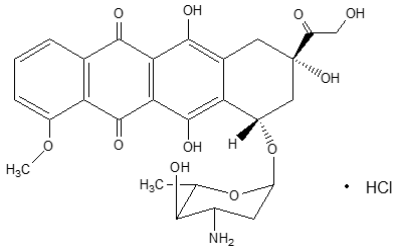
Extractable volume of injections Meets the requirements.

Assay Pipet 30 mL of Epinephrine Injection, transfer to a separatory funnel, add 25 mL of carbon tetrachloride, and shake vigorously to mix for 1 minute. Allow to stand, and discard the carbon tetrachloride layer. Repeat this procedure 3 times. Wash the stopper and inlet of the separatory funnel with a small amount of water, and introduce 0.2 mL of starch TS. While shaking, add iodine TS dropwise until the solution exhibits a persistent blue color, then immediately add sodium thiosulfate TS dropwise until the blue color disappears. Add 2.1 g of sodium bicarbonate to the liquid, preventing it from coming in contact with the inlet of the separatory funnel, and shake until most of the sodium bicarbonate dissolves. To this solution, immediately add 1.0 mL of acetic anhydride. Immediately stopper the separatory funnel loosely and allow to stand until the evolution of gas ceases. Shake vigorously, allow to stand for 5 minutes, extract six times with 25 mL volumes of chloroform. Filter each chloroform extract using cotton wool. Combine all chloroform extracts, evaporate on a steam bath to 3 mL with a current of air. Transfer this residue by means of small portions of chloroform to a tared beaker and heat again to evaporate to dryness. Dry the residue at 105 ºC for 30 minutes, cool in a desiccator (silica gel), weigh accurately the weight, W (mg), of the dried residue, and dissolve in chloroform to make exactly 5 mL. Determine the optical rotation, α_D, using a 100-mm cell as directed under the Optical Rotation.

$$\text{Amount (mg) of epinephrine } (C_9H_{13}NO_3) = 0.5923 \times W \times \left(0.5 + \frac{0.5 \times \alpha_D}{93}\right)$$

Packaging and storage Preserve in light-resistant, hermetic containers. Colored containers may be used for Epinephrine Injection.

Epirubicin Hydrochloride
에피루비신염산염



$C_{27}H_{29}NO_{11}$·HCl: 579.98

(8*R*,10*S*)-10-((2*S*,4*S*,5*R*,6*S*)-4-Amino-5-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)-6,8,11-tri-hydroxy-8-(2-hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione hydrochloride [*56390-09-1*]

Epirubicin Hydrochloride is the hydrochloride of a derivative of daunorubicin.

Epirubicin Hydrochloride contains NLT 970 μg and NMT 1020 μg (potency) of epirubicin hydrochloride ($C_{27}H_{29}NO_{11}$ · HCl) per mg, calculated on the anhydrous and solvent-free basis.

Description Epirubicin Hydrochloride occurs as a pale yellowish red to brownish red powder.
It is soluble in water or methanol, slightly soluble in ethanol(95) and practically insoluble in acetonitrile.
It is hygroscopic.

Identification (1) Determine the absorption spectra of solutions of Epirubicin Hydrochloride and epirubicin hydrochloride RS in methanol (3 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Epirubicin Hydrochloride and epirubicin hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +310° and +340° (10 mg calculated on the anhydrous and solvent-free basis, methanol, 20 mL, 100 mm).

pH Dissolve 10 mg of Epirubicin Hydrochloride in 2 mL of water; the pH of this solution is between 4.0 and 5.5.

Absorbance $E_{1cm}^{1\%}$ (495 nm): 200 to 230 (15 mg calculated on the anhydrous and solvent-free basis, methanol, 1000 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 50 mg of Epirubicin Hydrochloride in 5 mL of water; the solution is clear and dark red.

(2) ***Heavy metals***—Proceed with 1.0 g of Epirubicin Hydrochloride as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Weigh accurately an amount equivalent to 50 mg (potency) of Epirubicin Hydrochloride, dissolve in the internal standard solution to make exactly 50 mL. Use this solution as the test solution. Take 10 μL of the test solution and perform the test as directed under the Liquid Chromatography according to the following conditions. Determine each peak area as directed in the automatic integration method and calculate the total peak area of substances other than epirubicin and 2-naphthalenesulfonic acid by the percentage peak area method; it is NMT 5.0%.

Internal standard solution—A solution of sodium 2-naphthalenesulfonate in a mixture of water, acetonitrile, methanol and phosphoric acid (540 : 290 : 170 : 1) (1 in 2000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with trimethylsilyl silica gel for liquid chromatography (6 μm in particle diameter).

Column temperature: A constant temperature of about 35 ℃.

Mobile phase: Dissolve 2 g of sodium lauryl sulfate in a mixture of water, acetonitrile, methanol and phosphoric acid (540 : 290 : 170 : 1) to make 1000 mL.

Flow rate: Adjust so that the retention time of epirubicin is about 9.5 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the test solution, add the mobile phase to make exactly 100 mL, and use this solution as the system suitability solution (1). Pipet 1.0 mL of this solution and add the mobile phase to make exactly 10 mL. Confirm that the peak area of epirubicin obtained from 10 μL of this solution is equivalent to 7% to 13% of that obtained from 10 μL of the system suitability solution (1).

System performance: Weigh 50 mg (potency) of epirubicin hydrochloride RS and dissolve in the internal standard solution to make exactly 50 mL. Use this solution as the system suitability solution (2). Proceed with 10 μL of this solution according to the above conditions; the internal standard and epirubicin are eluted in this order with the resolution being NLT 20.

System repeatability: Repeat the test 5 times with 10 mL each of the system suitability solutions (2) according to the above conditions; the relative standard deviation of the ratios of the peak area of epirubicin to that of the internal standard is NMT 1.0%.

Time span of measurement: About 3 times the retention time of epirubicin after the solvent peak.

(4) ***Residual solvent***—Weigh accurately about 0.3 g of Epirubicin Hydrochloride, add exactly 0.6 mL of the internal standard solution, dissolve in dimethylacetamide to make 6 mL, and use it as the test solution. Separately, pipet 1 mL of methanol, add dimethylacetamide to make exactly 25 mL, and use this solution as the standard stock solution. Pipet 125 μL of acetone, 30 μL of ethanol(99.5), 32 μL of 1-propanol, and 17 μL of the standard stock solution each, add exactly 10 mL of the internal standard solution, then add dimethylacetamide to make 100 mL. Use this solution as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_{Ta} and Q_{Sa}, Q_{Tb} and Q_{Sb}, Q_{Tc} and Q_{Sc}, and Q_{Td} and Q_{Sd}, of peak areas of acetone, ethanol, 1-propanol and methanol to that of the internal standard, respectively. Calculate the amounts of acetone, ethanol, 1-propanol and methanol with the following equation: NMT 1.5%, NMT 0.5%, NMT 0.5% and NMT 0.1%, respectively.

$$\text{Content (\%) of acetone} = \frac{1}{W_T} \times \frac{Q_{Ta}}{Q_{Sa}} \times 593$$

$$\text{Content (\%) of ethanol} = \frac{1}{W_T} \times \frac{Q_{Tb}}{Q_{Sb}} \times 142$$

$$\text{Content (\%) of 1-propanol} = \frac{1}{W_T} \times \frac{Q_{Tc}}{Q_{Sc}} \times 154$$

$$\text{Content (\%) of methanol} = \frac{1}{W_T} \times \frac{Q_{Td}}{Q_{Sd}} \times 2.23$$

W_T: Amount (mg) of Epirubicin Hydrochloride taken

Internal standard solution—A solution of toluene in dimethylacetamide (1 in 100).

Operating conditions

Detector: A flame ionization detector

Column: A glass column about 0.25 mm in internal diameter and about 30 m in length, packed with 5% phenylmethyl silicone polymer for gas chromatography coated at 0.25 μm thick.

Column temperature: Maintain the temperature at 30 ℃ for the first 5 minutes, then raise the temperature at the rate of 2 ℃ per minute up to 40 ℃, and raise at the rate of 25 ℃ per minute up to 200 ℃ if necessary. Keep at 200 ℃ for 5 minutes.

Sample injection port temperature: A constant temperature of about 200 ℃.

Detector temperature: A constant temperature of about 200 ℃.

Carrier gas: Helium

Flow rate: About 1.0 mL per minute.

Split ratio: 1 : 100

System suitability

System performance: Proceed with 1 μL of the standard solution according to the above operation condi-

tions; acetone, methanol, ethanol, 1-propanol and the internal standard are eluted in this order. The resolution between the peaks of acetone and the internal standard is NLT 30.

System repeatability: Repeat the test 6 times with 1 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of acetone, methanol, ethanol and 1-propanol is NMT 4.0% each.

Water NMT 8.0% (0.1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.5% (0.1 g).

Sterility It meets the requirements when used in sterile preparations.

Bacterial endotoxins It is less than 1.1 EU per mg (potency) of epirubicin when used in the manufacturing of sterile preparations.

Histamine It meets the requirements when used in manufacturing of sterile preparations. Weigh an appropriate amount of Epirubicin Hydrochloride to prepare an aqueous solution containing 2.0 mg (potency) per mL and use the solution as the test solution. The amount of the test solution is 0.5 mL.

Assay Weigh accurately about 50 mg each of Epirubicin Hydrochloride and epirubicin hydrochloride RS, dissolve in the mobile phase to make exactly 50 mL each, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of the peak area of epirubicin hydrochloride to that of the internal standard.

$$\text{Potency (μg) of epirubicin hydrochloride } (C_{27}H_{29}NO_{11}\cdot HCl) = \text{Potency (μg) of epirubicin hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of sodium 2-naphthalenesulfonate in a mixture of water, acetonitrile, methanol and phosphoric acid (540 : 290 : 170 : 1) (1 in 2000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with trimethylsilyl silica gel for liquid chromatography (6 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: Dissolve 2 g of sodium lauryl sulfate in a mixture of water, acetonitrile, methanol and phosphoric acid (540 : 290 : 170 : 1) to make 1000 mL.

Flow rate: Adjust so that the retention time of epirubicin hydrochloride is about 9.5 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; the internal standard and epirubicin are eluted in this order with the resolution being NLT 20.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solutions according to the above operating conditions; the relative standard deviation of the ratios of the peak area of epirubicin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers (0 to 5 °C).

Epirubicin Hydrochloride Injection
에피루비신염산염 주사액

Epirubicin Hydrochloride Injection contains NLT 90.0% and NMT 120.0% of the labeled amount of epirubicin hydrochloride ($C_{27}H_{29}NO_{11}\cdot HCl$: 579.98).

Method of preparation Prepare as directed under Injections, with Epirubicin Hydrochloride.

Identification The retention time ratios of the major peaks from the test solution and standard solution obtained under the Assay to the peaks of the internal standard are the same.

pH Between 2.5 and 3.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 1.1 EU per mg (potency) of epirubicin hydrochloride. Weigh an appropriate amount of Epirubicin Hydrochloride Injection, dissolve in water for endotoxin assay to obtain a solution having known concentration of 0.125 mg (potency) per mL, and use this solution as the test solution.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Weigh accurately about 10 mg of Epirubicin Hydrochloride Injection according to the labeled potency, dissolve in 4.0 mL of internal standard solution, add the

mobile phase to make 10 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg (potency) of epirubicin hydrochloride RS, dissolve in exactly 4.0 mL of the internal standard solution, add the mobile phase to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and calculate the ratios, QT and QS, of the peak area of epirubicin hydrochloride to that of the internal standard.

$$\text{Potency (μg) of epirubicin hydrochloride } (C_{27}H_{29}NO_{11}\cdot HCl) = \text{Potency (μg) of epirubicin hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh 1 g of sodium 2-naphthalenesulfonate and dissolve in a mixture of water and acetonitrile (69 : 31) to make 500 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: A mixture of water and acetonitrile (69 : 31), adjusted the pH to 2.0 with phosphoric acid.

Flow rate: Adjust the flow rate so that the retention time of epirubicin hydrochloride is about 10 minutes.

System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; the internal standard and epirubicin hydrochloride are eluted in this order with the resolution being NLT 8.0.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak area ratio of epirubicin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in hermetic containers.

Epirubicin Hydrochloride for Injection
주사용 에피루비신염산염

Epirubicin Hydrochloride for Injection is an injection to be dissolved before use and contains NLT 90.0% and NMT 120.0% of the labeled amount of epirubicin hydrochloride ($C_{27}H_{29}NO_{11}\cdot HCl$: 579.98).

Method of preparation Prepare as directed under Injections, with Epirubicin Hydrochloride.

Description Epirubicin Hydrochloride for Injection occurs as a red powder or a mass.

Identification The retention time ratios of the major peaks from the test solution and the standard solution obtained under the Assay to the peak of the internal standard are the same.

pH Dissolve Epirubicin Hydrochloride for Injection in water to make 2 mg (potency) per mL; the pH of the solution is between 4.5 and 6.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 1.1 EU per mg (potency) of epirubicin hydrochloride for injection. Weigh an appropriate amount of Epirubicin Hydrochloride for Injection to obtain a solution having known concentration of 0.125 mg (potency) per mL using water for endotoxin assay, and use this solution as the test solution.

Histamine Meets the requirements. Weigh an appropriate amount of Epirubicin Hydrochloride for Injection to obtain an aqueous solution having known concentration of 2.0 mg per mL, and use this solution as the test solution. The amount of test solution is 0.5 mL.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Water NMT 4.0% (0.2 g, volumetric titration, direct titration).

Assay Weigh accurately about 10 mg (potency) of Epirubicin Hydrochloride for Injection according to the labeled potency, dissolve in the internal standard solution to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg (potency) of epirubicin hydrochloride RS, dissolve in the internal standard solution to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and determine the ratios, QT and QS, of the peak area of epirubicin hydrochloride to that of the internal standard in each solution.

$$\text{Potency (μg) of epirubicin hydrochloride } (C_{27}H_{29}NO_{11}\cdot HCl) = \text{Potency (μg) of epirubicin hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh 1 g of sodium 2-naphthalenesulfonate and dissolved in a mixture of water and acetonitrile (69 : 31) to make 500 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: A mixture of water and acetonitrile (69 : 31), adjusted the pH to 2.0 with phosphoric acid.

Flow rate: Adjust the flow rate so that the retention time of epirubicin hydrochloride is about 10 minutes.

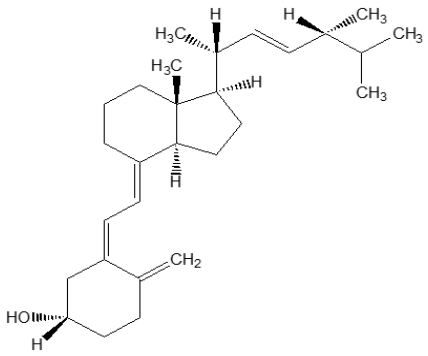
System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; the internal standard and epirubicin hydrochloride are eluted in this order with the resolution being NLT 8.0.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak area ratio of epirubicin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in hermetic containers.

Ergocalciferol
에르고칼시페롤



Vitamin D_2

Calciferol $C_{28}H_{44}O$: 396.65

(5*Z*,7*E*,22*E*)-(3*S*)-9,10-Seco-5,7,10(19),22-ergostatetraen-3-ol [*50-14-6*]

Ergocalciferol contains NLT 97.0% and NMT 103.0% of ergocalciferol ($C_{28}H_{44}O$).

Description Ergocalciferol occurs as white crystals. It is odorless or has a slightly characteristic odor.

It is freely soluble in ethanol(95), chloroform or ether, sparingly soluble in isooctane, and practically insoluble in water.

It is affected by air or light.

Melting point—Between 115 and 118 ℃ [Put Ergocalciferol into a capillary tube, and dry in a desiccator (in vacuum, NMT 2.67 kPa) for 3 hours, immediately seal the capillary tube and put the tube into a bath fluid, previously heated at a temperature 10 ℃ lower than the expected melting point, and measure the melting point with heating at a rate of 3°C per minute.]

Identification (1) Dissolve 0.5 mg of Ergocalciferol in 5 mL of chloroform, add 0.3 mL of acetic anhydride and 0.1 mL of sulfuric acid, and shake to mix; the resulting solution exhibits a red color, and rapidly changes through violet and blue to green.

(2) Determine the infrared spectra of Ergocalciferol and ergocalciferol RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +102° and +107° (0.3 g, ethanol(95), 20 mL, 100 mm). Dissolve Ergocalciferol within 30 minutes after the container has been opened, and determine the rotation within 30 minutes after the solution has been prepared.

Absorbance $E_{1cm}^{1\%}$ (265 nm): Between 445 and 485 (10 mg, ethanol(95), 1000 mL).

Purity (1) ***Ergosterol***—Dissolve 10 mg of Ergocalciferol in 20 mL of diluted ethanol (9 in 10), add a solution of 20 mg of digitonin dissolved in 2.0 mL of ethanol (9 in 10), and allow to stand for 18 hours; no precipitate is formed.

(2) ***Reducing substances***—To 10 mL of a solution of Ergocalciferol in ethanol(99.5) (1 in 100), add 0.5 mL of a solution of blue tetrazolium in methanol (1 in 200) and 0.5 mL of a solution of tetramethylammonium hydroxide in ethanol(99.5) (1 in 10), and allow to stand for 5 minutes. After exactly 5 minutes, add 1 mL of acetic acid(100), and use this solution as the test solution. Proceed with 10 mg of ethanol(95.5) in the same manner, and use the resulting solution as the blank test solution. Dissolve an appropriate amount of hydroquinone in anhydrous alcohol to make a solution containing 0.2 μg per mL, proceed with this solution in the same manner, and use the resulting solution as the standard solution. Determine the absorption spectra of the test solution and the standard solution, using the blank test solution as the control solution, as directed under the Ultraviolet-visible Spectroscopy at the absorbance maximum wavelength around 525 nm; the absorbance of the test solution is not greater than that of the standard solution.

Assay Weigh accurately about 30 mg each of Ergocalciferol and ergocalciferol RS and dissolve them in isooctane, respectively, to make exactly 50 mL. Pipet 10 mL each of these solutions, add exactly 3 ml of the internal standard solution to each, add the mobile phase to make 50 mL, and use these solutions as the test solution and the standard solution. Perform the test with 10 μL to 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios Q_T and Q_S,

of peak area of ergocalciferol to that of the internal standard from each solution. Perform the procedure quickly avoiding contact with air or other oxidizing agents as much as possible and using light-resistant containers.

$$\text{Amount (mg) of ergocalciferol } (C_{28}H_{44}O) = \text{Amount (mg) of ergocalciferol RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of dimethyl phthalate in isooctane (1 in 100).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 10 cm to 30 cm in length, packed with silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 20 °C.

Mobile phase: A mixture of hexane and *n*-amyl alcohol (997 : 3).

Flow rate: Adjust the flow rate so that the retention time of ergocalciferol is about 25 minutes.

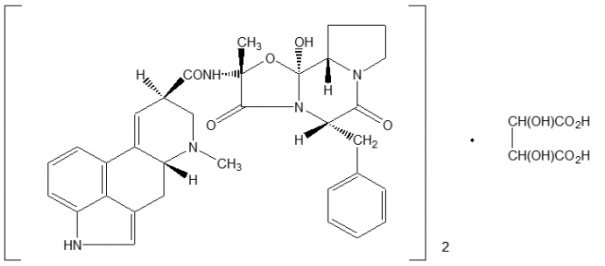
System suitability

System performance: Dissolve 15 mg of ergocalciferol RS in 25 mL of isooctane, transfer the resulting solution into a flask, heat in an oil bath under a reflux condenser for 2 hours, and then cool immediately to room temperature. Transfer the cooled solution to a quartz test tube and irradiate with a short-wavelength lamp (main wavelength: 254 nm) and a long-wavelength lamp (main wavelength: 365 nm) for 3 hours. To 10 mL of this solution, add the mobile phase to make 50 mL. Proceed with 10 μL of this solution according to the above operating conditions; the relative retention times of previtamin D_2, transvitamin D_2 and tachysterol$_2$ to that of ergocalciferol are about 0.5, about 0.6 and about 1.1, respectively, and the resolution between previtamin D_2 and transvitamin D_2 is NLT 0.7, and the resolution between ergocalciferol and tachysterol$_2$ is NLT 1.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the ratios of the peak area of ergocalciferol to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light -resistant, hermetic containers under nitrogen atmosphere in a cold place.

Ergotamine Tartrate
에르고타민타르타르산염



$(C_{33}H_{35}N_5O_5)_2\ C_4H_6O_6$: 1313.41

(5'*S*)-5'-Benzyl-12'-hydroxy-2'-methylergotaman-3',6',18-trione hemitartrate [*379-79-3*]

Ergotamine Tartrate contains NLT 98.0% and NMT 101.0% of ergotamine tartrate [$(C_{33}H_{35}N_5O_5)_2 \cdot C_4H_6O_6$], calculated on the dried basis.

Description Ergotamine Tartrate occurs as a colorless crystal, or a white to pale yellowish white or grayish white crystalline powder.

It is slightly soluble in water or ethanol(95).

Melting point—About 180 °C (with decomposition).

Identification (1) Dissolve 1 mg of Ergotamine Tartrate in a mixture of acetic acid(100) and ethyl acetate (1 : 1), pipet 0.5 mL of this solution, shake to mix in cold water, add 0.5 mL of sulfuric acid, and allow to stand; the resulting solution exhibits a violet color. Add 0.1 mL of diluted iron(III) chloride TS (1 in 12) to the solution; the color of the solution turns blue to bluish purple.

(2) Dissolve 1 mg of Ergotamine Tartrate in 5 mL of L-tartaric acid (1 in 100). To 1 mL of this solution, add 2 mL of 4-dimethylaminobenzaldehyde-iron(III) chloride TS, and shake to mix; the resulting solution exhibits a blue color.

Optical rotation ***Ergotamine base*** $[\alpha]_D^{20}$: Between -155° and -165°. Dissolve 0.35 g of Ergotamine Tartrate in 25 mL of L-tartaric acid (1 in 100), add 0.5 g of sodium bicarbonate, shake gently and sufficiently to mix, and extract with four 10 mL portions of ethanol-free chloroform. Filter each chloroform extract through a small filter paper, moistened with ethanol-free chloroform, into a 50-mL volumetric flask, allow to stand on a steam bath at 20 ℃ for 10 minutes, and add 20 ℃ ethanol-free chloroform to make 50 mL. Determine the optical rotation of this solution in a 100 mm cell. Pipet 25 mL of this solution, and evaporate to dryness in vacuum at below 45 ℃. Dissolve the residue in 25 mL of acetic acid(100), and titrate with 0.05 mol/L perchloric acid VS (indicator: 1 drop of methylosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction. Calculate the specific optical rotation of ergotamine base from the consumed volume of 0.05 mol/L perchloric acid and the optical rotation.

$$\text{Each mL of 0.05 mol/L perchloric acid VS} = 29.084 \text{ mg of } C_{33}H_{35}N_5O_5$$

Purity ***Related substances***—Perform this test using light-resistant containers. Weight 40 mg of Ergotamine Tartrate, add exactly 10 mL of a solution of L-tartaric acid in diluted methanol (1 in 2) (1 in 1000), dissolve by shaking well to mist, and use the resulting solution as the test solution. Pipet 1 mL of this solution, add a solution of L-tartaric acid in diluted ethanol (1 in 2) (1 in 1000) to make exactly 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform and methanol (9 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly 4-dimethylaminobenzaldehyde TS on the plate; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 5.0% (0.1 g, in vacuum, 60 ℃, 4 hours).

Assay Weigh accurately about 0.2 g of Ergotamine Tartrate, dissolve in 15 mL of a mixture of acetic acid(100) and acetic anhydride (50 : 3), and titrate with 0.05 mol/L perchloric acid VS (indicator: 1 drop of methylrosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L perchloric acid VS
= 32.836 mg of $(C_{33}H_{35}N_5O_5)_2 \cdot C_4H_6O_6$

Packaging and storage Preserve in light-resistant, tight containers. Fill the container almost full or replace the air in the empty part with nitrogen and store at below 5℃.

Ergotamine Tartrate Tablets
에르고타민타르타르산염 정

Ergotamine Tartrate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of ergotamine tartrate [$(C_{33}H_{35}N_5O_5)_2 \cdot C_4H_6O_6$: 1313.41].

Method of preparation Prepare as directed under Tablets, with Ergotamine Tartrate.

Identification Weigh an amount of Ergotamine Tartrate Tablets, previously powdered, equivalent to 5 mg of ergotamine tartrate according to the labeled amount, add 10 mL of hexane, shake for a few minutes to mix, and allow to stand. Then, discard the hexane extracts, add 10 mL of ammonia water(28)-saturated chloroform to the residue, shake for a few minutes to mix, filter, and evaporate the filtrate to dryness on a steam bath. Dissolve the residue with 8 mL of a mixture of acetic acid(100) and ethyl acetate (1 : 1), take 1 mL of this solution, and slowly add 1 mL of sulfuric acid dropwise while shaking to mix in iced water; the resulting solution exhibits a violet color. To this solution, add 0.1 mL of diluted iron(III) chloride TS (1 in 2); the solution turns blue to bluish purple.

Disintegration It meets the requirements when it is a sublingual tablet. However, the time of the test is 5 minutes.

Dissolution This test is applicable when it is not a sublingual tablet. Perform the test with 1 tablet of Ergotamine Tartrate Tablets at 75 revolutions per minute according to Method 2 under the Dissolution, using 1000 mL of L-tartaric acid solution (1 in 100) as the dissolution medium. Take the dissolved solution 30 minutes after starting the dissolution test, filter, and use the filtrate as the test solution. Separately, weigh accurately an appropriate amount of ergotamine tartrate RS, add the dissolution medium to make the constant concentration, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Fluorescence Spectroscopy using the dissolution medium as a control solution, and determine the absorbances at an excitation wavelength of 327 nm and a fluorescence wavelength of 427 nm.

It meets the requirements when the dissolution rate of Ergotamine Tartrate Tablets for 30 minutes is NLT 75%.

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed as directed under the Assay.

Assay Weigh accurately the mass of NLT 20 Ergotamine Tartrate Tablets, and powder. Weigh an amount equivalent to about 10 mg of ergotamine tartrate [$(C_{33}H_{35}N_5O_5)_2 \cdot C_4H_6O_6$], add 50.0 mL of the internal standard solution and 300 mL of a mixture of acetonitrile and water (55 : 45), sonicate for 10 minutes, and shake to mix. Then, add a mixture of acetonitrile and water (55 : 45) to make exactly 500 mL, mix, and filter. Discard the first filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately about 10 mg ergotamine tartrate RS, previously dried at 60 ℃ in vacuum for 4 hours, and dissolve in a mixture of acetonitrile and water (55 in 45) to make exactly 50 mL. Pipet 5 mL of this solution, add 5.0 mL of the internal standard solution, add a mixture of acetonitrile and water (55 : 45) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of ergotamine to the peak area of the internal standard, respectively.

Amount (mg) of ergotamine tartrate
$[(C_{33}H_{35}N_5O_5)_2 \cdot C_4H_6O_6]$

= Amount (mg) of ergotamine tartrate RS× $\frac{Q_T}{Q_S}$

Internal standard solution—Dissolve about 40 mg of ergometrine maleate in a mixture of acetonitrile and water to make 250 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 to 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and 0.01 mol/L potassium dihydrogen phosphate solution (55 : 45).

Flow rate: 1 mL/min

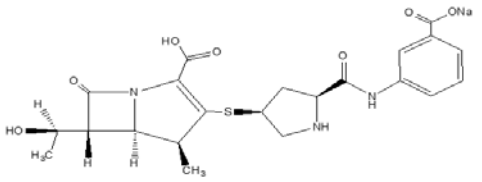
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the symmetry factor of ergotamine is NMT 2.0 with the resolution between the standard solution and the internal standard being NLT 3.0.

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio is NMT 2.0%.

Packaging and storage Preserve in light-resistant, well-closed containers.

Ertapenem Sodium
에르타페넴나트륨



Ertapenem Sodium $C_{22}H_{24}N_3NaO_7S$: 497.50
Sodium 3-({[(2*S*,4*S*)-4-({(4*R*,5*S*,6*S*)-2-carboxy-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-3-yl}sulfanyl)pyrrolidin-2-yl]carbonyl}amino)benzoate, [*153773-82-1*]

Ertapenem Sodium contains NLT 917 μg and NMT 970 μg (potency) of ertapenem ($C_{22}H_{25}N_3O_7S$: 475.52) per mg, calculated on the anhydrous and solvent-free basis.

Description Ertapenem Sodium occurs as a white to grayish white powder.
It is freely soluble in water, and practically insoluble in ethanol.
It is hygroscopic.

Identification (1) Determine the infrared spectra of Ertapenem Sodium and ertapenem sodium RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve 0.1 g (potency) of Ertapenem Sodium in 10 mL of water; the resulting solution responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_{405nm}^{25}$: Between +216° and +238° (1.0 g, calculated on the anhydrous and solvent-free basis, water, 100 mL, 100 mm).

Purity (1) ***Related substances***—Just before starting this test, weigh accurately about 20 mg (potency) of Ertapenem Sodium, dissolve in water to make exactly 100 mL, and use this solution as the test solution. Perform the test with 10 μL of the test solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios of the peak area of each related substance to total area of the peaks excluding solvent peak from the test solution (ring-opened compound: NMT 1.4%,xazinone: NMT 0.2%, ProMABA: NMT 0.6%, total dimer: NMT 1.3%, other individual related substances: NMT 0.1%, total related substances: NMT 3.1%).

Contents (%) of individual related substances

$$= \frac{Peak\ areas\ of\ individual\ related\ substances\ in\ test\ solution}{\left[Sum\ of\ all\ peak\ areas\ other\ than\ solvent\ peak\ in\ test\ solution\right]}$$

Total content (%) of related substances
= Sum of contents (%) of all related substances

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with phenylated silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase

Mobile phase A: 15 mmol/L sodium phosphate TS (pH 8.0).

Mobile phase B: Acetonitrile

Mobile phase gradient elution conditions

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0 - 3	98 → 95	2 → 5
3 - 25	95 → 85	5 → 15
25 - 35	85 → 75	15 → 25
35 - 45	75	25

Flow rate: 1.0 mL/min

The relative retention time of each related substance peak to the ertapenem peak is as follows.

Component	Relative Retention time	Component	Relative Retention time
Oxazinon peak I	0.27	Dimer VI	1.10
Oxazinon peak II	0.28	Dimer III	1.15
cis-Hydroxy proMABA	0.44	*trans*-Methanolysis product	1.18
Ring-opened compound	0.50	L-749345 Side-chain product	1.45
trans-Hydroxy proMABA	0.56	Dimer-H_2O(a)+dimer-H_2O(b)	1.55
ProMABA	0.65	Dimer V	1.65
Dimer I	0.85	PAB-L-749345	1.79
Dimer II	0.90	Disulfide	1.82
cis-Methanolysis product	0.97	Dimethylamide	2.04
Ertapenem	1.00	PAB side-chain	2.29

(2) ***Residual solvent***—Weigh accurately about 50 mg (potency) of Ertapenem Sodium, dissolve in water to make exactly 10 mL, and use this solution as the test solution. Pipet 1 mL each of methyl acetate, methanol, 2-propanol and 1-propanol, add water to make exactly 100 mL, and use this solution as the standard stock solution. Dilute this standard stock solution with water to prepare 0.01 vol% and 0.0001 vol% standard solutions, and use water as a blank test solution. Pipet accurately 1 mL each of the test solution, the standard solution and the blank test solution, transfer them to headspace vials, close with appropriate elastomeric closures, perform the test as directed under the Gas Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of the residual solvent from the test solution and the standard solution (methyl acetate: NMT 1.3%, methanol: NMT 0.3%, 2-propanol: NMT 0.5%, 1-propanol: NMT 0.1%).

$$\text{Content (\%) of residual solvent} = \frac{A_T}{A_S} \times \frac{d \times Volume\ (\%)\ of\ residual\ solvent\ in\ standard\ solution}{Amount\ (g)\ of\ sample\ taken} \times \text{Dilution factor of the test solution}$$

d: Density (g/mL) of residual solvent (methyl acetate: 0.93, methanol and 2-propanol: 0.79, 1-propanol: 0.80)

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A stainless steel column about 0.32 mm in internal diameter and about 30 m in length, packed with porous dimethylpolysiloxane for gas chromatography (5 μm in particle diameter).

Column temperature: Maintain at 35 °C for 8 minutes, and then raise to 125 °C at a rate of 50 °C per minute.

Temperature of injection port: About 180 °C.

Temperature of detector: About 250 °C.

Carrier gas: Helium

Conditions of headspace

Temperature of injection port: 85 °C

Injection time of test solution: 0.1 minute

Temperature of needle: 125 °C

Temperature of conveying port: 135 °C

Circulation time of gas chromatograph: 20 minutes

Constant temperature retention time: 15 minutes

Pressurization time: 2.0 minutes

Sterility It meets the requirements when used in sterile preparations. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing process of sterile preparations.

Water Between 15.5% and 19.0% (0.1 g, volumetric titration, direct titration).

Assay Weigh accurately bout 30 mg (potency) of Ertapenem Sodium and ertapenem sodium RS at places with the relative humidity of 50% to 60% and NMT 10%, respectively, dissolve in 10 mmol/L 3-(*N*-morpholine) propanesulfonic acid buffer solution, pH 7.0, and use these solutions as the test solution and the standard solution, respectively. Store the test solution and the standard solution at 4 °C and use within 18 hours. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas A_T and A_S, of ertapenem from each solution.

$$\text{Potency (μg) of ertapenem } (C_{22}H_{25}N_3O_7S) = \text{Potency (μg) of ertapenem sodium RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 307 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 10 cm in length, packed with octylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: 0.1% phosphoric acid

Mobile phase B: Acetonitrile.

Mobile phase gradient elution conditions

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 5	85	15
5 - 14	85 → 50	15 → 50
14 - 15	50 → 85	50 → 15
15 - 20	85	15

Flow rate: Adjust the flow rate so that the retention time of ertapenem is about 2.5 to 5.0 minutes.

Packaging and storage Preserve in tight containers.

Ertapenem Sodium for Injection
주사용 에르타페넴나트륨

Ertapenem Sodium for Injection is an injection, which is dissolved before use, and contains NLT 90.0% and NMT 120.0% of the labeled amount of ertapenem ($C_{22}H_{25}N_3O_7S$: 475.52).

Preparation Prepare as directed under Injections, with Ertapenem Sodium.

Description Ertapenem Sodium for Injection occurs as a white to grayish white powder.

Identification The retention times of the major peaks obtained from the test solution and standard solution in the Assay are the same.

pH Dissolve 1.0 g (potency) of Ertapenem Sodium for Injection in 0.9% sodium chloride injection to make 1 mL; the pH of this solution is 7.0 to 8.0.

Purity ***Related substances***—After performing the test as directed under the Assay, calculate as follows from the peak areas for each related substance (ring-opened NMT 10.0%; oxazinone NMT 1.2%; total dimers NMT 6.3%; NMT 0.2% each for other related substances; total related substances NMT 17.5%).

Content (%) of each related substance
= (A_D / A_S) × amount [mg (potency)] of ertapenem sodium RS / {labeled amount [mg (potency) / vial] of ertapenem sodium] × *RRF*} × 100

A_D: Peak area of related substance in test solution
A_S: Peak area of ertapenem in standard solution
RRF: Relative response factor of individual related substance peaks

Related substance	Relative response factor
Ring-opened	0.88
Oxazinone	0.98
Dimers I and II	0.66

Total dimers (%) = Sum of amounts (%) of all dimers (Dimers I, II, III, V, VI, Dimer IV + Dimer-H_2O).

Total related substances (%)
= Sum of amounts (%) of all related substances whose amount is NLT 0.1%.

Sterility Meets the requirements.

Bacterial endotoxins Ertapenem Sodium for Injection is NMT 0.35 EU per mg (potency) of ertapenem.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Water In a location of relative humidity NMT 25%, without removing the elastomeric closure and metal ring, weigh accurately the entire mass of 1 vial of Ertapenem Sodium for Injection, and inject 20.0 mL of a mixture of methanol and dimethylformamide (1 : 1) into the vial through a syringe. Shake to mix for 4 to 8 minutes until the sample is completely dissolved, and use a syringe to place the dissolved test solution in 2 1.5 mL test tubes, immediately insert the stoppers, and centrifuge for 2 minutes at 14000 revolutions per minute. From the two test tubes, weigh the clean supernatant and place in vials for gas chromatography. Use these solutions as the test solutions. Evacuate the remaining solution from the vial of Ertapenem Sodium for Injection, wash with methanol and dry, measure the sum of the masses of the vial, elastomeric closure and metal ring, and subtract this sum from the total mass. Use the difference as the amount (mg) of sample. Separately, place 100 μL of water each in 100-mL and 200-mL volumetric flasks, previously dried for 2 hours at 100 ℃ and cooled to room temperature before use, and add a mixture of methanol and dimethylformamide (1 : 1) to the gauge line. Immediately plug with an elastomeric closure and seal, and mix well. Use these solutions as the standard solution (1) (1 mg/mL) and the standard solution (2) (0.5 mg/mL). Place a mixture of methanol and dimethylformamide (1 : 1) in a volumetric flask previously dried for 2 hours at 100 ℃ and cooled to room temperature before use, immediately plug with an elastomeric closure and seal, and use this solution as the blank test solution. Perform the test with 1 μL each of the test solution and the standard solution (1) (1 mg/mL) as directed under the Gas Chromatography according to the following conditions, and measure the water peak areas, A_T and A_S of the test solution and the standard solution (NMT 2.3%). Use a mixture of methanol and dimethylformamide (1 : 1) prepared by placing

500 mL of methanol and 500 mL of dimethylformamide in a 1000-mL container, mixing well, substituting with nitrogen and sealing.

$$\text{Water (\%) in Ertapenem Sodium for Injection} = (A_T / A_S) \times (0.1 / \text{amount of sample (mg)}) \times 1000 \times (20 / 100) \times 100$$

0.1: Amount (mL) of water in the standard solution (1)

1000: Specific gravity of water (mg/mL)

20: Dilution factor of the test solution

100: Dilution factor of the standard solution

Operating conditions

Detector: Thermal conductivity detector

Column: A gas pipe about 0.53 mm in internal diameter and about 25 m in length, packed with porous polystyrene-divinylbenzene copolymer for gas chromatography (20 μm in particle diameter).

Column temperature: Hold at 90 ℃ for 5 minutes, heat at a rate of 25 ℃ per minute to 250 ℃, and hold at 250 ℃ for 5 minutes. Re-equilibrate for 1 minute at 90 ℃ before the next injection.

Injection port temperature: 200 ℃

Detector temperature: 250 ℃

Carrier gas: Helium

Flow rate: Adjust the flow rate so that the retention time of water is between 1 and 2 minutes.

Assay Weigh accurately about 20 mg (potency) of Ertapenem Sodium for Injection and ertapenem sodium RS, dissolve in the diluent to contain exactly 0.2 mg (potency) per mL. Use these solutions as the test solution and the standard solution. Store the test solution and the standard solution at 5±3 ℃, and use within 24 hours. Pipet 10 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of ertapenem for each solution.

$$\text{Amount [mg (potency)] of ertapenem } (C_{22}H_{25}N_3O_7S) = \text{Amount [mg (potency)] of ertapenem sodium RS} \times (A_T / A_S)$$

Diluent—Mixture of 15 mmol/L 4-morpholine propane sulfonate (pH 7.5) and acetonitrile (9 : 1).

4-morpholine propane sulfonate (pH 7.5)—Dissolve 3.5 g of 4-morpholine propane sulfate in 1000 mL of water, and adjust pH to 7.5.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 2.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: 0.1% phosphoric acid (pH 8.0)

Mobile phase B: Mixture of acetonitrile and 0.1% phosphoric acid (pH 8.0) (1 : 3).

Mobile phase gradient elution conditions

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 3	94	6
3 - 6	94 → 80	6 → 20
6 - 11	80 → 72	20 → 28
11 - 15	72	28
15 - 33	72 → 40	28 → 60
33 - 34	40 → 0	60 → 100
34 - 28	0	100

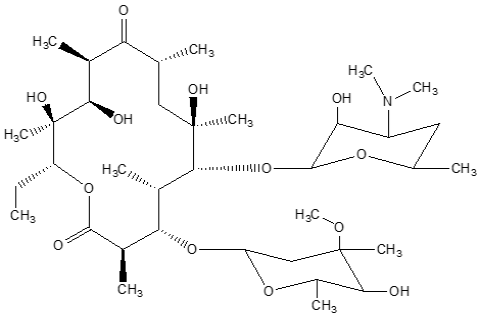
Flow rate: 1.0 mL/min

Relative retention time of each related substance

Component	Relative retention time
Oxazinone	0.25
Ring-opened	0.55
proMABA	0.64
Ertapenem	1.00
Dimers I + II	0.86, 0.91, 0.93
Dimer VI	1.2
Dimer III	1.3
Dimer IV + Dimer-H_2O	1.7
Dimer V	1.8

Packaging and storage Preserve in hermetic containers.

Erythromycin
에리트로마이신



Erythromycin $C_{37}H_{67}NO_{13}$: 733.93
(3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-6-[(2*S*,3*R*,4*S*,6*R*)-4-(Dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy-14-ethyl-7,12,13-trihydroxy-4-[(2*R*,4*R*,5*S*,6*S*)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-3,5,7,9,11,13-hexamethyl-oxacyclo-tetradecane-2,10-dione [*114-07-8*]

Erythromycin is a macrolide substance having antifungal activity produced by the growth of *Saccharopolyspora erythraea*.

Erythromycin contains NLT 930 μg and NMT 1020 μg (potency) of erythromycin ($C_{37}H_{67}NO_{13}$) per mg, calculated on the anhydrous basis.

Description Erythromycin occurs as a white to pale yellowish white powder.
It is very soluble in *N*,*N*-dimethylformamide, freely soluble in methanol or ethanol(95), and slightly soluble in water.

Identification (1) Determine the infrared spectra of Erythromycin and erythromycin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve 10 mg each of Erythromycin and erythromycin RS in 1 mL of methanol, and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol and ammonia water(28) (50 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly 4-methoxybenzaldehyde-sulfuric acid TS on the plate, and heat at 100 ℃ for 15 minutes; the spots obtained from the test solution and the standard solution show a dark purple color and the R_f values are the same.

Optical rotation $[\alpha]_D^{20}$: Between -71° and -78° (1g, calculated on the anhydrous basis, ethanol(95), 50 mL, 100 mm).

pH Dissolve 0.1 g of Erythromycin in 150 mL of water; the pH of this solution is between 8.0 and 10.5.

Purity (1) ***Thiocyanate*—**Weigh accurately about 0.1 g of Erythromycin, transfer into a 50-mL brown volumetric flask, dissolve by adding 20 mL of methanol, add 1 mL of iron(III) chloride TS and methanol to make to 50 mL, and use this solution as the test solution. Separately, weigh accurately potassium thiocyanate, previously dried at 105 ℃ for 1 hour and cooled, transfer into two 50-mL volumetric flasks, and add methanol to make 50 mL. Take accurately 5.0 mL each of these solutions, add methanol to make 50 mL, then take exactly 5.0 mL each of the resulting solutions, transfer into 50-mL brown volumetric flasks, add exactly 1.0 mL of iron(III) chloride TS to each solution, add methanol to make 50 mL, and use these solutions as the standard solutions. Separately, transfer 1 mL of the iron(III) chloride TS into a 50-mL brown volumetric flask, dissolve in methanol to make 50 mL, and use this solution as the standard test solution. Use the test solution, the standard solutions and the standard test solution within 30 minutes after the preparation. Perform the test with the test and standard solutions as directed in the potassium bromide disk method under the Ultraviolet-visible Spectroscopy using the blank test solution as the control solution, determine the absorbance at 492 nm, and calculate the amount of thiocyanate by the following formula; it is NMT 0.3%.

$$\text{Content (\%) of thiocyanate} = \frac{58.08}{97.18} \times \frac{A_T}{W_T} \times 0.5 \times \left[\frac{W_1}{A_1} + \frac{W_2}{A_2}\right]$$

A_T: Absorbance of the test solution
W_T: Amount (mg) of sample taken
A_1, A_2: Absorbance of each standard solution
W_1, W_2: Amount (mg) of potassium thiocyanate taken from each standard solution
58.08: Molecular weight of thiocyanate
97.18: Molecular weight of potassium thiocyanate

System suitability**:** Determine the absorption spectrum of each standard solution, and calculate suitability factor (S) by the following formula; it is between 0.985 and 1.015.

$$S = \frac{A_1}{W_1} + \frac{W_2}{A_2}$$

A_1, A_2: Absorbance of each standard solution
W_1, W_2: Amount (mg) of potassium thiocyanate taken from each standard solution

(2) ***Heavy metals*—**Proceed with 1.0 g of Ceftazidime Hydrate according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic*—**Proceed with 1.0 g of Erythromycin

according to Method 5 and perform the test with hydrochloric acid instead of dilute hydrochloric acid (1 in 2) (NMT 2 ppm).

(4) **Related substances**—Dissolve 40 mg of Erythromycin in 2 mL of methanol, add a mixture of phosphate buffer solution, pH 7.0 and methanol (15 : 1) to make exactly 10 mL, and use this solution as the test solution. Separately, dissolve 16 mg of erythromycin RS in 2 mL of methanol, add a mixture of phosphate buffer solution, pH 7.0 and methanol (15 : 1) to make exactly 10 mL, and use this solution as the standard stock solution. Dissolve 5 mg each of erythromycin B and erythromycin C in 2 mL of methanol, add exactly 2 mL of the standard stock solution, add a mixture of phosphate buffer solution, pH 7.0 and methanol (15 : 1) to make exactly 25 mL, and use this solution as the standard solution. Take exactly each 100 μL of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of each solution by the automatic integration method; the peak areas of erythromycin B and erythromycin C from the test solution are not greater than the peak areas of erythromycin B and erythromycin C in the standard solution. In addition, the peak areas other than erythromycin, erythromycin B and erythromycin C are not greater than the peak area of erythromycin from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm - 10 μm in particle diameter).

Column temperature: A constant temperature of about 70 °C.

Mobile phase: Dissolve 3.5 g of dibasic potassium phosphate in water to make 100 mL, adjust pH to 9.0 with diluted phosphoric acid (1 in 10). To 50 mL of this solution, add 190 mL of *t*-butyl alcohol, 30 mL of acetonitrile and water to make 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of erythromycin is about 20 minutes.

System suitability

System performance: Dissolve 2 mg of N-demethylerythromycin in 10 mL of the standard solution. Proceed with 100 μL of this solution according to the above conditions; N-demethylerythromycin, erythromycin C, erythromycin and erythromycin B are eluted in this order with the resolution between N-demethylerythromycin and erythromycin C being NLT 0.8, and the resolution between N-demethylerythromycin and erythromycin being NLT 5.5.

System repeatability: Repeat the test 3 times with 100 μL each of the standard solutions according to the above operating conditions; the relative standard deviation of the peak area of erythromycin is NMT 3.0%.

Time span of measurement: About 4 times the retention time of erythromycin after the solvent peak.

Water NMT 10.0% (0.2 g, volumetric titration, direct titration).

Residue on ignition NMT 0.2% (1 g).

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, it is exempt from the requirements when there is a terminal sterilization process in the manufacturing process of sterile preparations.

Pyrogen It meets the requirements when used in the manufacturing of sterile preparations. Proceed with an appropriate amount of Erythromycin to prepare a solution containing 1.0 mg per mL, use 50 ml of this solution as the test solution. However, inject the test solution to a rabbit by 1.0 mL per kg of the rabbit weight.

Assay Weigh accurately about 50 mg (potency) each of Erythromycin and erythromycin RS, dissolve in 25 mL of methanol, add the mobile phase to make exactly 50 mL, and use these solutions as the test solution and the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S of erythromycin.

$$\text{Potency (μg) of erythromycin } (C_{37}H_{67}NO_{13}) = \text{Potency (μg) of erythromycin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of methanol and 0.067 mol/L potassium dihydrogen phosphate (3 : 2).

System suitability

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above operating conditions; the relative standard deviation of the peak area of erythromycin is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Erythromycin Delayed-Release Capsules
에리트로마이신 장용캡슐

Erythromycin Delayed-Release Capsules contain NLT 90.0% and NMT 120.0% of the labeled amount of

erythromycin ($C_{37}H_{67}NO_{13}$: 733.93).

Method of preparation Prepare as directed under Capsules, with Erythromycin.

Identification Perform the test as directed under the Identification of Erythromycin Delayed-Release Tablets.

Water NMT 7.5% (0.1 g, volumetric titration, direct titration).

Dissolution Perform the test with 1 capsule of Erythromycin Delayed-Release Capsules at 50 revolutions per minute for 60 minutes according to Method 1 under the Dissolution, using 900 mL of 0.06 mol/L hydrochloric acid as the dissolution medium. Immediately wash the remaining contents and the basket with water to remove hydrochloric acid, and perform the test for 60 minutes under the conditions described in the above test method, using 900 mL of 0.2 mol/L phosphate buffer solution, pH 6.8, as the dissolution medium. Take 5 mL of the dissolved solution 60 minutes after starting the second dissolution test, and use the filtrate as the test solution.

Uniformity of dosage units Meets the requirements.

Assay Proceed as directed under the Assay under Erythromycin. Take NLT 20 capsules of Erythromycin Delayed-Release Capsules, weigh accurately the mass of the contents equivalent to about 50 mg (potency) according to the labeled potency, dissolve in 25 mL of methanol, add the mobile phase to make exactly 50 mL, and use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Erythromycin Gel
에리트로마이신 겔

Erythromycin Gel contains NLT 90.0% and NMT 120.0% of the labeled amount of erythromycin ($C_{37}H_{67}NO_{13}$: 733.93).

Method of preparation Prepare as directed under Gels, with Erythromycin.

Identification Perform the test under the Identification (2) of Erythromycin Tropical Solution. However, weigh accurately an appropriate amount of Erythromycin Gel and erythromycin RS, and dissolve in methanol to make a solution containing 2.5 mg (potency) per mL; use this solution as the test solution and standard solution, respectively.

Assay Proceed as directed under the Assay of Erythromycin. However, weigh accurately an amount of Erythromycin Gel equivalent to about 50 mg (potency) according to the labeled potency, dissolve in 25 mL of methanol, and use the mobile phase to make exactly 50 mL; use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Erythromycin Topical Solution
에리트로마이신 외용액

Erythromycin Topical Solution contains NLT 90.0% and NMT 120.0% of the labeled amount of erythromycin ($C_{37}H_{67}NO_{13}$: 733.93), when quantified as a topical solution.

Method of preparation Prepare as directed under the Liquids, with Erythromycin.

Identification (1) Take 1 mL of Erythromycin Topical Solution, add acetone to make 10 mL then add 2 mL of hydrochloric acid; the solution exhibits amber to a reddish purple color.

(2) Take 1 mL of Erythromycin Topical Solution, add 7 mL of methanol, and use this solution as the test solution. Separately, dissolve 26 mg (potency) of erythromycin RS in methanol to make 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of methanol and chloroform (85 : 15) as the developing solvent, dry the plate at room temperature, spray evenly a mixture of ethanol(95), *p*-methoxybenzaldehyde and sulfuric acid (90 : 5 : 5), and heat at 100 ℃ for 10 minutes; the R_f values are the same when comparing the spots of the test solution and the standard solution.

Water (1) When using only ethanol as a solvent in the prescription: (1) NMT 8.0%, when 20 mg (potency) per mL, (2) NMT 5.0%, when 15 mg (potency) per mL.

(2) When using ethanol and acetone as a solvent in the prescription: NMT 2.0%.

(3) When using neither ethanol as a solvent nor stabilizer in the prescription: no criteria to apply.

However, use a mixture of pyridine and methanol for water determination (1 : 1), instead of methanol for water determination.

Assay Perform the test as directed under the Assay of Erythromycin. Weigh accurately an amount of Erythromycin Gel equivalent to about 50 mg (potency) according to the labeled potency, dissolve in 25 mL of methanol, and add the mobile phase to make exactly 50 mL. Use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Erythromycin Enteric-Coated Tablets
에리트로마이신 장용정

Erythromycin Enteric-Coated Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of erythromycin ($C_{37}H_{67}NO_{13}$: 733.93). Erythromycin Enteric-Coated Tablets are delayed-release preparations.

Method of preparation Prepare as directed under Tablets, with Erythromycin.

Identification Perform the test as directed under the Identification (2) of Erythromycin. Weigh an amount of powdered Erythromycin Enteric-Coated Tablets, equivalent to 10 mg (potency) of erythromycin according to the labeled amount, add 1 mL of methanol, shake to mix, filter, and use this solution as the test solution.

Loss on drying NMT 10.0% (0.2 g, 0.67 kPa, 60 ℃, 3 hours).

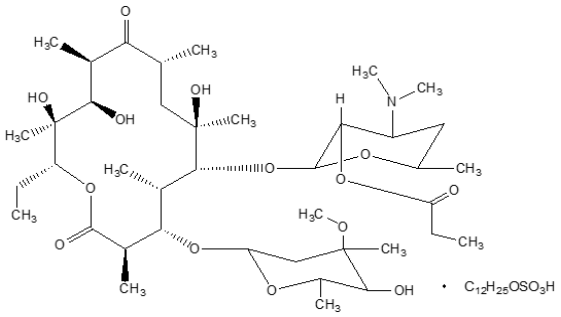
Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Perform the test as directed under the Assay of Erythromycin. Weigh accurately the mass of NLT 20 tablets of Erythromycin Enteric-Coated Tablets, powder, weigh accurately an amount of this powder, equivalent to about 50 mg (potency) of eythromycin according to the labeled potency, dissolve in 25 mL of methanol, add the mobile phase to make exactly 50 mL, and use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Erythromycin Estolate
에리트로마이신에스톨산염



Erythromycin Estolate

$C_{40}H_{71}NO_{14}\cdot C_{12}H_{25}OSO_3H$: 1056.39

[(2*S*,3*R*,4*S*,6*R*)-4-(Dimethylamino)-2-[[(3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-14-ethyl-7,12,13-trihydroxy-4-[(2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-3,5,7,9,11,13-hexamethyl-2,10-dioxo-oxacyclotetradec-6-yl]oxy]-6-methyloxan-3-yl] propanoate dodecyl hydrogen sulfate [*3521-62-8*]

Erythromycin Estolate, when dried, contains NLT 600 μg (potency) of Erythromycin (C37H67NO13: 733.93) per mg, calculated on the anhydrous basis.

Description Erythromycin Estolate occurs as a white crystalline powder or a powder. It is odorless and has a bitter taste.
It is sparingly soluble in methanol or ethanol(95) and very slightly insoluble in water or benzene.

Identification Determine the infrared spectra of Erythromycin Estolate and erythromycin estolate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

pH Dissolve 1.0 g of Erythromycin Estolate in 10 mL of water; the pH of this solution is between 4.5 and 7.0.

Purity ***Free erythromycin***—Dissolve 0.250g of this drug, weighed accurately, in 5.0 mL of the mobile phase and use this solution as the test solution. Separately, weigh accurately 75.0 mg of erythromycin RS and dissolve in the mobile phase to make exactly 50 mL. Take exactly 5.0 mL of this solution, add acetonitrile to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions; the peak area obtained from the test solution is not larger than the major peak area obtained from the standard solution (NMT 6.0%).

Buffer solution—Dissolve 3.4 g of potassium dihydrogen phosphate and 2.75 mL of Triethylamine in water to make 1000 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 195 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Adjust the pH of a mixture of acetonitrile and buffer solution (35:65) to 3.0 by adding dilute phosphoric acid.

Flow rate: 1 mL/min

System suitability

System performance: Proceed with 25 μL of the standard solution and the test solution according to the above conditions; the retention time of the first major

peak in the test solution and erythromycin in the standard solution is about 5 minutes and about 10 minutes.

Time span of measurement: About twice the retention time of the erythromycin peak for the standard solution, and about 4.5 times the first peak retention time of erythromycin propionate for the test solution.

Water NMT 4.0% (0.2 g, 20 mL of methanol containing 10% imidazole, volumetric titration, direct titration).

Assay Proceed as directed under the Assay under Erythromycin. However, weigh accurately an appropriate amount of Erythromycin Estolate, dissolve in 25 mL of methanol, add 0.1 mol/L phosphate buffer solution (pH 8.0) to contain 1.0 mg (potency) per mL, and then warm this solution on a steam bath at 60 °C for 2 hours, or allow to stand at room temperature of 16 to 18 hours. Use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Erythromycin Estolate Capsules
에리트로마이신에스톨산염 캡슐

Erythromycin Estolate Capsules contain NLT 90.0% and NMT 120.0% of the labeled amount of erythromycin ($C_{37}H_{67}NO_{13}$: 733.93).

Method of preparation Prepare as directed under Capsules, with Erythromycin Estolate.

Identification Weigh the appropriate amount of each Erythromycin Estolate Capsules and erythromycin estolate RS, dissolve in a small amount of methanol, add water to make a solution containing 500 μg (potency) per mL, respectively, and use these solutions as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol and 2-propanol (85 : 15) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Apply iodine vapor on the thin-layer chromatographic plate or evenly spray 10% sulfuric acid solution; the R_f values of the spots obtained from the test solution and the standard solution are the same.

Loss on drying NMT 5.0% (0.1 g, in vacuum, 60 °C, 3 hours).

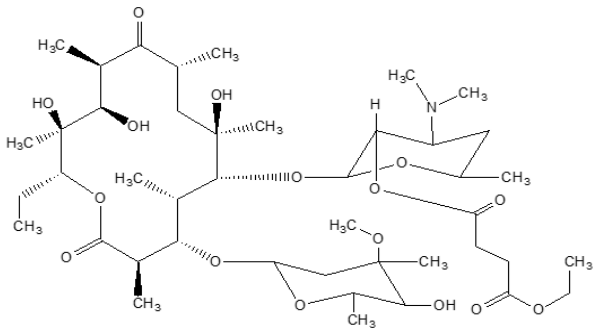
Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Proceed as directed under the Assay under Erythromycin. Take NLT 20 capsules of Erythromycin Estolate Capsules, weigh accurately the mass of the contents, and weigh accurately an amount equivalent to about 50 mg (potency) according to the labeled potency, dissolve in 25 mL of methanol, and dilute with 0.1 mol/L phosphate buffer solution, pH 8.0, to contain 1.0 mg (potency) per mL. Then warm this solution in a 60 °C water bath for 2 hours or allow it to stand at room temperature for 16 to 18 hours, and use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Erythromycin Ethylsuccinate
에리트로마이신에틸숙시네이트



$C_{43}H_{75}NO_{16}$: 862.05

4-*O*-[(2*S*,3*R*,4*S*,6*R*)-4-(Dimethylamino)-2-[[(3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-14-ethyl-7,12,13-trihydroxy-4-[(2*R*,4*R*,5*S*,6*S*)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-3,5,7,9,11,13-hexamethyl-2,10-dioxo-oxacyclotetradec-6-yl]oxy]-6-methyloxan-3-yl] 1-O-ethyl-butanedioate [*1264-62-6*]

Erythromycin Ethylsuccinate is a derivative of erythromycin.

Erythromycin Ethylsuccinate contains NLT 780 μg and NMT 900 μg (potency) of erythromycin ($C_{37}H_{67}NO_{13}$: 733.93) per mg, calculated on the anhydrous basis.

Description Erythromycin Ethylsuccinate occurs as a white powder.
It is freely soluble in methanol, soluble in ethanol(95) and practically insoluble in water.

Identification (1) Dissolve 3 mg of Erythromycin Ethylsuccinate in 2 mL of acetone and add 2 mL of hydrochloric acid; the solution exhibits an orange color and immediately changes into red to dark purple.

(2) Determine the infrared spectra of Erythromycin Ethylsuccinate and erythromycin ethylsuccinate RS, previously dried in a desiccator (in vacuum, silica gel) for 24 hours, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibits similar intensities of absorption at the same wavenumbers.

pH The pH of a solution obtained by suspending 0.1 g of Erythromycin Ethylsuccinate in 10 mL of water is between 6.0 and 8.5.

Purity (1) ***Free erythromycin***—Weigh accurately 0.250 g of Erythromycin Ethylsuccinate, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 75.0 mg of the erythromycin RS and dissolve in the mobile phase to make exactly 50 mL. Pipet 5.0 mL of this solution, add acetonitrile to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions; the peak area obtained from the test solution is not larger than the area of the major peak obtained from the standard solution (NMT 6.0%).

Operating conditions

Proceed as directed under the operating conditions for free erythromycin under the Purity of Erythromycin Estolate.

System suitability

System performance: Proceed with 25 μL each of the standard solution and the test solution under the above conditions; the peak retention times of erythromycin in the standard solution and erythromycin ethylsuccinate in the test solution are about 8 min and about 24 min, respectively.

Time span of measurement: About 2 times the peak retention time of erythromycin for the standard solution, and about 2 times the peak retention time of erythromycin ethylsuccinate for the test solution.

(2) ***Related substances***—Weigh accurately about 0.115 g of Erythromycin Ethylsuccinate, put it into a 50-mL Erlenmeyer flask, dissolve in 25 mL of methanol, and add 20 mL of hydrolysis TS to mix. Allow to stand at room temperature for about 12 hours, add the hydrolysis TS to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of erythromycin, dissolve it in 12.5 mL of methanol, add hydrolysis TS to make exactly 25 mL, and use this solution as the standard solution (1). Separately, weigh accurately about 5 mg each of erythromycin B and erythromycin C, dissolve them in 25 mL of methanol, add 2.5 mL of standard solution (1), and then add hydrolysis solution to make exactly 50 mL. Use this solution as the standard solution (2). Perform the test with 200 μL each of the test solution and the standard solution (2) as directed under the Liquid Chromatography according to the following conditions and calculate the amount of individual related substances other than erythromycin A, erythromycin B, erythromycin C, erythromycin A enolether and erythromycin *N*-ethylsuccinate and the amount of erythromycin A enolether and erythromycin *N*-ethylsuccinate according to the following formula; each is NMT 3.0%. However, the relative retention time of erythromycin *N*-ethylsuccinate to the retention time of erythromycin A is about 1.3, and the peak areas of erythromycin A enolether and erythromycin *N*-ethylsuccinate are calculated by multiplying the area obtained by the automatic integration method by the sensitivity coefficients for erythromycin A of 0.09 and 0.14, respectively.

$$\text{Content (\%) related substances} = 50 \times \frac{C \times P}{W} \times \frac{A_T}{A_S}$$

C: Concentration (mg/mL) of erythromycin in the standard solution (2)

P: Content (%) of erythromycin A in erythromycin RS

W: Amount (mg) of sample taken

A_T: Peak areas of each related substance, other than erythromycin A, erythromycin B, erythromycin C, erythromycin A enol ether and erythromycin *N*-ethylsuccinate obtained from the test solution, and erythromycin A enol ether and erythromycin *N*-ethylsuccinate

AS: Peak area of erythromycin A obtained from the standard solution (2)

Hydrolysis TS—A solution prepared by dissolving 2 g of dibasic potassium phosphate in water to make 100 mL and adjust the pH to 8.0 with phosphoric acid.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with spherical styrene-divinylbenzene copolymer for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 70 °C.

Mobile phase: Add 400 mL of water, 175 mL of *t*-butyl alcohol and 30 mL of acetonitrile to 50 mL of buffer solution, pH 8.0, and add water to make 1000 mL.

Flow rate: 2 mL/min

System suitability

System performance: Proceed with 200 μL of the system suitability solution (1) under the above conditions; *N*-demethylerythromycin, erythromycin C, erythromycin A and erythromycin B are eluted in this order with the resolution of *N*-demethylerythromycin and erythromycin C being NLT 0.8 and the resolution of *N*-demethylerythromycin and erythromycin A being NLT 5.5. Additionally, proceed with 100 μL of the system suitability solution (2) under the above conditions; the relative retention time of erythromycin A enol ether to the retention time of erythromycin A is about 4.3 to 4.7.

System repeatability: Repeat the test 5 times with 200 μL each of standard solution (1) under the above operating conditions; the relative standard deviation of the peak area of erythromycin is NMT 1.0%.

System suitability solution (1)—Dissolve about 2 mg of *N*-demethylerythromycin in 20 mL of the standard

solution (2).

System suitability solution (2)—Dissolve about 10 mg of erythromycin in 2 mL of methanol, then add 10 mL of buffer solution, pH 3.5, and allow to stand for 30 min. Keep refrigerated until use and discard after 8 hours after preparation.

Buffer solution, pH 8.0—A solution obtained by dissolving 2 g of dibasic potassium phosphate in water to make 100 mL and adjusting the pH to 8.0 with phosphoric acid.

Buffer solution, pH 3.5—A solution obtained by adjusting 20 mL of the buffer solution, pH 8.0 to pH 3.5 with phosphoric acid.

Water NMT 5.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 1.0% (1 g).

Sterility It meets the requirements when used in the manufacturing of a sterile preparation. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of a sterile preparation.

Pyrogen It meets the requirements when used in a sterile preparation. However, weigh an appropriate amount of Erythromycin Ethylsuccinate to make an aqueous suspension containing 50 mg per mL, use this solution as the test solution, and inject 0.1 mL of the test solution into the lower extremity muscle. However, the test solution injected to a rabbit shall be 1.0 mL per kg of the rabbit weight.

Assay ***Cylindrical plate method*** (1) Medium Agar medium for seed and base layer: Use the medium in (A) (2) (a) ② ⓑ under the Microbial Assays for Antibiotics. However, adjust the pH to 7.8 to 8.0.

(2) Test organism: Use *Staphylococcus aureus* ATCC 6538 P as the test organism.

(3) Weigh accurately about 50 mg (potency) of Erythromycin Ethylsuccinate, dissolve in 50 mL of methanol, and add 0.1 mol/L phosphate buffer solution (pH 8.0) to make exactly 100 mL. Take exactly an appropriate amount of this solution, dilute with 0.1 mol/L phosphate buffer solution (pH 8.0) to contain 20.0 and 5.0 μg (potency) per mL, and use these solutions as the high concentration and low-concentration test solutions, respectively. Separately, weigh accurately about 50 mg (potency) of the erythromycin RS, dissolve in 50 mL of methanol, add again 0.1 mol/L phosphate buffer solution (pH 8.0) to make exactly 100 mL, and use this solution as the standard stock solution. Store the standard stock solution at below 5 °C and use it within 7 days. Take exactly an appropriate amount of this standard stock solution, dilute with 0.1 mol/L phosphate buffer solution (pH 8.0) to contain 20.0 and 5.0 μg (potency) per mL, and use these solutions as the high-concentration standard solution and the low-concentration standard solution, respectively. With these solutions, perform the test according to (A) (8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in tight containers.

Erythromycin and Tretinoin Topical Gel
에리트로마이신·트레티노인 외용겔

Erythromycin and Tretinoin Topical Gel contains NLT 90.0% and NMT 120.0% of the labeled amount of erythromycin ($C_{37}H_{67}NO_{13}$: 733.93); NLT 90.0% and NMT 130.0% of the labeled amount of tretinoin ($C_{20}H_{28}O_2$: 300.44).

Method of preparation Prepare as directed under Gels, with Erythromycin and Tretinoin.

Identification (1) ***Erythromycin***—(i) Dissolve Erythromycin and Tretinoin Topical Gel and erythromycin RS in methanol to make a solution containing 2.5 mg (potency) per mL, and use this solution as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of methanol and chloroform (85 : 15) as the developing solvent, and take it out to dry at room temperature. Spray evenly a mixture of ethanol, *p*-methoxybenzaldehyde and sulfuric acid (90 : 5 : 5), and warm at 100 °C for 10 minutes; when comparing the black-purple spots of the test solution and the standard solution, the R_f values of them are the same.

(ii) Dissolve Erythromycin and Tretinoin Topical Gel in methanol to make a solution containing 2.5 mg (potency) per mL. Take 1 mL of this solution, add acetone to make 10 mL, and add 2 mL of hydrochloric acid; the resulting solution turns from orange to reddish purple.

(2) ***Tretinoin***—The retention times of the major peaks obtained from the test solution and the standard solution under the Assay are the same.

Assay (1) ***Erythromycin***

(i) Microbial Assays for Antibiotics (i) Cylindrical plate method

⑴ Medium: Agar medium for seed and base layer Microbial Assays for Antibiotics: Use the medium in (i) ⑵ (a) ② ⓑ. However, adjust the pH to 7.8 to 8.0.

⑵ Test organism: Use *Staphylococcus aureus* ATCC 6538P as the test organism.

⑶ Common standard solution: Weigh accurately an amount equivalent to about 40 mg (potency) of erythro-

mycin RS, dissolve in 25 mL of methanol, add 0.1 mol/L phosphate buffer solution, pH 8.0, to make 100 mL, and shake well to mix. Use this solution as the common standard stock solution. Store the common standard stock solution at below 5 ℃ and use within 7 days. Pipet an appropriate amount of the common standard stock solution, dilute with the above buffer solution to contain 20.0 and 5.0 μg (potency) per mL, and use this solution as the common standard solution.

⑷ Test solution: Weigh accurately an amount of Erythromycin and Tretinoin Topical Gel, equivalent to about 40 mg (potency), dissolve in 25 mL of methanol, and add 0.1 mol/L phosphate buffer solution, pH 8.0, to make 100 mL. Take an appropriate amount of this solution, dissolve in the above buffer solution, and dilute it to contain 20.0 and 5.0 μg (potency) per mL. Use this solution as the test solution.

(ii) Standard curve method

⑴ Medium: Agar medium for seed and base layer Microbial Assays for Antibiotics Use the medium in (i) ⑵ (a) ② ⓑ.

⑵ Test organism: Use *Micrococcus luteus* ATCC 9341 as the test organism.

⑶ Common standard solution: Microbial Assays for Antibiotics Pipet an appropriate amount of the common standard solution in (i) ⑶, dilute it with 0.1 mol/L phosphate buffer solution, pH 8.0, to contain 0.64, 0.80, 1.00, 1.25 and 1.56 μg (potency) per mL, and use this solution as the common standard solution. Use the solution containing 1.0 μg (potency) per mL as the common standard intermediate diluent.

⑷ Test solution: Microbial Assays for Antibiotics Pipet an appropriate amount of the solution in (i) ⑷, dilute it with 0.1 mol/L phosphate buffer solution, pH 8.0 to contain 1.0 μg (potency) per mL, and use this solution as the test solution.

(iii) Weigh accurately about 40 mg (potency) each of Erythromycin and Tretinoin Topical Gel and erythromycin RS, dissolve in 25 mL of methanol, add the mobile phase to make 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of erythromycin, A_T and A_S, in each solution.

$$\text{Potency (μg/mg) of Erythromycin and Tretinoin Topical Gel} = \frac{A_T}{A_S} \times \frac{\textit{Potency (mg) of erythromycin RS}}{\textit{Amount (mg) of}\ \text{Erythromycin and Tretinoin Topical Gel taken}} \times 1000$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Mobile phase: A mixture of methanol and 0.067 mol/L potassium dihydrogen phosphate solution (3 : 2).

(2) ***Tretinoin***—Weigh accurately about 250 mg of tretinoin ($C_{20}H_{28}O_2$), dissolve in 50 mL tetrahydrofuran, and filter if necessary. Take 5 mL of this solution, add a mixture of tetrahydrofuran and phosphoric acid (1 in 100) (3 : 2) to make 25 mL, and use this solution as the test solution. Separately, proceed in the same manner as in the preparation of the test solution with about 250 mg of tretinoin RS, and use this solution as the standard solution. Perform the test with 5 mL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of tretinoin from each solution, A_T and A_S, respectively.

$$\text{Amount (mg) of tretinoin } (C_{20}H_{28}O_2) = \text{Amount (mg) of tretinoin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 365 nm).

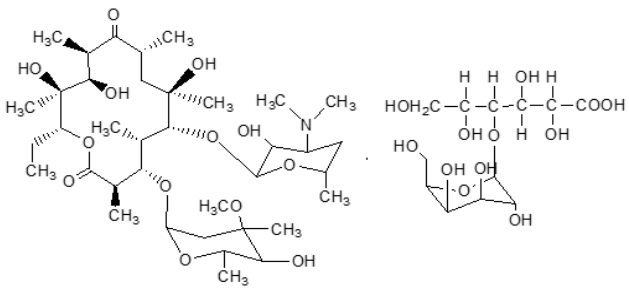
Column: A stainless steel column about 3.9 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (4 μm in particle diameter).

Mobile phase: A mixture of phosphate buffer solution, pH 3.0, and tetrahydrofuran (58 : 42).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Erythromycin Lactobionate
에리트로마이신락토비온산염



$C_{37}H_{67}NO_1 \cdot C_{12}H_{22}O_{12}$: 1092.22

(3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-6-[(2*S*,3*R*,4*S*,6*R*)-4-(Dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy-

14-ethyl-7,12,13-trihydroxy-4-[(2*R*,4*R*,5*S*,6*S*)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-3,5,7,9,11,13-hexamethyl-oxacyclo-tetradecane-2,10-dione(2*R*,3*R*,4*R*,5*R*)-2,3,5,6-tetrahydroxy-4-[(2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyhexanoate [*3847-29-8*]

Erythromycin Lactobionate is the lactobionate of erythromycin.

Erythromycin Lactobionate contains NLT 590 μg and NMT 700 μg (potency) of erythromycin ($C_{37}H_{67}NO_{13}$) per mg, calculated on the anhydrous basis.

Description Erythromycin Lactobionate occurs as a white powder.
It is freely soluble in water, methanol or ethanol(99.5) and slightly soluble in acetone.

Identification (1) To the 3 mg of Erythromycin Lactobionate, add 2 mL of acetone and 2 mL of hydrochloric acid; the resulting solution exhibits an orange color and immediately turns red to dark violet.

(2) To 0.3 g of Erythromycin Lactobionate, add 15 mL of ammonia TS and 15 mL of chloroform, shake to mix, and take the separated aqueous layer. Wash this solution with three 15 mL portions of chloroform, and evaporate to dryness on a steam bath. Dissolve the residue in 10 mL of a mixture of methanol and water (3 : 2), and use this solution as the test solution. Separately, dissolve 0.10 g of lactobionic acid in a mixture of methanol and water (3 : 2), and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of water, 1-butanol and acetic acid(100) (3 : 3 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly dilute sulfuric acid on the plate, and heat at 105 ℃ for 20 minutes; the principal spot obtained from the test solution exhibits a dark brown color and has the same R_f value as the spot obtained from the standard solution.

pH Dissolve 0.5 g of Erythromycin Lactobionate in 10 mL of water; the pH of this solution is between 5.0 and 7.5.

Purity ***Heavy metals***—Proceed with 0.5 g of Erythromycin Lactobionate according to Method 2 and perform the test. Prepare the control solution with 2.5 mL of lead standard solution (NMT 50 ppm).

Water NMT 5.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 2.0% (1 g). However, moisten the charred residue with 2 mL of nitric acid and 5 drops of sulfuric acid.

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, it is exempt from the requirements there is a terminal sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins Less than 1.0 EU per mg (potency) of erythromycin when used in the manufacturing of sterile preparations.

Assay ***Cylinder-plate method*—**(1) Medium: Agar media for seed and base layer Use the medium in (A) (2) (a) ② ⓑ under the Microbial Assays for Antibiotics. However, adjust the pH to 7.8 to 8.0.

(2) Test organism: Use *Staphylococcus aureus* ATCC 6538P as the test organism.

(3) Weigh accurately about 50 mg (potency) of Erythromycin Lactobionate, dissolve in 50 mL of methanol, and add 0.1 mol/L phosphate buffer solution, pH 8.0 to make exactly 100 mL. Take exactly an appropriate amount of this solution, dilute with 0.1 mol/L phosphate buffer solution, pH 8.0 to make solutions containing 20.0 μg (potency) and 5.0 μg (potency) per mL, and use these solutions as the high concentration test solution and low concentration test solution, respectively. Separately, dissolve approximately 50 mg (potency) of erythromycin lactobionate RS in 50 mL of methanol, add 0.1 mol/L phosphate buffer solution, pH 8.0 to make exactly 100 mL, and use this solution as the standard stock solution. Store the standard stock solution at below 5 ℃ and use it within 7 days. Take exactly an appropriate amount of the standard stock solution, dilute with 0.1 mol/L phosphate buffer solution, pH 8.0 to make solutions containing 20.0 μg (potency) and 5.0 μg (potency) per mL, and use these solutions as the high concentration standard solution and the low concentration standard solution, respectively. With these solutions, perform the test according to (A)(8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in tight containers.

Erythromycin Lactobionate and Colistin Sodium Methanesulfonate Ophthalmic Ointment

에리트로마이신락토비온산염·콜리스틴메탄설포네이트나트륨 안연고

Erythromycin Lactobionate and Colistin Sodium Methanesulfonate Ophthalmic Ointment contains NLT 90.0% and NMT 120.0% of the labeled amount of erythromycin ($C_{37}H_{67}NO_{13}$: 733.93) and colistin A ($C_{53}H_{100}N_{16}O_{13}$: 1169.47).

Method of preparation Prepare as directed under Ophthalmic Ointments, with Erythromycin Lactobionate and

Colistin Sodium Methanesulfonate.

Identification (1) ***Erythromycin lactobionate***—Put about 1 g of Erythromycin Lactobionate and Colistin Sodium Methanesulfonate Ophthalmic Ointment in a stoppered flask, and turn it into liquid by warming. Add 3 mL of warmed acetone, shake vigorously to mix, cool, and take the acetone layer. Add 2 mL of hydrochloric acid to the solution; the resulting solution turns from orange to red, and finally to reddish purple. Add 2 mL of chloroform again and shake; the chloroform layer exhibits a purple color.

(2) ***Colistin sodium methanesulfonate***—Put about 1 g of Erythromycin Lactobionate and Colistin Sodium Methanesulfonate Ophthalmic Ointment in a stoppered flask, and turn it into liquid by warming. Add 5 mL of water, shake vigorously to mix, cool, and take the water layer. Add 10% sodium hydroxide solution to this solution, and shake well. Add 5 drops of 1% copper sulfate solution, and shake well to mix; the resulting solution exhibits a reddish purple color.

Sterility Meets the requirements.

Foreign metallic matter Meets the requirements.

Water NMT 1.0% (1.0 g, volumetric titration, direct titration).

Assay (1) ***Erythromycin lactobionate*—Cylinder plate method** (i) Medium: Agar media for seed and base layer Microbial Assays for Antibiotics Use the medium in (i) (2) (a) ① ⓐ.

(ii) Test organism: Use *Bacillus subtilis* ATCC 6633 as the test organism.

(iii) Weigh accurately Erythromycin Lactobionate and Colistin Sodium Methanesulfonate Ophthalmic Ointment, equivalent to about 25 mg (potency) of erythromycin, according to the labeled potency, place it in a separatory funnel, add 50 mL of ether, shake until the mixture becomes homogeneous, and then add 25 mL of 0.1 mol/L phosphate buffer solution (pH 8.0). Extract three times, combine all extracts, dilute with 0.1 mol/L phosphate buffer solution, pH 8.0, and use these solutions as the high concentration test solution and the low concentration test solution, respectively. Separately, weigh accurately about 25 mg (potency) of erythromycin lactobionate RS, dissolve in 25 mL of methanol, add 0.1 mol/L phosphate buffer solution (pH 8.0) to make exactly 100 mL, and shake well to mix. Use this solution as the standard stock solution. Store the standard stock solution at a temperature NMT 5 ℃, and use it within 7 days. Pipet an appropriate amount of the standard stock solution, dilute with 0.1 mol/L phosphate buffer solution (pH 8.0) to contain 2.0 μg and 0.5 μg (potency) per mL, and use these solutions as the high concentration standard solution and the low concentration standard solution, respectively. With these solutions, perform the test according to (i) (8) under the Microbial Assays for Antibiotics.

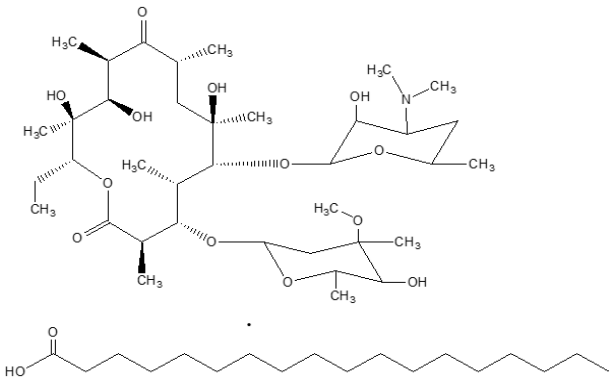
(2) ***Colistin sodium methanesulfonate*—Cylinder plate method** (i) Medium: Agar media for seed and base layer Microbial Assays for Antibiotics Use the medium in (ii) (2) (a) ① ⓐ.

(ii) Test organism: Use *Escherichia coli* NIHJ as the test organism.

(iii) Weigh accurately about 600000 units (potency) of Erythromycin Lactobionate and Colistin Sodium Methanesulfonate Ophthalmic Ointment according to the labeled potency of colistin to place in a separatory funnel, add 50 mL of ether, and shake until the mixture becomes homogeneous. Extract 3 times with 10 mL each of water, combine all extracts, and add 1% phosphate buffer solution (pH 6.0) to make exactly 60 mL. Pipet an appropriate amount of this solution, dilute with 1% phosphate buffer solution (pH 6.0), and use these solutions as the high concentration test solution and the low concentration test solution, respectivley. Separately, weigh accurately an appropriate amount of colistin sodium methanesulfonate RS and dissolve in water. Weigh accurately an appropriate amount of the erythromycin RS in this solution, add a small amount of methanol, and add water to make a solution containing 30000 units (potency) of colistin and 1 mg (potency) of erythromycin per mL. Pipet an appropriate amount of this solution, dilute with 1% phosphate buffer solution (pH 6.0) to contain 10000 and 2500 units (potency) per mL, and use these solutions as the high concentration standard solution and the low concentration standard solution, respectively. With these solutions, perform the test according (A) (8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in tight containers.

Erythromycin Stearate
에리트로마이신스테아르산염



$C_{55}H_{103}NO_{15}$: 1018.40

(3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-6-[(2*S*,3*R*,4*S*,6*R*)-4-(Dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy-14-ethyl-7,12,13-trihydroxy-4-[(2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-

3,5,7,9,11,13-hexamethyl-oxacyclo-tetradecane-2,10-dione octadecanoate [*643-22-1*]

Erythromycin Stearate is the stearate of erythromycin.

Erythromycin Stearate contains NLT 600 μg and NMT 720 μg (potency) of erythromycin ($C_{37}H_{67}NO_{13}$) per mg, calculated on the anhydrous basis.

Description Erythromycin Stearate occurs as a white powder.
It is freely soluble in ethanol(95) or acetone, soluble in methanol and practically insoluble in water.

Identification (1) Dissolve 3 mg of Erythromycin Stearate in 2 mL of acetone, and add 2 mL of hydrochloric acid; the resulting solution exhibits an orange color and immediately turns red to dark violet.

(2) Determine the infrared spectra of Erythromycin Stearate and erythromycin stearate RS, previously dried in a desiccator (in vacuum, silica gel) for 24 hours, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

pH Dissolve 0.1 g of Erythromycin Stearate in 10 mL of water; the pH of this solution is between 6.0 and 11.0.

Purity ***Related substances*—**Weigh accurately 0.165 g of Erythromycin Stearate, transfer into a 100-mL Erlenmeyer flask, dissolve in 15 mL of methanol, and add 15 mL of buffer solution, pH 8.0. After mixing, filter through a 0.2 μm filter, and use the filtrate as the test solution. Separately, weigh accurately 6 mg each of erythromycin RS, erythromycin B, erythromycin C and N-demethylerythromycin, and dissolve them in 15 mL of methanol, and add 15 mL of buffer solution, pH 8.0, and use this solution as the standard solution. Perform the test with 100 μL each of the test and standard solutions as directed under the Liquid Chromatography according to the following conditions, and determine the amount of individual related substances other than erythromycin A, erythromycin B, erythromycin C, erythromycin A enol ether and pseudoerythromycin A enol ether, and the amount of erythromycin A enol ether and pseudoerythromycin A enol ether by the following formula; NMT 3.0% However, the relative retention time of pseudoerythromycin A enol ether to erythromycin A is about 1.5, and the peak areas of ethyl erythromycin A enol ether and pseudoerythromycin A enol ether are calculated by multiplying the area obtained according to the automatic integration method by the correction factors for erythromycin A of 0.09 and 0.15, respectively.

$$\text{Content (\%) of related substances} = 30 \times \frac{C \times P}{W} \times \frac{A_T}{A_S}$$

C: Concentration (mg/mL) of erythromycin in the standard solution

P: Content (%) of erythromycin A in erythromycin RS

W: Weight (mg) of sample taken

A_T: Peak areas of individual related substances other than erythromycin A, erythromycin B, erythromycin C, erythromycin A enol ether, pseudoerythromycin A enol ether, and erythromycin A enol ether and pseudoerythromycin A enol ether obtained from the test solution

A_S: Peak area of erythromycin A obtained from standard solution

pH 8.0 buffer solution—A solution prepared by dissolving 2 g of dibasic potassium phosphate in water to make 100 mL and adjusting pH to 8.0 with phosphoric acid.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with spherical styrene-
divinylbenzene copolymer for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 70 °C.

Mobile phase: Dissolve 3.5 g of dibasic potassium phosphate in water to make 100 mL, and adjust pH to 9.0 with dilute phosphoric acid (1 in 10). To 50 mL of this solution, add 400 mL of water, 175 mL of *t*-butyl alcohol, 30 mL of acetonitrile, and add water to make 1000 mL.

Flow rate: 2 mL/min

System suitability

System performance: Proceed with 100 μL of the standard solution according to the above conditions; N-demethylerythromycin, erythromycin C, erythromycin A and erythromycin B are eluted in this order with the resolution between N-demethylerythromycin and erythromycin C being NLT 0.8, and the resolution between N-demethylerythromycin and erythromycin A being NLT 5.5. Separately, weigh accurately 5 mg of erythromycin RS, dissolve in 1 mL of methanol, add 5 mL of pH 3.5 buffer solution, and allow to stand for 30 minutes, and use this solution as the system suitability solution (1). Proceed with 100 μL of this solution according to the above conditions; the relative retention time of erythromycin A enol ether to that of erythromycin A is between 4.3 and 4.7.

pH 3.5 buffer solution—A solution prepared by adjusting the pH of 20 mL of pH 8.0 buffer solution to pH 3.5 with phosphoric acid.

System repeatability: Weigh accurately about 40 mg of erythromycin stearate RS, transfer into a 100-mL Erlenmeyer flask, dissolve in 5 mL of methanol, add 5 mL of pH 8.0 buffer solution, and use this solution as the system suitability solution (2). Repeat the test 5 times with 100 μL each of this solution according to the above

conditions; the relative standard deviation of the peak area of Erythromycin is NMT 2.0%.

Water NMT 5.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 2.0% (1 g).

Assay Perform the test as directed under the Assay of Erythromycin. However, weigh accurately about 50 mg (potency) of Erythromycin Stearate, dissolve in 25 mL of methanol, add the mobile phase to make exactly 50 mL, and use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Erythromycin Stearate Tablets
에리트로마이신스테아르산염 정

Erythromycin Stearate Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of erythromycin ($C_{37}H_{67}NO_{13}$: 733.93).

Method of preparation Prepare as directed under Tablets, with Erythromycin Stearate.

Identification Weigh an amount of powdered Erythromycin Stearate Tablets, equivalent to about 100 mg (potency) of erythromycin stearate according to the labeled potency, add 50 mL of chloroform, shake well to mix, filtrate, and use the filtrate as the test solution. Separately, dissolve 10 mg of erythromycin RS in 5 mL of chloroform, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, acetic acid and water (3 : 1 : 1), and air-dry the plate. Apply iodine vapor or spray 10% sulfuric acid on the plate to examine the spots; the R_f values of the spots obtained from the test solution and the standard solution are the same.

Water NMT 5.0% (0.2 g, volumetric titration, direct titration).

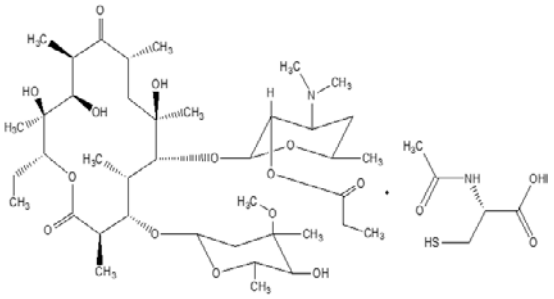
Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Proceed as directed under the Assay under Erythromycin. However, weigh accurately the mass of NLT 20 tablets of Erythromycin Stearate Tablets, powder, weigh accurately an amount of this powder, equivalent to about 50 mg (potency) of erythromycin stearate according to the labeled potency, dissolve in 25 mL of methanol, add the mobile phase to make exactly 50 mL, and use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Erythromycin Stinoprate
에리트로마이신스티노프레이트



Erythromycin Stinoprate
$C_{40}H_{71}NO_{14}\cdot C_5H_9NO_3S$: 953.18
2'-Propanoate erythromycin *N*-acetyl-L-cysteine (1:1), [*84252-03-9*]

Erythromycin Stinoprate contains NLT 704 μg (potency) of erythromycin ($C_{37}H_{67}NO_{13}$: 733.93) per mg, calculated on the anhydrous basis, and contains NLT 16.3% and NMT 18.0% of acetylcysteine and NLT 78.7% and NMT 87.0% of erythromycin propionate per mg, calculated on the anhydrous basis.

Description Erythromycin Stinoprate occurs as a white, crystalline powder and has a characteristic odor.
It is soluble in methanol, acetone or chloroform and slightly soluble in water.

Identification (1) Dissolve 3 mg (potency) of Erythromycin Stinoprate in 2 mL of acetone, and add 2 mL of hydrochloric acid; the resulting solution exhibits an orange color and immediately turns red to dark purple.

(2) Determine the infrared spectra of Erythromycin Stinoprate and erythromycin stinoprate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -51° and -58° (1.0 g, calculated on the anhydrous basis, ethanol anhydrous, 50 mL, after 30 min, 100 mm).

pH Dissolve Erythromycin Stinoprate in water to make 1 mg (potency)/mL; the pH of the solution is between 4.0 and 5.0.

Purity (1) ***Heavy metals***—Perform the test with 1.0 g of Erythromycin Stinoprate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—(i) *N,N*-diacetylcystine: Weigh accurately about 0.2 g (potency) of Erythromycin Stinoprate, dissolve in methanol to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of *N,N*-diacetylcystine RS, and add methanol to make exactly 100 mL. Pipet 1 mL and 6 mL of this solution, add methanol to make exactly 100 mL, and use these solutions as the detection limit solution and the standard solution. Within 30 minutes, perform the test with 20 μL each of the test and standard solutions as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas A_T and A_S of *N,N*-diacetylcystine from each solution (NMT 0.3%).

$$\text{Content (\%) of } N,N\text{-diacetylcystine} = \frac{A_T}{A_S} \times \frac{Amonut\ (mg)\ of\ N,N-diacetylcystine\ RS\ \times 6}{Amount\ (mg)\ of\ sample, calculated\ on\ the\ anhydrous\ basis}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of water and acetonitrile (99 : 5), adjusted pH to 2.5 with phosphoric acid.

Flow rate: 2.0 mL/min

(ii) Erythromycin propionate enol ether and other related substances: Weigh accurately about 0.5 g of Erythromycin Stinoprate, dissolve in ethanol to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of erythromycin propionate enol ether RS, add methanol to make exactly 200 mL, and use this solution as the standard solution. Pipet 10 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the detection limit solution. Perform the test with exactly 20 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, determine the peak areas A_T and A_S, of erythromycin propionate enol ether from each solution, and calculate total peak area after the erythromycin propionate peak other than the erythromycin propionate enol ether peak, S_T (NMT 0.5% for each of erythromycin propionate enol ether and other related substances).

$$\text{Content (\%) of erythromycin propionate enol ether} = \left[\frac{Amount\ (mg)\ of\ erythromycin\ propionate\ enol\ ether\ RS}{Amount\ (mg)\ of\ sample, calculated\ on\ the\ anhydrous\ basis}\right] \times \frac{A_T}{A_S} \times 25$$

$$\text{Content (\%) of other related substances} = \left[\frac{Amount\ (mg)\ of\ erythromycin\ propionate\ enol\ ether\ RS}{Amount\ (mg)\ of\ sample, calculated\ on\ the\ anhydrous\ basis}\right] \times \frac{S_T}{A_S} \times 25$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of water and acetonitrile (65 : 35), adjusted pH to 2.5 with phosphoric acid.

Flow rate: 2.0 mL/min

(iii) Free erythromycin: Weigh 0.1 g (potency) of Erythromycin Stinoprate, calculated on the anhydrous basis, dissolve in 10 mL of acetone, and use this solution as the test solution. Separately, weigh accurately 10.0 mg (potency) of erythromycin RS, dissolve in 20 mL of acetone, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution to the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with fluorescence agent), and develop the plate with a mixture of chloroform, ethanol and 15% ammonium acetate (85 : 15 : 1) to a distance of about 10 cm. Spray evenly a mixture of methanol acetic anhydride sulfuric acid and anisaldehyde (92 : 5 : 2 : 1) on the plate, and dry at 105 ℃ for about 5 minutes. The spots of erythromycin obtained from the test solution are not more intense than the spots obtained from the standard solution (NMT 5.0%).

(iv) Acetylcysteine: Weigh accurately about 0.6 g of Erythromycin Stinoprate, calculated on the anhydrous basis, and dissolve in methanol to make exactly 100 mL. Pipet 10 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of acetylcysteine RS, add methanol to make exactly 500 mL, and use this solution as the standard solution. Within 30 minutes, perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas A_T and A_S, of acetylcysteine from each solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octa-

decylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of water and acetonitrile (95 : 5), adjusted pH to 2.5 with phosphoric acid.

Flow rate: 2.0 mL/min

(v) Erythromycin propionate: Weigh accurately 0.24 g of Erythromycin Stinoprate, calculated on the anhydrous basis, dissolve in methanol to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 0.2 g (potency) of erythromycin propionate RS, dissolve in methanol to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas A_T and A_S, of erythromycin stinoprate from each solution.

$$\text{Potency (μg) of erythromycin stinoprate} = \text{Potency (μg) of erythromycin stinoprate RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of acetonitrile and phosphate buffer solution, pH 7.0 (53 : 47).

Flow rate: 2.0 mL/min

Water NMT 2.5% (0.4 g, volumetric titration, direct titration).

Residue on ignition NMT 0.5% (1 g).

Assay ***Cylinder-plate method***—(1) Medium: Agar media for seed and base layer Use the media in (A) (2) (a) ② ⓑ under the Microbial Assays for Antibiotics. However, adjust the pH to 7.8 to 8.0.

(2) Test organism: Use *Staphylococcus aureus* ATCC 6538P as the test organism.

(3) Weigh accurately about 0.1 g (potency) each of Erythromycin and erythromycin RS, dissolve in methanol to make 100 mL, and use these solutions as the test solution and the standard solution, respectively. Take exactly an appropriate amount each of these solutions, dilute with 0.1 mol/L phosphate buffer solution, pH 8.0, to make solutions containing 20.0 μg and 5.0 μg (potency) per mL, and use these solutions as the high concentration test solution and the low concentration test solution, respectively. Perform the test with these solutions according (A) (8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in tight containers.

Erythromycin Stinoprate Tablets
에리트로마이신스티노프레이트 정

Erythromycin Stinoprate Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of erythromycin ($C_{37}H_{67}NO_{13}$: 733.93). Also, Erythromycin Stinoprate Tablets contain NLT 16.3% and NMT 18.0% of acetylcysteine and NLT 78.7% and NMT 87.0% of erythromycin propionate, calculated on the anhydrous basis.

Method of preparation Prepare as directed under Tablets, with Erythromycin Stinoprate.

Identification Dissolve 0.1 g (potency) each of Erythromycin Stinoprate Tablets and erythromycin stinoprate RS in 10 mL of acetone, and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, and develop the plate with a mixture of chloroform, ethanol and 15% ammonium acetate solution (85 : 15 : 1) as the developing solvent to a distance of about 10 cm. Spray evenly a mixture of methanol, acetic acid(100), sulfuric acid and anisaldehyde (92 : 5 : 2 : 1) on the plate, and heat at 105 ℃ for 5 minutes; the R_f values of spots obtained from the test solution and the standard solution are the same.

Purity (1) ***Related substances***—① *N,N*-diacetylcystine: Perform the test as directed under the Purity (2) ① under Erythromycin Stinoprate. However, weigh accurately about 0.25 g (potency) of Erythromycin Stinoprate Tablets according to the labeled potency, dissolve in methanol to make exactly 100 mL, and then filter. Pipet 3.0 mL of the filtrate, add methanol to make exactly 10.0 mL, and use this solution as the test solution (NMT 0.7% for erythromycin stinoprate).

$$\text{Content (\%) of } N,N\text{-diacetylcystine} = \text{Amount (mg) of } N,N\text{-diacetylcystine RS} \times \frac{A_T}{A_S} \times \frac{733.94}{963.20} \times \frac{6}{Potency\ (mg)\ in\ amount\ of\ \text{Erythromycin Stinoprate Tablets taken}}$$

733.94: Molecular weight of erythromycin
953.20: Molecular weight of erythromycin stinoprate

(2) ***Erythromycin propionate enol ether and other related substances***—Perform the test as directed under the Purity (2) 2) under Erythromycin Stinoprate. However, weigh accurately about 0.2 g (potency) of Erythromycin Stinoprate Tablets according to the labeled potency, add methanol to make exactly 50 mL, and use this solution as the test solution (NMT 1.0% of erythromycin propionate enol ether and NMT 0.5% of the total amount of other related substances relative to erythromycin stinoprate).

$$\text{Content (\%) of erythromycin propionate enol ether RS} = \text{Amount (mg) of erythromycin propionate enol ether} \times \frac{A_T}{A_S} \times \frac{733.94}{963.20} \times \frac{25}{Potency\ (mg)\ in\ amount\ of\ \text{Erythromycin Stinoprate Tablets taken}}$$

$$\text{Content (\%) of other related substances} = \text{Amount (mg) of erythromycin propionate enol ether RS} \times \frac{S_T}{A_S} \times \frac{733.94}{963.20} \times \frac{25}{Potency\ (mg)\ in\ amount\ of\ \text{Erythromycin Stinoprate Tablets taken}}$$

Dissolution Perform the test with 1 tablet of Erythromycin Stinoprate Tablets at 100 revolutions per minute for 45 minutes according to Method 1 under the Dissolution, using 900 mL of phosphate buffer solution, pH 6.9, as the dissolution medium. Take 20 mL of the dissolved solution 45 minutes after starting the dissolution test, and filter. Discard the first 10 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately about 55 mg (potency) of erythromycin propionate RS, dissolve in acetonitrile to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 100 µL each of the test solution and the standard solution as directed under the Assay (4) under Erythromycin Stinoprate It meets the requirements when the dissolution rate of Erythromycin Stinoprate Tablets for 45 minutes is NLT 75% of the labeled potency.

$$\text{Dissolution rate (\%)} = \text{Potency (mg) of erythromycin propionate RS} \times \frac{A_T}{A_S} \times \frac{900}{Labled\ potency\ (mg)\ in\ 1\ tablent}$$

Uniformity of dosage units Meets the requirements.

Loss on drying NMT 5.0% (1.0 g, phosphorus pentoxide, 0.7 kPa, 50 °C, 4 hours).

Assay ***Cylinder plate method***—Perform the test as directed under the Assay under Erythromycin Stinoprate. However, weigh accurately the mass of NLT 20 Erythromycin Stinoprate Tablets, and then powder. Weigh accurately an amount equivalent to about 0.1 g (potency), and dissolve in methanol to make exactly 100 mL. Filter this solution, pipet an appropriate amount of the filtrate, dilute with 0.1 mol/L phosphate buffer solution (pH 8.0), and use this solution as the test solution.

Acetylcysteine—Perform the test as directed under the Acetylcysteine under Erythromycin Stinoprate. However, weigh accurately an amount of Erythromycin Stinoprate Tablets, equivalent to about 0.25 g (potency) according to the labeled potency, add acetonitrile, shake enough to mix, and then add another acetonitrile to make exactly 100 mL. Filter this solution, pipet 20 mL of the filtrate, add purified water to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 55 mg of acetylcysteine RS, and dissolve it in acetonitrile to make exactly 100 mL. Pipet 20 mL of this solution, add purified water to make exactly 100 mL, and use this solution as the standard solution.

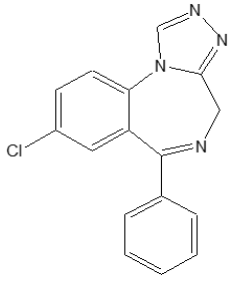
$$\text{Content (\%) of acetylcysteine} = \text{Amount (mg) of acetylcysteine RS} \times \frac{A_T}{A_S} \times \frac{733.94}{963.20} \times \frac{100}{Potency\ (mg)\ in\ amount\ of\ \text{Erythromycin Stinoprate Tablets taken}}$$

Erythromycin propionate—Perform the test as directed under the Erythromycin propionate under Erythromycin Stinoprate. However, weigh accurately an amount of Erythromycin Stinoprate Tablets, equivalent to about 0.185 g (potency) according to the labeled potency, dissolve in methanol to make 50 mL, and use this solution as the test solution.

$$\text{Content (\%) of erythromycin propionate} = \text{Amount (mg) of erythromycin propionate RS} \times \frac{A_T}{A_S} \times \frac{733.94}{963.20} \times \frac{100}{Potency\ (mg)\ in\ amount\ of\ \text{Erythromycin Stinoprate Tablets taken}}$$

Packaging and storage Preserve in tight containers.

Estazolam
에스타졸람



Estazolam $C_{16}H_{11}ClN_4$: 294.74
8-Chloro-6-phenyl-4*H*-`1,2,4-triazolo[4,3-a]-1,4-benzodiazepine [*29975-16-4*]

Estazolam, when dried, contains NLT 98.5% and NMT 101.0% of estazolam ($C_{16}H_{11}ClN_4$).

Description Estazolam occurs as a white to pale yellowish white crystals or crystalline powder. It is odorless and has a bitter taste.
It is soluble in methanol and in acetic anhydride, sparingly soluble in ethanol(95), and practically insoluble in water and in ether.

Identification (1) Dissolve about 10 mg of Estazolam in 3 mL of sulfuric acid and examine the solution under ultraviolet light (wavelength of 365 nm); the resulting solution exhibits a yellowish green fluorescent color.

(2) Determine the absorption spectra of the solutions of Estazolam and estazolam RS in 1 mol/L hydrochloric acid (1 in 100000) as directed under Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Perform the test with Lorazepam as directed under the Flame Coloration (2); it exhibits a green color.

Melting point Between 229 and 233 ºC.

Purity (1) ***Clarity and color of solution***—Dissolve about 0.1 g of Estazolam in 10 mL of ethanol(95); the resulting solution is colorless and clear.

(2) ***Chloride***—Dissolve 1.0 g of Estazolam in 10 mL of ethanol(95) by heating, add 40 mL of water, cool with shaking in iced water, allow to stand until it reaches room temperature, and filter. To 30 mL of the filtrate, add 6 mL of dilute nitric acid and water to make 50 mL. Using this solution as the test solution, perform the test. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid and 6 mL of ethanol (NMT 0.015%).

(3) ***Heavy metals*—**Proceed with 1.0 g of Estazolam according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic*—**Prepare the test solution with 1.0 g of Estazolam according to Method 3 and perform the test (NMT 2 ppm).

(5) ***Related substances*—**Dissolve 0.2 g of Estazolam in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography, develop the plate with a mixture of hexane, chloroform and methanol (5 : 3 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 1.0% (1 g, 105 ℃, 4 hours).

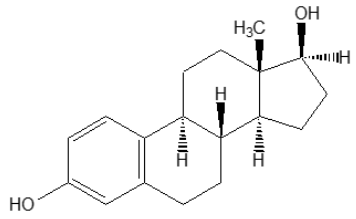
Residue on ignition NMT 0.1% (2 g).

Assay Weigh accurately about 0.25 g of Estazolam, previously dried, dissolve in 100 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). The endpoint of the titration is when the solution changes to the equivalence point 2. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 14.737 mg of $C_{16}H_{11}ClN_4$

Packaging and storage Preserve in well-closed containers.

Estradiol
에스트라디올



Estradiol $C_{18}H_{24}O_2$: 272.38
(17β)-Eestra-1,3,5(10)-triene-3,17-diol [*50-28-2*]

Estradiol, when dried, contains NLT 97.0% and NMT 103.0% of Estradiol ($C_{18}H_{24}O_2$).

Description Estradiol occurs as white crystals or a crystalline powder and is odorless.
It is freely soluble in 1,4-dioxane, soluble in acetone, sparingly soluble in ethanol(95), slightly soluble in sesame oil and practically insoluble in water.

Identification (1) Determine the absorption spectra of solutions of Estradiol and estradiol RS, respectively, in ethanol(95) (1 in 20000) as directed under Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths. The difference of absorption maxima in each absorption spectra is NLT 3.0% at about 280 nm.

(2) Determine the infrared spectra of Estradiol and estradiol RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +76.0° and +83.0° (0.250 g, calculated on the anhydrous basis, ethanol(95),

25 mL, 100 mm).

Melting point Between 173 and 179 ºC.

Purity ***Related substances***—Weigh about 70 mg of Estradiol, add a mixture of n-butyl chloride and methanol (5 : 1), shake vigorously, add a mixture of n-butyl chloride and methanol (5 : 1) to make 10 mL, and use this solution as the test solution. Perform the test with 10 μL of the test solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area by the automatic integration method and calculate the peak area, A_i of each related substance and the total area of all peaks AS by the percentage peak area method; the amount of each related substance is NMT 0.5%, and the total amount of related substances is NMT 1.0%.

$$\text{Content (\%) of each related substance} = 100\times \frac{A_i}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with porous silanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of isooctane, n-butyl chloride, and methanol (45 : 4 : 1).

Flow rate: 2 mL/min

System suitability

System performance: Proceed with 10 μL of the test solution under the above operating conditions; the resolution between the peaks of estradiol and each related substance is NLT 1.0, and the number of theoretical plates and symmetry factor are NLT 800 and NMT 1.5, respectively.

System repeatability: Repeat the test 5 times according to the above conditions with 10 μL each of the test solution; the relative standard deviation of the peak area of estradiol is NMT 2.0%.

Water NMT 3.5% (0.5 g, volumetric titration, direct titration).

Assay Weigh accurately about 0.1 g of Estradiol, previously dried, and dissolve in methanol to make exactly 250 mL. Pipet 10 mL of this solution, add 5.0 mL of the internal standard solution and 100 mL of methanol and water to make exactly 200 mL and use this solution as the test solution. Separately, weigh accurately a sufficient amount each of estradiol RS (previously determined water contents) and estrone RS and dissolve separately in methanol to contain about 400 μg of estradiol and 240 μg of estrone per mL. Pipet 10 mL each of these solutions, add 5.0 mL of the internal standard solution, 100 mL of methanol and add water to make exactly 200 mL and use these solutions as the standard solutions. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of estradiol to internal standard, respectively.

$$\text{Amount (mg) of estradiol } (C_{18}H_{24}O_2) = 5\times C \times \frac{Q_T}{Q_S}$$

C: Final concentration of Estradiol in the standard solution (μg/mL)

Internal standard solution—A solution of ethylparabene in methanol (0.6 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and water (55 : 45).

Flow rate: 1 mL/min

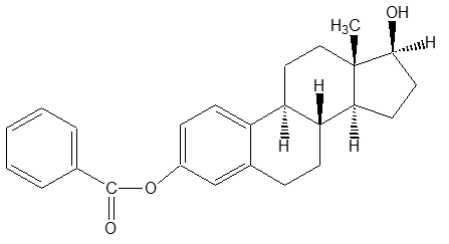
System suitability

System performance: Proceed with 25 μL of the standard solution under the above conditions; the internal standard, estradiol, and estrone are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 25 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Estradiol Benzoate
에스트라디올벤조에이트



$C_{25}H_{28}O_3$: 376.49

(17β)-3-Hydroxyestra-1,3,5(10)-trien-3-yl benzoate [*50-50-0*]

Estradiol Benzoate, when dried, contains NLT 97.0% and NMT 101.0% of estradiol benzoate

($C_{25}H_{28}O_3$).

Description Estradiol Benzoate occurs as a white crystalline powder and is odorless.
It is sparingly in acetone, slightly soluble in methanol, ethanol(95) and ethanol(95), and practically insoluble in water.

Identification (1) Add 2 mL of sulfuric acid to 2 mg of Estradiol Benzoate; the resulting solution exhibits a yellowish green color with blue fluorescence. Carefully add 2 mL of water; the color of the solution changes to light orange.

(2) Determine the infrared spectra of Estradiol Benzoate and estradiol benzoate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +54° and +58° (after drying, 0.1 g, acetone, 10 mL, 100 mm).

Melting point Between 191 and 198 ºC.

Purity (1) ***3,17α-Estradiol***—Dissolve 5.0 mg each of Estradiol Benzoate and estradiol benzoate RS in acetone to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Put exactly 2 mL each of the test solution and standard solution in separate glass-stoppered test tube, add boiling stones, evaporate the acetone by heating on a steam bath, and dry the residue in a desiccator (in vacuum, phosphorus (V) oxide) for 1 hour. Add 1.0 mL of dilute iron-phenol TS to each test tube. Stopper the test tubes loosely, heat for 30 seconds on a steam bath, shake on a steam bath for several seconds, and heat for 2 minutes again. After cooling the solutions in ice again for 2 minutes, add 4.0 mL of diluted sulfuric acid (7 in 20) and mix well; the solution obtained from the test solution has no more intense than that from the standard solution.

(2) ***Related substances***—Dissolve 40 mg of Estradiol Benzoate in 2 mL of acetone, and use this solution as the test solution. Pipet 1 mL of this solution, add acetone to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform and diethylamine (19 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (0.5 g, in vacuum, phosphorus (V) pentoxide, 4 hours).

Residue on ignition NMT 0.2% (0.1 g).

Assay Weigh accurately about 10 mg each of Estradiol Benzoate and estradiol benzoate RS, previously dried, dissolve separately in methanol to make exactly 20 mL. Pipet 5 mL each of these solutions, add exactly 5 mL of the internal standard solution, then add methanol to make 20 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 5 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of estradiol benzoate to that of the internal standard for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of estradiol benzoate } (C_{25}H_{28}O_3) = \text{Amount (mg) of estradiol benzoate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of progesterone in methanol (13 in 80000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of acetonitrile and water (7 : 3).

Flow rate: Adjust the flow rate so that the retention time of estradiol benzoate is about 10 minutes.

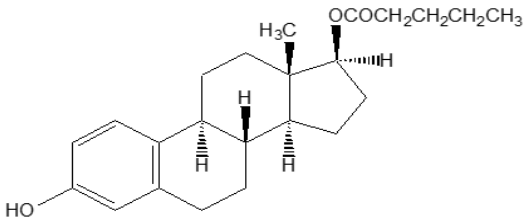
System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; the internal standard and estradiol benzoate are eluted in this order with the resolution being NLT 9.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution as directed in the above conditions; the relative standard deviation of the peak area ratios of estradiol benzoate to the peak area of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Estradiol Valerate
에스트라디올발레레이트



$C_{23}H_{32}O_3$: 356.50
(17β)-3-Hydroxyestra-1,3,5(10)-trien-17-yl pentanoate
[*979-32-8*]

Estradiol Valerate contains NLT 98.0% and NMT 102.0% of Estradiol Valerate ($C_{23}H_{32}O_3$).

Description Estradiol Valerate occurs as a white crystalline powder, is odorless or has a slightly oily odor.
It is soluble in castor oil, methanol, benzylbenzoate or 1,4-dioxane, sparingly soluble in sesame oil or peanut oil, and practically insoluble in water.

Identification Determine the infrared spectra of Estradiol Valerate and estradiol valerate RS, prepared by adding chloroform and potassium bromide to Estradiol Valerate or estradiol valerate RS, then grinding and drying at 105 ºC, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibits similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +41° and +47° (0.5 g, calculated on the anhydrous basis, methanol, 20 mL, 100 mm).

Melting point Between 143 and 150 ℃ (Method 1).

Purity (1) ***Estradiol***—Dissolve 50 mg of Estradiol Valerate in 10 mL of acetone and use this solution as the test solution. Separately, dissolve 5 mg of estradiol valerate RS in 100 mL of acetone and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of cyclohexane and ethyl acetate (7 : 3) as the developing solvent to a distance of about 15 cm and dry the plate at 90 ºC for 30 minutes. Spray evenly a solution of sulfuric acid in methanol (3 in 10) on the plate and heat at 90 ºC for 30 minutes; spots other than the principal spot from the test solution or the spot corresponding to estradiol are not more intense or not greater than the spots from the standard solution (NMT 1.0%).

(2) ***Free acid***—Neutralize 25 mL of ethanol(95) in an Erlenmeyer flask with 0.01 mol/L sodium hydroxide VS to a pale blue color, using bromothymol blue TS. Weigh accurately about 0.50 g of Estradiol Valerate and dissolve in the neutralized ethanol. Titrate with 0.01 mol/L sodium hydroxide VS to a pale blue color. (NMT 0.5% of valeric acid)

Each mL of 0.01 mol/L sodium hydroxide VS
= 1.021 mg of $C_5H_{10}O_2$

(3) ***Related substances***—Dissolve 0.1 g of Estradiol Valerate in 10 mL of acetone and use this solution as the test solution. Separately, weigh 10 mg of estradiol valerate RS and add acetone to make 10 mL. Pipet 0.1 mL, 0.5 mL, 1 mL and 2 mL of this solution and add acetone to each to make exactly 10 mL and use these solutions as the standard solutions (1),(2), (3) and (4). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solutions (1), (2), (3) and (4) on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of cyclohexane and ether (4 : 1) as the developing solvent to a distance of about 15 cm and air-dry the plate. Spray evenly sulfuric acid in ethanol(95) (1 in 10) on the plate, heat the plate until burn and cool. Examine under ultraviolet light (main wavelength: 254 nm and 366 nm). Compare the intensities of any spot other than the principal spot from the test solution with those from the standard solution; the relative intensity is NMT 2.0%.

Water NMT 0.1% (5 g, direct titration).

Assay Weigh accurately about 25 mg of Estradiol Valerate and estradiol valerate RS, dissolve each in the internal standard solution to make exactly 25 mL and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak area of Estradiol Valerate to that of the internal standard, Q_T and Q_S.

$$\text{Amount (mg) estradiol valerate } (C_{23}H_{32}O_3) = \text{Amount (mg) of estradiol valerate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Testosterone benzoate solution in tetrahydrofuran (2 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 5 μm to 10 μm in particle diameter).

Mobile phase: Dissolve 0.8 g of ammonium nitrate in 300 mL of water, add 700 mL of acetonitrile and mix.

Flow rate: 2 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; estradiol valerate and the internal standard are eluted in this order with the resolution being NLT 3.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio is NMT 1.5%.

Packaging and storage Preserve in light-resistant, tight containers.

Estradiol Valerate Injection
에스트라디올발레레이트 주사액

Estradiol Valerate Injection is an oily preparation for injection, and contains NLT 90.0% and NMT 115.0% of the labeled amount of estradiol valerate ($C_{23}H_{32}O_3$: 356.50).

Method of preparation Prepare as directed under Injections, with Estradiol Valerate.

Description Estradiol Valerate Injection occurs as a pale yellow distillate.

Identification Add 0.5 mL of Estradiol Valerate Injection in a separatory funnel with 10 mL of hexane and 10 mL of 80% methanol, shake for 2 minutes to mix, and allow to stand to separate the layers. To 1 mL of the bottom layer solution, add 1 mL of Folin TS (dilute by adding 2 mL of water to 1 mL of stock solution when using) and 3 mL of sodium carbonate solution (1 in 5); the resulting solution exhibits a blue color.

Purity ***Estradiol*—**Pipet an appropriate amount of Estradiol Valerate Injection according to the labeled amount, and add acetone to obtain a solution containing 30%. To 1.0 mL of this solution, add the oil used in the injection to make exactly 10 mL, and use this solution as the estradiol solution. Perform the test with this solution and estradiol valerate injection as directed under the Thin Layer Chromatography. Spot 5 μL each of these solutions on the plate made of silica gel for thin-layer chromatography. Proceed as directed under Estradiol of Estradiol Valerate (NMT 3.0%).

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Estradiol Valerate Injection equivalent to about 20 mg of estradiol valerate ($C_{23}H_{32}O_3$) according to the labeled amount, wash the pipet with tetrahydrofuran, add 5.0 mL of the internal standard solution, and then add tetrahydrofuran to make exactly 25 mL. Use this solution as the test solution. Separately, weigh accurately about 20 mg of estradiol valerate RS, add 5.0 mL of the internal standard solution, add tetrahydrofuran to make exactly 25 mL, and use this solution as the standard solution. Perform the test as directed in the Assay of Estradiol Valerate.

$$\text{Amount (mg) estradiol valerate } (C_{23}H_{32}O_3) = \text{Amount (mg) of estradiol valerate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Solution of testosterone benzoate in tetrahydrofuran (8 in 1000).

Packaging and storage Preserve in light-resistant, hermetic containers.

Estradiol Valerate Tablets
에스트라디올발레레이트 정

Estradiol Valerate Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of estradiol valerate ($C_{23}H_{32}O_3$: 356.50).

Method of preparation Prepare as directed under Tablets, with Estradiol Valerate.

Identification Weigh an amount of Estradiol Valerate Tablets, equivalent to 10 mg of estradiol valerate, according to the labeled amount, dissolve in 25 mL of 80% methanol, and filter. Use the filtrate as the test solution. Separately, weigh 10 mg of estradiol valerate RS, add 80% methanol to make 25 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of hexane and ethyl acetate (8 : 2) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly the coloring agent (dissolve 20 g of toluenesulfonic acid in ethanol to make 100 mL), and then examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values and the colors of the spots obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Estradiol Valerate Tablets and powder. Weigh accurately an amount equivalent to about 2 mg of estradiol valerate,

add 1 mL of 0.1 mol/L hydrochloric acid, shake to mix, and warm on a steam bath at 50 ℃ for 10 minutes. Then, add 4.0 mL of internal standard solution, warm for 20 minutes, filter, and use the filtrate as the test solution. Separately, weigh accurately about 0.1 g of estradiol valerate RS and add the internal standard solution to make 200 mL. Take 20.0 mL of this solution, add 5.0 mL of 0.1 mol/L hydrochloric acid, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions; determine the peak area ratios, Q_T and Q_S, of estradiol to the peak area of the internal standard, respectively.

$$\text{Amount (mg) of estradiol valerate } (C_{23}H_{32}O_3) = \text{Amount (mg) of estradiol valerate RS} \times \frac{Q_T}{Q_S} \times \frac{1}{50}$$

Internal standard solution—A solution of diflucortolone valerate in methanol (5 in 10000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

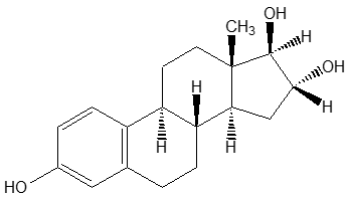
Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 to 10 μm in particle diameter).

Mobile phase: A mixture of methanol and water (725: 275).

Flow rate: 2.0 mL/min

Packaging and storage Preserve in well-closed containers.

Estriol
에스트리올



Estriol $C_{18}H_{24}O_3$: 288.38

(16α,17β)-Estra-1,3,5(10)-triene-3,16,17-triol [*50-27-1*]

Estriol, when dried, contains NLT 97.0% and NMT 102.0% of estriol ($C_{18}H_{24}O_3$).

Description Estriol occurs as a white crystalline powder and is odorless.

It is sparingly soluble in methanol, slightly soluble in ethanol(95) or 1,4-Dioxane and practically insoluble in water or ether.

Identification (1) Dissolve 10 mg of Estriol in 100 mL of ethanol(95) by warming, and use this solution as the test solution. Evaporate 1 mL of this solution on a steam bath to dryness, add 5 mL of a solution of sodium p-phenolsulfonate in phosphoric acid (1 in 50), heat at 150 ℃ for 10 minutes, and cool; the resulting solution exhibits a purple color.

(2) Dissolve 10 mg of Estriol and estriol RS in 100 mL of ethanol(95) by warming, determine the absorption spectra as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Estriol and estriol RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +60° and +65° (after drying, 80 mg, ethanol(99.5), 10 mL, 100 mm).

Melting point Between 281 and 286 ºC.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Estriol according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve about 40 mg of Estriol in 10 mL of ethanol(95) by warming and use this solution as the test solution. Pipet 1 mL of this solution, add ethanol(95) to make 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of chloroform, methanol, acetone, and acetic acid(100) (18 : 1 : 1 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray evenly diluted sulfuric acid (1 in 2) on the plate and heat at 105 ℃ for 15 minutes; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (0.5 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately the average about 25 mg each of Estriol and estriol RS, previously dried, dissolve separately in methanol to make exactly 50 mL. Pipet 10 mL each of these solutions, add exactly 5 ml of the internal standard solution, add methanol to make 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak area of Estriol to that of the internal standard, Q_T and Q_S.

$$\text{Amount (mg) of estriol } (C_{18}H_{24}O_3) = \text{Amount (mg) of estriol RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of methyl benzoate in methanol (1 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of water and methanol (51:49).

Flow rate: Adjust the flow rate so that the retention time of Estriol is about 10 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; estriol and the internal standard are eluted in this order with the resolution being NLT 8.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area ratios of estriol to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Estriol Tablets
에스트리올 정

Estriol Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of estriol ($C_{18}H_{24}O_3$: 288.38).

Method of preparation Prepare as directed under Tablets, with Estriol.

Identification Weigh an amount of Estriol Tablets, previously powdered, equivalent to 2 mg of estriol according to the labeled amount, add 20 mL of ethanol(95), shake to mix for 10 minutes, and centrifuge. Use the clear supernatant as the test solution. Perform the Identification (1) and (2) of Estriol with the test solution.

Dissolution Perform the test with 1 tablet of Estriol Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take NLT 20 mL of the dissolved solution 30 minutes after starting the test, and filter through a membrane filter with a pore size of NMT 0.8 μm. Discard the first 10 mL of the filtrate, pipet V mL of the subsequent filtrate, add water to make exactly V' mL of solution containing about 0.1 μg of estriol ($C_{18}H_{24}O_3$) per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 10 mg of estriol RS, previously dried at 105 ℃ for 3 hours, and dissolve in methanol to make exactly 100 mL. Pipet 5 mL of this solution and add water to make 100 mL. Pipet 2 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 100 μL each of the test solution and the standard solution according to the operating conditions under the Assay of Estriol, and measure the peak areas, A_T and A_S, of estriol, respectively.

It meets the requirements when the dissolution rate of Estriol Tablets in 30 minutes is NLT 80%.

$$\text{Dissolution rate (\%) of the labeled amount of estriol } (C_{18}H_{24}O_3) = W_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times \frac{9}{10}$$

W_S: Amount (mg) of estriol RS

C: Labeled amount (mg) of estriol ($C_{18}H_{24}O_3$) in 1 tablet

Uniformity of dosage units It meets the requirements when the Content uniformity test is performed according to the following procedure. Take 1 tablet of Estriol Tablets, add exactly 5 mL of water, sonicate to disperse, and add exactly 15 mL of methanol. Shake to mix for 15 minutes. Centrifuge this solution for 10 minutes, pipet a certain amount of the clear supernatant, and add methanol to obtain a solution having known concentration of about 5 μg of estriol ($C_{18}H_{24}O_3$) per mL. Pipet 5 mL of this solution, add exactly 1 mL of the internal standard solution, and use this solution as the test solution. Perform the test solution with 20 μL of the test solution under the Assay of Estriol as follow. However, prepare the internal standard solution with a solution of methyl benzoate in methanol (1 in 40000). Measure the average value from the peak area ratios of individual 10 tablets of Estriol Tablets; it meets the requirements when the deviation (%) between the value and the individual peak area ratio is within 15%. Also, perform the test with another 20 tablets of Estriol Tablets when there is 1 tablet with a deviation (%) of more than 15% and less than 25%. Calculate the deviation (%) between the average value of total 30 tablets from the two tests and each peak area ratio; it meets the requirements when there is NMT 1 tablet with a deviation of more than 15% and less than 25%, and there are no tablets with a deviation of more than 25%.

Assay Weigh accurately NLT 20 tablets of Estriol Tablets, and powder. Weigh accurately an amount equivalent to about 1 mg of estriol ($C_{18}H_{24}O_3$), add exactly 5 mL of water, sonicate to disperse, and add 25 mL of methanol. Shake to mix for 10 minutes, centrifuge, and take the clear supernatant. Add 25 mL of methanol, repeat the

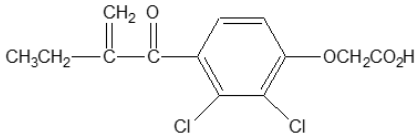
procedure 2 times in the same manner, combine the clear supernatant, and add 5.0 mL of the internal standard solution, and add methanol to make exactly 100 mL. Use this solution as the test solution. Separately, weigh accurately about 25 mg of estriol RS, previously dried at 105 ℃ for 3 hours, and dissolve in methanol to make exactly 100 mL. Pipet 4 mL of this solution, add 5.0 mL of the internal standard solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the test solution and the standard solution under the Assay of Estriol.

$$\text{Amount (mg) of estriol } (C_{18}H_{24}O_3) = \text{Amount (mg) of estriol RS} \times \frac{Q_T}{Q_S} \times \frac{1}{25}$$

Internal standard solution—A solution of methyl benzoate in methanol (1 in 5000).

Packaging and storage Preserve in tight containers.

Etacrynic Acid
에타크린산



Etacrynic Acid $C_{13}H_{12}Cl_2O_4$: 303.14
[2,3-Dichloro-4-(2-methylenebutanoyl)phenoxy]acetic acid [*58-54-8*]

Etacrynic Acid, when dried, contains NLT 98.0 and NMT 101.0% of etacrynic acid ($C_{13}H_{12}Cl_2O_4$).

Description Etacrynic Acid occurs as a white, crystalline powder. It is odorless and has a slightly bitter taste.
It is very soluble in methanol, freely soluble in ethanol(95), acetic acid(100) and ether, and very slightly soluble in water.

Identification (1) Dissolve 0.2 g of Etacrynic Acid in 10 mL of acetic acid(100), and to 5 mL of this solution, add 0.1 mL of bromine TS; the color of the test solution disappears. To the remaining 5 mL of the solution, add 0.1 mL of potassium permanganate TS; the color of the test solution immediately changes to light orange.

(2) Add 1 mL of sodium hydroxide TS to 0.01 g of Etacrynic Acid, and heat on a steam bath for 3 minutes. After cooling, add 1 mL of chromotropic acid TS, and heat on a steam bath for 10 minutes; the solution exhibits an intense purple color.

(3) Determine the absorption spectra of solutions of Etacrynic Acid and etacrynic acid RS in methanol (1 in 20000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Perform the test with Etacrynic Acid as directed under the Flame Coloration (2); it exhibits a green color.

Melting point Between 121 and 125 ºC.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Etacrynic Acid in 10 mL of methanol; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Etacrynic Acid according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Etacrynic Acid according to Method 3 and perform the test. Add 10 mL of a solution of magnesium nitrate hexahydrate in ethanol(95) (1 in 50), then add 1.5 mL of hydrogen peroxide(30), and fire to burn (NMT 2 ppm).

(4) ***Related substances***—Dissolve about 0.20 g of Etacrynic Acid in 10 mL of ethanol(95) and use this solution as the test solution. Pipet 3 mL of this solution, add ethanol(95) to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, ethyl acetate, and acetic acid(100) (6 : 5 : 2) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.25% (1 g, in vacuum, 60 ℃, 2 hours).

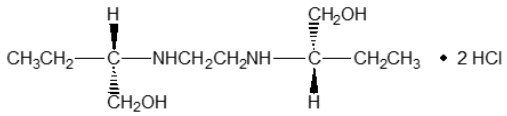
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.1 g of Etacrynic Acid, previously dried, put in an iodine bottle, dissolve in 20 mL of acetic acid(100), and add exactly 20 mL of 0.05 mol/L bromine. To this solution, add 3 mL of hydrochloric acid, stopper tightly at once, shake, and allow to stand in a dark place for 60 minutes. Then, carefully add 50 mL of water and 15 mL of potassium iodide TS, stopper tightly immediately, shake well, and titrate the liberated iodine with 0.1 mol/L sodium thiosulfate VS (indicator: 1 mL of starch TS). Perform a blank test in the same manner and make any necessary correction.

$$\text{Each mL of 0.05 mol/L bromine VS} = 15.157 \text{ mg of } C_{13}H_{12}Cl_2O_4$$

Packaging and storage Preserve in well-closed containers.

Ethambutol Hydrochloride
에탐부톨염산염



$C_{10}H_{24}N_2O_2 \cdot 2HCl$: 277.23

(2*S*,2'*S*)-2,2'-(Ethane-1,2-diyldiimino)dibutan-1-ol dihydrochloride [*1070-11-7*]

Ethambutol Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of ethambutol hydrochloride ($C_{10}H_{24}N_2O_2 \cdot 2HCl$).

Description Ethambutol Hydrochloride occurs as white crystals or a crystalline powder, is odorless and has a bitter taste.
It is very soluble in water, soluble in methanol and in ethanol(95), and practically insoluble in ether.
The pH of a solution of Ethambutol Hydrochloride (1 in 20) in 20 mL of water is between 3.4 and 4.0.

Identification (1) Determine the infrared spectra of Ethambutol Hydrochloride and ethambutol hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Ethambutol Hydrochloride (1 in 30) responds to the Qualitative Analysis for chloride.

Optical rotation $[\alpha]_D^{20}$: Between +5.5 and +6.1° (after drying, 5.0 g, water, 50 mL, 200 mm).

Melting point Between 200 ºC and 204 ºC.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Ethambutol Hydrochloride in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 2.0 g of Ethambutol Hydrochloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Prepare the test solution with 1.0 g of Ethambutol Hydrochloride, according to Method 1 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.10 g of Ethambutol Hydrochloride in 10 mL of methanol and use this solution as the test solution. Separately, dissolve 2 mg of ethambutol hydrochloride RS in 10 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of methanol and ammonia water(28) (18 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray evenly iodine chloroform solution TS for spray on the plate; the spots other than the principal spots from the test solution are not more intense than the spots from the standard solution (2.0%).

(5) ***2-Aminobutanol***—Weigh accurately about 50 mg of Ethambutol Hydrochloride, dissolve in water to make exactly 100 mL and use this solution as the test solution. Separately, dissolve adequate amount of 2-aminobutanol RS, weighed accurately, in water and dilute sequentially to make a solution containing 5 μg per mL and use this solution as the standard solution. Transfer 10 mL of the test solution into a 100-mL Erlenmeyer flask with glass stopper and add 10 mL of water and 20 mL of boric acid buffer solution. Separately, mix 10.0 mL of the test solution, 10.0 mL of the standard solution, and 20 mL of boric acid buffer solution in a 100-mL Erlenmeyer flask. While the contents in two flasks are mixed on shaker, quickly add 10 mL of fluorescamine solution and stopper them and mix briefly. Perform the test after exactly 1 minute with these solutions as directed under the Fluorescence Spectroscopy. Determine the fluorescence intensity at 385 nm of excitation wavelength and 485 nm of emission wavelength: the fluorescence intensity obtained from the test solution is NMT that of the difference between two solutions (NMT 1.0%).

Boric acid buffer solution—Weigh about 1.24 g of boric acid, dissolve in 90 mL of water, adjust with 5 mol/L sodium hydroxide to pH 9.0, and dilute with water to exactly 100 mL and mix.

Fluorescamine solution—Transfer 5 mg of fluorescamine into a cylinder with stopper and scale line, and dissolve in 50 mL of acetone.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Ethambutol Hydrochloride, previously dried, dissolve in 50 mL of water, add 1 mL of 0.1 mol/L hydrochloric acid TS and titrate with 0.1 mol/L sodium hydroxide TS from the first equivalence point to the second equivalence point (potentiometric titration under the Titrimetry).

Each mL of 0.1 mol/L sodium hydroxide VS
= 27.723 mg of $C_{10}H_{24}N_2O_2 \cdot 2HCl$

Packaging and storage Preserve in tight containers.

Ethambutol Hydrochloride Tablets
에탐부톨염산염 정

Ethambutol Hydrochloride Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of eth-

ambutol hydrochloride ($C_{10}H_{24}N_2O_2 \cdot 2HCl$: 277.23).

Method of preparation Prepare as directed under Tablets, with Ethambutol Hydrochloride.

Identification (1) Weigh an amount of Ethambutol Hydrochloride Tablets, previously powdered, equivalent to 0.1 g of ethambutol hydrochloride, according to the labeled amount, add 3 mL of methanol, transfer into a glass mortar, and stir to mix. Again, add 5 mL of methanol make a suspension, and filter through a filter paper, previously moistened with methanol. Transfer the filtrate to a beaker containing 100 mL of acetone, stir to mix, allow to stand for 15 minutes, and extract crystals. Discard the clear supernatant by inclining the container, and air-dry the crystals until there is no methanol odor. Determine the infrared spectra of these crystals and ethambutol hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit maxima at the same wavenumber.

(2) An aqueous solution of the crystals (1 in 10), obtained from (1), responds to the Qualitative Analysis for chloride.

Purity ***2-Aminobutanol***—Take an appropriate number of tablets, equivalent to 400 mg of ethambutol hydrochloride, transfer in a beaker, add acetone until the tablets are submerged, and allow to stand for 15 minutes. Discard the acetone, then dry, powder the tablet with the coating removed, and add methanol, shake to mix, make exactly 100 mL, and filter. Pipet 25 mL of the filtrate, and dilute with water to make exactly 200 mL. Allow to stand for 15 minutes, filter through a dried filter paper, discard the first turbid filtrate, and use the subsequent filtrate as the test solution. Proceed with this solution under the Purity (5) of Ethambutol Hydrochloride.

Dissolution Perform the test with 1 tablet of Ethambutol Hydrochloride Tablets at 100 revolutions per minute according to Method 1 under the Dissolution, using 900 mL of water as the dissolution medium. Take the dissolved solution 45 minutes after starting the test, filter, and use the filtrate as the test solution. Separately, weigh an appropriate amount of ethambutol hydrochloride RS, previously dried at 105 ℃ for 2 hours, dissolve in water to make a solution containing 0.1 mg per mL, and use this solution as the standard solution. Transfer 1 mL each of the test solution, the standard solution and water to 3 glass-stoppered centrifuge tubes, add 5.0 mL of bromocresol green solution and 10.0 mL of chloroform, respectively, close with the stoppers, and shake vigorously to mix. Allow to stand until the chloroform layer separates, discard the supernatant water layer, and filter the chloroform layer through cotton. Perform the test with these solutions as directed under the Ultraviolet-visible Spectroscopy, and measure the absorbance at the absorbance maximum wavelength at about 415 nm.

The acceptable dissolution criterion of Ethambutol Hydrochloride Tablets is NLT 75% (Q) dissolved in 45 minutes.

Phosphate buffer solution—Dissolve 38.0 g of sodium dihydrogen phosphate dihydrate and 2.0 g of anhydrous sodium dihydrogen phosphate in water to make 1000 mL.

Bromocresol green solution—Weigh 0.2 g of bromocresol green, dissolve in 30 mL of water and 6.5 mL of 0.1 mol/L sodium hydroxide, add phosphate buffer solution to make 500 mL, and mix. Then, add 0.1 mol/L hydrochloric acid to adjust the pH to 4.6 ± 0.1.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately NLT 20 tablets of Ethambutol Hydrochloride Tablets, and powder. Weigh accurately about 30 mg of ethambutol hydrochloride ($C_{10}H_{24}N_2O_2 \cdot 2HCl$), dissolve in water by shaking to mix, then add water to make exactly 100 mL, and filter. Discard the first 10 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately about 30 mg of ethambutol hydrochloride RS, dissolve in water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and measure the peak areas, A_T and A_S, of ethambutol hydrochloride in each solution.

$$\text{Amount (mg) of ethambutol hydrochloride } (C_{10}H_{24}N_2O_2 \cdot 2HCl) = \text{Amount (mg) of ethambutol hydrochloride RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 200 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with nitrile silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of a solution, obtained by mixing 1.0 mL of triethylamine and 1000 mL of water to adjust the pH to 7.0 with phosphoric acid, and acetonitrile (1 : 1).

Flow rate: 1.0 mL/min

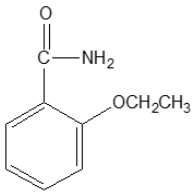
System suitability

System performance: Proceed with 50 μL of the standard solution according to the conditions above; the symmetry factor is NMT 2.0.

System repeatability: Repeat the test 6 times with 50 μL each of the standard solution according to the conditions above; the relative standard deviation of the peak areas of ethambutol hydrochloride is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Ethenzamide
에텐자미드



2-Ethoxybenzamide $C_9H_{11}NO_2$: 165.19
2-Ethoxybenzamide [*938-73-8*]

Ethenzamide, when dried, contains NLT 98.0% and NMT 101% of ethenzamide ($C_9H_{11}NO_2$).

Description Ethenzamide occurs as white crystals or a crystalline powder.
It is soluble in methanol, ethanol(95) or acetone and practically insoluble in water.
It begins to sublime slightly at about 105 ℃.

Identification (1) Take 0.5 g of Ethenzamide, add 5 mL of sodium hydroxide TS and heat the mixture gently; the gas produced turns moistened red litmus paper to blue.

(2) Take 0.2 g of Ethenzamide, add 10 mL of hydrobromic acid and boil the mixture gently for 1 hour under a reflux condenser. Cool in ice-water, filter and collect the separated crystalline precipitate, wash 3 times with 5 mL each of ice-water and dry in a desiccator (in vacuum, silica gel) for 2 hours; the precipitate melts between 158 ºC and 161 ºC.

(3) Determine the absorption spectra of solutions of Ethenzamide and ethenzamide RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared spectra of Ethenzamide and ethenzamide RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 131 and 134 ℃.

Purity (1) ***Chloride***—Dissolve 0.5 g of Ethenzamide in 30 mL of acetone, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.7 mL of 0.01 mol/L hydrochloric acid, 30 mL of acetone, 6 mL of dilute nitric acid and water to make 50 mL (NMT 0.050%).

(2) ***Sulfate***—Dissolve 0.5 g of Ethenzamide in 30 mL of acetone and add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid, add 30 mL of acetone, 1 mL of dilute hydrochloric acid and water to 50 mL (NMT 0.048%).

(3) ***Heavy metals***—Proceed with 2.0 g of Ethenzamide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Take 0.40 g of Ethenzamide, add 0.3 g of potassium nitrate and 0.5 g of anhydrous sodium carbonate, mix thoroughly, ignite the mixture gradually. After cooling, dissolve the residue in 10 mL of dilute sulfuric acid and heat the solution until white fumes are produced. After cooling, add water carefully to make 5 mL. Use this solution as the test solution (NMT 5 ppm).

(5) ***Salicylamide***—Dissolve 0.20 g of Ethenzamide in 15 mL of dilute ethanol (2 in 3) and add 2 to 3 drops of dilute iron(III) chloride TS; the resulting solution does not exhibit a purple color.

Loss on drying NMT 1.0% (1 g, silica gel, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 20 mg each of Ethenzamide and ethenzamide RS, previously dried, and dissolve each in 70 mL of ethanol(95) by warming. After cooling, add ethanol(95) to make exactly 100 mL. Pipet 5.0 mL each of these solutions, add ethanol(95) to make exactly 50 mL and use these solutions as the test solution and the standard solution, respectively. Determine the absorbances, A_T and A_S of the test solution and the standard solution, respectively, at 290 nm as directed under the Ultraviolet-visible Spectroscopy, using ethanol(95) as the blank.

$$\text{Amount (mg) of ethenzamide } (C_9H_{11}NO_2) = \text{Amount (mg) of ethenzamide RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in well-closed containers.

Anesthetic Ether
마취용 에테르

$CH_3CH_2OCH_2CH_3$

$C_4H_{10}O$: 74.12
Ethoxyethane [*60-29-7*]

Anesthetic Ether contains NLT 96.0% and NMT 98.0% (by specific gravity) of ether ($C_4H_{10}O$).

Anesthetic Ether contains small quantities of ethanol(95) and water, and suitable stabilizers may be added.

Anesthetic Ether is not to be used for anesthesia if it has been removed from the original container for more than 24 hours.

Description Anesthetic Ether occurs as a colorless, clear, mobile liquid, and has a characteristic odor.

It is miscible with ethanol(95).
It is soluble in water.
It is highly volatile and flammable.
It is slowly oxidized by the action of air and light, producing peroxides.
The vapor of Anesthetic Ether, when mixed with air and ignited, may explode violently.

Boiling point—Between 35 and 37 ℃.

Specific gravity d_{20}^{20}: Between 0.718 and 0.721.

Purity (1) ***Characteristic odor***—Put 10 mL of Anesthetic Ether in an evaporating dish and allow it to evaporate spontaneously to a volume of 1 mL; no characteristic odor is perceptible. Pour the remaining solution onto a piece of clean, odorless filter paper to evaporate ether; no characteristic odor is perceptible.

(2) ***Acid***—Put 10 mL of diluted ethanol(4 in 5) and 0.5 mL of phenolphthalein TS in a glass-stoppered flask and add 0.02 mol/L sodium hydroxide VS dropwise to produce a red color which persists for 30 seconds after mixing by shaking. To this solution, add 25 mL of Anesthetic Ether, stopper the flask, shake gently, and add 0.40 mL of 0.02 mol/L sodium hydroxide VS while mixing by shaking; a red color develops.

(3) ***Aldehyde***—To 100 mL of water in a glass-stoppered flask, add 10 mL of Anesthetic Ether and 1 mL of a solution of sodium bisulfite (1 in 1000), stopper tightly, shake vigorously for 10 seconds, and allow the mixture to stand in a cool place for 30 minutes, protected from light. Then, add 2 mL of starch TS and add 0.01 mol/L iodine VS dropwise until a pale blue color appears. To this solution, add about 2 g of sodium bicarbonate, shake to mix until the blue color disappears, and add 1 mL of diluted 0.01 mol/L iodine VS (9 in 40); the solution turns blue. Keep the temperature of the solution below 18 ºC during the procedure.

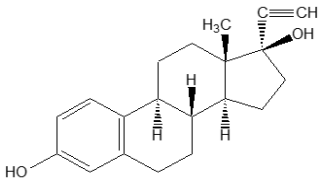
(4) ***Peroxide***—Put 10 mL of Anesthetic Ether in a Nessler tube, add 1 mL of a freshly prepared solution of potassium iodide (1 in 10), allow to stand for 1 hour while shaking occasionally and protecting from light, then add 1 mL of starch TS, and shake well to mix; no color is produced in the aqueous layer and in the ether layer.

(5) ***Residue on evaporation***—Evaporate 50 mL of Anesthetic Ether and dry the residue at 105 ºC for 1 hour; the weight of the residue is NMT 1.0 mg.

Water NMT 0.2% (0.1 g, volumetric titration, direct titration).

Packaging and storage Preserve in light-resistant, tight containers at a temperature not exceeding 25 ºC, without filling up and protected from fire.

Ethinylestradiol
에티닐에스트라디올



$C_{20}H_{24}O_2$: 296.40
19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol [*57-63-6*]

Ethinylestradiol, when dried, contains NLT 98.0% and NMT 101.0% of ethinylestradiol ($C_{20}H_{24}O_2$).

Description Ethinylestradiol occurs as white or pale yellow crystals or a crystalline powder and is odorless.
It is freely soluble in pyridine and tetrahydrofuran, soluble in ethanol(95) and ether, and practically insoluble in water.
It dissolves in sodium hydroxide TS.

Identification (1) Dissolve 2 mg of Ethinylestradiol in 1 mL of a mixture of sulfuric acid and ethanol(95) (1 : 1); the solution exhibits a purplish red color with yellowish green fluorescence. Carefully add 2 mL of water to this solution; the color of the solution changes to reddish purple.

(2) Transfer 20 mg of Ethinylestradiol to a glass stoppered test tube, dissolve in 10 mL of a solution of potassium hydroxide (1 in 20), add 0.1 g of benzoyl chloride, and shake. Collect the resulting precipitate by filtering. Recrystallize from methanol, and dry in a desiccator (in vacuum, phosphorus (V) pentoxide); the precipitate melts between 200 and 202 ℃.

Optical rotation $[\alpha]_D^{20}$: Between -26° and -31° (after drying, 0.1 g, pyridine, 25 mL, 100 mm).

Melting point Between 180 and 186 ℃ or 142 and 146 ℃.

Purity ***Estrone***—Dissolve 5 mg of Ethinylestradiol in 0.5 mL of ethanol(95), and add 50 mg of m-dinitrobenzene. Add 0.5 mL of freshly prepared dilute potassium hydroxide-ethanol TS, allow to stand in a dark place for 1 hour, and add 10 mL of ethanol(95); the color of the solution is no more intense than that of the following control solution.

Control solution—Proceed in the same manner in the preparation of the test solution, omitting Ethinylestradiol.

Loss on drying NMT 0.5% (0.5 g, in vacuum, phosphorus pentoxide, 4 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately about 0.2 g of Ethinylestradiol, previously dried, dissolve in 40 mL of tetrahydrofuran, add 10 mL of a solution of silver nitrate (1 in 20) and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner, and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 29.640 mg of $C_{20}H_{24}O_2$

Packaging and storage Preserve in light-resistant, tight containers.

Ethinylestradiol Tablets
에티닐에스트라디올 정

Ethinylestradiol Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of ethinylestradiol ($C_{20}H_{24}O_2$: 296.40).

Method of preparation Prepare as directed under Tablets, with Ethinylestradiol.

Identification (1) Evaporate 5 mL of the test solution from the Assay to dryness, and dissolve the residue in 2 mL of a mixture of sulfuric acid and ethanol (2 : 1); the resulting solution exhibits a pale red color and a yellow fluorescence. Add carefully 4 mL of water to this solution; the color of the solution changes to purple.

(2) Evaporate 10 mL of the test solution from the Assay to dryness, add 0.2 mL of acetic acid(31) and 2 mL of phosphoric acid to the residue, and heat on a steam bath for 5 minutes; the resulting solution exhibits a red color and a yellowish green fluorescence.

Disintegration Meets the requirements.

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following procedure.

Transfer 1 tablet of Ethinylestradiol Tablets into a separatory funnel, add 10 mL of Solution 2 from the Disintegration, and shake to mix until disintegration. Add 10 mL of dilute sulfuric acid and 20 mL of chloroform, shake vigorously for 5 minutes to mix, and filter the chloroform layer through a filter paper containing 5 g of anhydrous sodium sulfate into an Erlenmeyer flask. Extract the water layer twice with 20 mL each of chloroform, proceed in the same manner, and combine with the previous filtrate. Evaporate gently on a steam bath while passing through nitrogen, add exactly 100 mL of methanol to the residue, dissolve, and centrifuge, if necessary. Pipet χ mL of the supernatant clear liquid, add methanol to obtain exactly V mL of a solution containing about 0.04 μg of ethinylestradiol ($C_{20}H_{24}O_2$) per mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of ethinylestradiol RS, previously dried in a desiccator (in vacuum, phosphorus pentoxide) for 4 hours, dissolve in methanol to obtain a solution containing about 0.04 μg of ethinylestradiol ($C_{20}H_{24}O_2$) per mL, and use this solution as the standard solution. To the glass-stoppered test tubes T, S and B, put exactly 4 mL of sulfuric acid-methanol TS, respectively, cool with ice, add exactly 1 mL each of the test solution, the standard solution and methanol, and shake immediately. Allow to stand on a steam bath at 30 ℃ for 40 minutes, and then allow to stand on a steam bath at 20 ℃ for 5 minutes. Perform the test with these solutions as directed under the Fluorescence Spectroscopy. Determine the fluorescence intensity, F_T, F_S, and F_B at an excitation wavelength of 460 mm and a fluorescence wavelength of 493 mm.

$$\text{Amount (mg) ethinylestradiol } (C_{20}H_{24}O_2) = \text{Amount (mg) of ethinylestradiol RS} \times \frac{F_T - F_B}{F_S - F_B} \times \frac{V}{2500} \times \frac{1}{x}$$

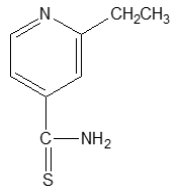
Assay Weigh accurately the mass of NLT 20 tablets of Ethinylestradiol Tablets, and powder. Weigh accurately an amount equivalent to about 0.5 mg of ethinylestradiol ($C_{20}H_{24}O_2$), transfer into a 50-mL beaker, add 2 mL of water, and shake well to mix. Then add 3 mL of chloroform and shake well to mix. Add 4 g of diatomaceous earth for chromatography, mix well until the contents do not adhere to the wall, and use this as the sample. Add 5 g of diatomaceous earth for chromatography, previously weighed, to a 200-mL beaker, put 4 mL of 1 mol/L hydrochloric acid TS to mix thoroughly. Prepare a column for chromatography about 25 mm in internal diameter and about 30 cm in length with a glass wool at the bottom and 5 g of anhydrous sodium sulfate on top. Put the well-mixed solution to the column by pressing appropriately with a glass rod to fill the column homogeneously until the layer reaches 60 to 80 mm. Use this as the chromatographic column. Add the sample, using a funnel, and pack appropriately and tightly. Add 0.5 g of diatomaceous earth for chromatography to the sample sticking to the beaker, mix well, and transfer to the column. Again, wash the sample sticking to the beaker and the glass rod with glass wool, transfer to the column along with the glass wool, and press gently with a glass rod to make the height of the column to 110 - 130 mm. Next, take 70 mL of chloroform, and wash the inner wall of the column for chromatography. Collect the eluate at a rate of NMT 0.8 mL per minute for 1 minute. After the elution is complete, wash the bottom of the column with a small amount of chloroform, combine the washings with the eluate, add chloroform to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of ethinylestradiol RS, previously dried in a desiccator (in vacuum, phosphorus pentoxide) for 4 hours, and dissolve in chloroform to make exactly 100 mL. Pipet 5 mL of this solution, add chloroform to make 100 mL, and use this solution as the standard solu-

tion. Pipet 6 mL each of the test solution, the standard solution and chloroform, transfer into a separatory funnel, and add 20 mL of isooctane. Then, add 10 mL of a mixture of sulfuric acid and methanol (7 : 3), shake vigorously for 5 minutes, allow to stand in the dark for 15 minutes, and centrifuge. Perform the test with the obtained coloring solution as directed under the Ultraviolet-visible Spectroscopy using a solution, proceeded with 6 mL of chloroform in the same manner, as the control solution. Determine the absorbances of each solution, A_T and A_S, obtained from the test solution and the standard solution, at a wavelength of 540 nm.

$$\text{Amount (mg) ethinylestradiol } (C_{20}H_{24}O_2) = \text{Amount (mg) of ethinylestradiol RS} \times \frac{A_T}{A_S} \times \frac{1}{20}$$

Packaging and storage Preserve in tight containers.

Ethionamide
에티온아미드



$C_8H_{10}N_2S$: 166.24

2-Ethylpyridine-4-carbothioamide [*536-33-4*]

Ethionamide, when dried, contains NLT 98.5% and NMT 101.0% of ethionamide ($C_8H_{10}N_2S$).

Description Ethionamide occurs as yellow crystals or a crystalline powder and has a characteristic odor and taste. It is soluble in methanol and in acetic acid(100), sparingly soluble in ethanol(95), slightly soluble in ether, and practically insoluble in water.

Identification (1) Determine the absorption spectra of Ethionamide and ethionamide RS in methanol (3 in 160000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Ethionamide and ethionamide RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 161 ºC and 165 ºC.

Purity (1) ***Acidity***—Dissolve 3.0 g of Ethionamide in 30 mL of methanol by warming, add 90 mL of water, allow to stand in iced water for 1 hour, and filter. To 80 mL of the filtrate, add 0.8 mL of cresol red TS and 0.20 mL of 0.1 mol/L sodium hydroxide VS; the resulting solution exhibits a red color.

(2) ***Heavy metals*—**Proceed with 1.0 g of Ethionamide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Ethionamide according to Method 3 and perform the test. Add 10 mL of a solution of magnesium nitrate hexahydrate in ethanol(95) (1 in 50), then add 1.5 mL of hydrogen peroxide(30), and fire to burn (NMT 2 ppm).

(4) ***Selenium***—Weigh about 0.2 g of Ethionamide and combust as directed under the Oxygen Flask Combustion with 25 mL of diluted nitric acid (1 in 30) as an absorbent. Use a combustion flask with a volume of 1000 mL, combust, wash the stopper and the inner wall of the flask with 10 mL of water, and use 20 mL of water to move the solution in the combustion flask into a 150-mL beaker. Heat lightly until it boils, boil for 10 minutes, allow it to cool down to room temperature, and use this solution as the test solution. Separately, pipet 6.0 mL of standard selenium stock solution, add 25 mL of diluted nitric acid (1 in 30) and 25 mL of water, and use this solution as the standard solution. Add diluted ammonia water(28) (1 in 2) to each of the test and standard solutions, adjust the pH to 2.0, add water to dilute to 60 mL, and add 10 mL of water to move to a separatory funnel. Then, wash the separatory funnel with 10 mL of water. Add 0.2 g of hydroxylamine hydrochloride, dissolve by mixing, add 5.0 mL of 2,3-diaminonaphthalene TS, and close the stopper. Mix by stirring and allow to stand at room temperature for 100 minutes. Add 5.0 mL of cyclohexane, shake well, and allow to stand. If the layer is separated, remove the water layer, centrifuge cyclohexane extract, remove water, and take the cyclohexane layer. With these solutions and a control solution prepared with water added to 25 mL of diluted nitric acid (1 in 30) in the same way, perform the test as directed under the Ultraviolet-visible Spectroscopy. Determine the absorption at the absorption maximum wavelength around 380 nm; the absorption of the solution from the test solution is not greater than the absorption from the standard solution (NMT 30 ppm).

(5) ***Related substances*—**Perform the test without exposure to daylight using light-resistant vessels. Dissolve 0.20 g of Ethionamide in 10 mL of methanol, and use this solution as the test solution. Pipet 0.5 mL of this solution, add acetone to make exactly 100 mL, and use this solution as the standard solution (1). Pipet 0.2 mL of the test solution, add acetone to make exactly 100 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 µL each of the test solution, the standard solution (1) and (2) on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, hexane, and methanol (6 : 2 : 1) to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm);

the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution (1). The number of the spots other than the principal spot from the test solution which is more intense than the spot from the standard solution (2) is NMT one.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

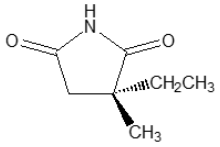
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Ethionamide, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 mL of p-naphtholbenzein TS). The endpoint of titration is when the color of the solution changes from orange-red to dark orange-brown. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 16.624 mg of $C_8H_{10}N_2O$

Packaging and storage Preserve in light-resistant, well-closed containers.

Ethosuximid
에토숙시미드



and enantiomer

$C_7H_{11}NO_2$: 141.17
3-Ethyl-3-methylpyrrolidine-2,5-dione [*77-67-8*]

Ethosuximid contains NLT 98.5% and NMT 101.0% of Ethosuximid ($C_7H_{11}NO_2$), calculated on the anhydrous basis.

Description Ethosuximid occurs as a white, paraffin-like solid or a powder. It is odorless or has a slight, characteristic odor.
It is very soluble in methanol, ethanol(95), ether and *N*,*N*-dimethylformamide, and freely soluble in water.

Melting point—About 48 °C.

Identification (1) Add 10 mL of sodium hydroxide TS to about 0.2 g of Ethosuximid, and boil; the gas produced turns a moistened red litmus paper blue

(2) Dissolve 50 mg of Ethosuximide in 1 mL of ethanol(95), add 3 drops of a solution of cupric acetate (1 in 100), warm slightly, and add 1 to 2 drops of sodium hydroxide TS; the resulting solution exhibits a purple color.

(3) Determine the absorption spectra of ethanol(95) solutions of Ethosuximide and ethosuximide RS (1 in 2000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Ethosuximide in 10 mL of water; the solution is clear and colorless.

(2) ***Chloride***—Perform the test with about 1.0 g of Ethosuximide. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.011%).

(3) ***Heavy metals—***Proceed with about 1.0 g of Ethosuximide according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic***—Prepare the test solution with about 1.0 g of Ethosuximide according to Method 1 and perform the test (NMT 2 ppm).

(5) ***Acid anhydride***—Dissolve about 0.50 g of Ethosuximide in 1 mL of ethanol(95), add 1 mL of hydroxylamine hydrochloride-iron(III) chloride TS, and allow to stand for 5 minutes. Add 3 mL of water and mix. Allow to stand for 5 minutes; the red to reddish purple color of this solution is not more intense than that of the following control solution.

Control solution—Dissolve 70 mg of succinic anhydride in ethanol(95) to make exactly 100 mL. To 1.0 mL of this solution, add 1 mL of hydroxylamine hydrochloride-iron(III) chloride TS and proceed in the same manner.

(6) ***Cyanide***—Dissolve 1.0 g of Ethosuximide in 10 mL of ethanol(95), and add 3 drops of iron(II) sulfate TS, 1 mL of sodium hydroxide TS and 2 to 3 drops of iron(III) chloride TS. Warm gently, and acidify with dilute sulfuric acid; no blue precipitates are formed and a blue color is not exhibited within 15 minutes.

(7) ***Related substances***—Weigh accurately 1.0 g of Ethosuximide, dissolve in the mobile phase to make 10 mL, and use this solution as the test solution. Separately, weigh accurately 10.0 mg each of ethosuximide RS and 2-ethyl-2-methylsuccinic acid, add the mobile phase to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions; the amount of 2-ethyl-2-methylsuccinic acid by equation (1) is NMT 0.1%. Calculate the amount of each related substance by equation (2): NMT 0.1%, and the total amount of related substances is NMT 0.5%.

Content (%) of 2-ethyl-2-methylsuccinic acid
$$= \frac{C}{W} \times \frac{A_T}{A_S} (1)$$

C: Concentration (mg/mL) of 2-ethyl-2-methylsuccinic acid in the standard solution
W: Amount of Ethosuximide taken (g)
A_T: Peak area of 2-ethyl-2-methylsuccinic acid ob-

tained from the test solution

A_S: Peak area of 2-ethyl-2-methylsuccinic acid obtained from the standard solution

$$\text{Content (\%) of related substances} = \frac{C}{W} \times \frac{A_i}{A_S} \quad (2)$$

C: Concentration of Ethosuximide in the standard solution (mg/mL)

W: Amount of Ethosuximide taken (g)

A_i: Peak area of each related substance obtained from the test solution

A_S: Peak area of Ethosuximide obtained from the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography.

Mobile phase: A mixture of pH 3.0 phosphate buffer solution and acetonitrile (9 : 1).

Flow rate: 1 mL/min

System suitability

System performance: Weigh accurately a suitable amount each of 2-ethyl-2-methylsuccinic acid and ethosuximide RS, dissolve in the mobile phase to obtain a solution containing 2 mg of 2-ethyl-2-methylsuccinic acid and 10 mg of ethosuximide per mL, and use this solution as the system suitability solution. Proceed with 10 μL of this solution under the above operating conditions; the resolution between the peaks of 2-ethyl-2-methylsuccinic acid and ethosuximide is NLT 6.6, the number of theoretical plates is NLT 2900, and the symmetry factor of the peak of ethosuximide is NMT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the system suitability solution under the above operating conditions; the relative standard deviation of the peak areas of ethosuximide and 2-ethyl-2-methylsuccinic acid is NMT 0.4%, respectively.

Phosphate buffer solution, pH 3.0—To 4.1 mL of phosphoric acid add water to make 1000 mL. To this solution, add sodium hydroxide TS to adjust the pH to 3.0.

Water NMT 0.5% (2 g, volumetric titration, direct titration).

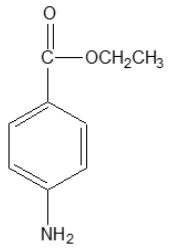
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Ethosuximide, previously dried, dissolve in 20 mL of *N,N*-Dimethylformamide, and titrate with 0.1 mol/L tetramethylammonium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L tetramethylammonium hydroxide VS
= 14.117 mg of $C_7H_{11}NO_2$

Packaging and storage Preserve in tight containers.

Ethyl Aminobenzoate
아미노벤조산에틸



Benzocaine
Anestesine $C_9H_{11}NO_2$:165.19
Ethyl 4-aminobenzoate [*94-09-7*]

Ethyl Aminobenzoate, when dried, contains NLT 99.0% and NMT 101.0% of ethyl aminobenzoate ($C_9H_{11}NO_2$).

Description Ethyl Aminobenzoate occurs as white crystals or a crystalline powder. It is odorless and has a slightly bitter taste, numbing the tongue.
It is freely soluble in ethanol(95) or in ether and very slightly soluble in water.
It dissolves in dilute hydrochloric acid.

Identification (1) Dissolve 10 mg of Ethyl Aminobenzoate in 1 mL of dilute hydrochloric acid and 4 mL of water; the resulting solution responds to the Qualitative Analysis for primary aromatic amines.

(2) Dissolve 0.1 g of Ethyl Aminobenzoate in 5 mL of water with the aid of dilute hydrochloric acid added dropwise and add iodine TS dropwise; a brown precipitate is formed.

(3) Warm 50 mg of Ethyl Aminobenzoate with 2 drops of acetic acid(31) and 5 drops of sulfuric acid; the characteristic odor of ethyl acetate comes out.

Melting point Between 89 and 91 ℃.

Purity (1) ***Acid***—Dissolve about 1.0 g of Ethyl Aminobenzoate in 10 mL of neutralized ethanol and add 10 mL of water, 2 drops of phenolphthalein TS and 0.50 mL of 0.01 mol/L sodium hydroxide solution; the resulting solution exhibits a red color.

(2) ***Chloride***—Dissolve 0.20 g of Ethyl Aminobenzoate in ethanol(95) and add 2 to 3 drops each of dilute nitric acid and silver nitrate TS; there is no immediate change in the solution.

(3) ***Heavy metals***—Dissolve 2.0 g of Ethyl Aminobenzoate in 20 mL of ethanol(95) and add 2 mL of dilute

acetic acid and ethanol(95) to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution as follows: to 2.0 mL of lead standard solution, add 2 mL of dilute acetic acid and ethanol(95) to make 50 mL (NMT 10 ppm).

(4) ***Readily carbonizable substances***—Perform the test with 0.5 g of Ethyl Aminobenzoate. The color of this solution is not more intense than that of the matching fluid A.

Loss on drying NMT 1.0% (1 g, silica gel, 3 hours).

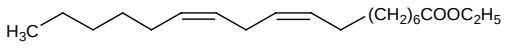
Residue on ignition NMT 0.1% (1 g).

Assay Weight accurately about 0.25 g of Ethyl Aminobenzoate, previously dried, dissolved in 10 mL of hydrochloric acid and 70 mL of water, add 10 mL of a solution of potassium bromide (3 in 10), and cool down to a temperature below 15 ºC. Then, titrate with 0.1 mol/L sodium nitrite VS. (potentiometric titration or amperometric titration under the Titrimetry).

Each mL of 0.1 mol/L sodium nitrite VS
= 16.519 mg of $C_9H_{11}NO_2$

Packaging and storage Preserve in well-closed containers.

Ethyl Linoleate
리놀레산에틸



Ethyl Linoleate $C_{20}H_{36}O_2$: 308.50
Ethyl (9*Z*,12*Z*)-9,12-octadecadienoic acid ester, [*544-35-4*]

Ethyl Linoleate contains NLT 88.0% and NMT 101.0% of ethyl linoleate ($C_{20}H_{36}O_2$: 308.50).

Description Ethyl Linoleate occurs as a colorless to pale yellow and clear liquid. It has a slightly characteristic odor.
It is soluble in methanol, ethanol, ether, chloroform or petroleum ether.

Identification To about 4 g of Ethyl Linoleate, add 20 mL of potassium hydroxide-ethanol TS, and heat on a steam bath with a reflux condenser attached for 30 minutes. After cooling, add dilute hydrochloric acid to make the solution acidic. Transfer it to a separatory funnel, take the separated oil layer, wash with 2 mL of water, and add 10 mL of ligroin for mixing. To this solution, add 3 g of anhydrous sodium sulfate, allow the solution to stand for 10 minutes, and filter. Well shake and maintain the filtrate at between 10 and 15 ℃, add 1 mL of bromine, and allow it to stand for 30 minutes with occasional shaking. Take the produced precipitate, wash with 3 mL of ligroin 3 times for recrystallization, dry in a desiccator, and determine the melting point of the dried material. The melting point is between 113 and 117 ℃.

Specific gravity d_{20}^{20}: Between 0.875 and 0.885.

Refractive index $[\alpha]_D^{20}$: Between 1.455 and 1.465.

Saponification value Between 180 and 185.

Acid value NMT 15.

Iodine value Between 150 and 163 (when the test is performed with 0.15 g of Ethyl Linoleate).

Purity (1) ***Chloride***—To 1.0 g of Ethyl Linoleate, add Ethanol to make 50 mL, and add 1 mL of silver nitrate-ethanol solution (1 in 50). The turbidity of the solution is not greater than the following control solution. Control solution: To 0.40 mL of 0.01 mol/L Hydrochloric Acid, add Ethanol to make 50 mL and add 1 mL of silver nitrate-ethanol solution (1 in 50).

(2) ***Heavy metals***—Dissolve 1.0 g of Ethyl Linoleate in ethanol, add 2 mL of dilute acetic acid and ethanol to make 50 mL. Use this solution as the test solution and perform the test with this solution. Prepare the control solution by adding 2 mL of dilute acetic acid and 2.0 mL of lead standard solution as well as ethanol to make 50 mL (NMT 20 ppm).

(3) ***Arsenic***—To 1.0 g of Ethyl Linoleate, add 10 mL of diluted hydrochloric acid (1 in 2) and 20 mL of ether, shake vigorously for 3 minutes to mix, allow to stand, and perform the test with this solution (NMT 2 ppm).

(4) ***Peroxide***—Put 10.0 mL of chloroform in a 250 mL stoppered flask and replace the air in the flask with dry carbon dioxide. Weigh accurately 1 g of Ethyl Linoleate and put it in a glass cup. Put the glass cup in the flask and slowly shake to mix and dissolve. To this, add 15.0 mL of acetic acid(100) and 1.0 mL of saturated potassium iodide solution, stopper the flask, shake well for 1 minute to mix, and allow to stand in the dark for 5 minutes. Add 75 mL of water, stopper the flask, shake vigorously to mix, and allow to stand in the dark for 5 minutes. Then, add 75 mL of water, stopper the flask, shake vigorously to mix, and titrate with 0.01 mol/L sodium thiosulfate VS (indicator: starch TS). Perform a blank test in the same manner and make any necessary correction.

$$\text{Peroxide value} = \frac{(A - B)}{\text{Amount (g) of sample}} \times 10$$

A: Consumed amount (mL) of 0.01 mol/L sodium thiosulfate VS used for the sample

B: Consumed amount (mL) of 0.01 mol/L sodium thiosulfate VS used for the blank test

The peroxide value is NMT 20.

Residue on ignition NMT 0.1% (1 g). Put 1 g of Ethyl Linoleate in a crucible, previously weighed accurately its mass, and weigh accurately the mass. Heat with weak flame to boil, stop heating once boiling starts, and directly fire to burn. After cooling, wet the residue with 1 or 2 drops of sulfuric acid, carefully ignite to a constant mass, and weigh the mass of the residue.

Assay Weigh accurately about 60 mg of Ethyl Linoleate and put it in a glass cup. Heat potassium hydroxide-glycerin solution at 100 ℃ and put 10 mL each of this solution to 3 stoppered test tubes (A, B and C). Place a thermometer in the stoppered test tube C. Put the 3 stoppered test tubes in a 180 ± 3 ℃ oil bath and heat until the thermometer in the stoppered test tube C indicates 180 ℃. Then, blow nitrogen gas into the stoppered test tubes A and B. Take the stoppered test tubes from the oil bath. Place the glass cup containing the sample in the stoppered tube A, place an empty glass cup in the stoppered test tube B, shake vigorously the 3 stoppered test tubes for 2 minutes, and place the 3 stoppered test tubes in the oil bath. When the temperature of the stoppered test tube reaches 175 ℃, heat for exactly 45 minutes. For at least 30 minutes of this period, take care to maintain 180 ℃. Take out the stoppered test tubes A and B from the oil bath and cool them down to 60 ℃. Wash them with hot methanol, place each in a 100-mL volumetric flask, cool, and add methanol to make 100.0 mL each. To 10.0 mL each of the solutions, add methanol to make 100.0 mL each, and use each of the resulting solutions as the solution A and solution B, respectively. Perform the test with the solution A, using the solution B for comparison, as directed under the Ultraviolet-visible Spectroscopy and determine the absorbance at the wavelength 268 nm, A_{268}. Additionally, to 10.0 mL each of the solutions A and B, add methanol to make 100 mL each, and use these solutions as the solution A' and solution B', respectively. Perform the test with the solution A', using the solution B' for comparison, as directed under the Ultraviolet-visible Spectroscopy and determine the absorbance at the wavelength 233 nm, A_{233}.

$$\text{Content (\%) of linoleic acid } (C_{18}O_{32}O_2) = \frac{A}{93.7} \times 100$$

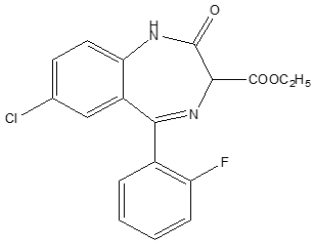
$$A = A_{233} \times \frac{10}{W} - 1206 \times A_{268} \times \frac{1}{W}$$

$$\text{Amount (mg) of ethyl linoleate } (C_{20}H_{36}O_2) = \text{Amount (mg) of linoleic acid} \times 1.100$$

Potassium hydroxide-glycerin TS—Add glycerin to 17.5 g of potassium hydroxide and warm to dissolve to make 100 mL.

Packaging and storage Preserve in light-resistant, tight containers.

Ethyl Loflazepate
에틸로플라제페이트



Ethyl Loflazepate $C_{18}H_{14}ClFN_2O_3$: 360.77
Ethyl 7-chloro-5-(2-fluorophenyl)-2,3 -dihydro-2-oxo-1*H*-1,4-benzodiazepine-3-carboxylic acid ester, [*29177-84-2*]

Ethyl Loflazepate contains NLT 98.0% and NMT 102.0% of ethyl loflazepate ($C_{18}H_{14}ClFN_2O_3$: 360.77).

Description Ethyl Loflazepate is white to pale yellow powder.
It is freely soluble in chloroform, soluble in acetonitrile, slightly soluble in ethanol(95) and practically insoluble in water.

Identification (1) Weigh 20 mg of Ethyl Loflazepate, dissolve in dichloromethane to make 4 mL, and use this solution as the test solution. Weigh 20 mg of ethyl loflazepate RS, dissolve in dichloromethane to make 4 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform, diisopropyl ether and ethanol(95) (14 : 5 : 1) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f value and the color of the spots obtained from the test solution and the standard solution are the same.

(2) Determine the infrared spectra of Ethyl Loflazepate and ethyl loflazepate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Determine the absorption spectra with a solution of Ethyl Loflazepate in ethanol(95) (1 in 100000); it exhibits maxima at wavelengths of about 231 nm and 318 nm.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Ethyl Loflazepate in chloroform to make 10 mL; the solution is clear.

(2) ***Heavy metals***—Proceed with 4.0 g of Ethyl

Loflazepate as directed under Method 4 and perform the test. Prepare the control solution with 4.0 mL of lead standard solution (NMT 40 ppm).

(3) ***Related substances***—Dissolve 20 mg of Ethyl Loflazepate in dichloromethane to make exactly 4 mL, and use this solution as the test solution. Separately, weigh accurately 20 mg of ethyl loflazepate RS, dissolve in dichloromethane to make exactly 4 mL, and use this solution as the standard solution I. Pipet 1 mL of the standard solution I, add dichloromethane to make exactly 200 mL, and use this solution as the standard solution II. Pipet 2 mL of the standard solution II, dilute with the same solvent to make exactly 5 mL, and use this solution as the standard solution III. Pipet 2 mL of the standard solution III, dilute with the same solvent to make exactly 10 mL, and use this solution as the standard solution IV. Spot 10 μL each of the test solution and the standard solutions on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform, diisopropyl ether and ethanol(95) (14 : 5 : 1) as the developing solvent, air-dry the plate, and examine it under ultraviolet light (main wavelength: 254 nm); The spots other than the principal spot obtained from the test solution are not more intense nor greater than the spots obtained from the standard solution II.

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.2 g of Ethyl Loflazepate, dissolve in 40 mL of a mixture of acetic anhydride and acetic acid(100) (3 : 1), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 36.08 mg of $C_{18}H_{14}ClFN_2O_3$

Packaging and storage Preserve in tight containers.

Ethyl Loplazepate Tablets
에틸로플라제페이트 정

Ethyl Loplazepate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of ethyl loflazepate ($C_{18}H_{14}ClFN_2O_3$: 360.77).

Method of preparation Prepare as directed under Tablets, with Ethyl Loflazepate.

Identification Weigh an amount of Ethyl Loplazepate Tablets, equivalent to about 4 mg of ethyl loflazepate. Add 5 mL of acetonitrile, shake to mix, then filter, and use the filtrate as the test solution. Separately, dissolve 20 mg of ethyl loflazepate RS in 25 mL of acetonitrile, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, diisopropyl ether and ethanol(95) (14 : 5 : 1) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

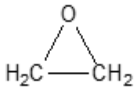
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Ethyl Loplazepate Tablets, and powder. Weigh accurately an amount, equivalent to about 8 mg of ethyl loflazepate ($C_{18}H_{14}ClFN_2O_3$), and add ethanol(95) to make exactly 100 mL. Filter this solution, discard the first 20 mL of the filtrate, pipet 10 mL of the subsequent filtrate, add ethanol(95) to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of ethyl loflazepate RS, and dissolve in ethanol(95) to make exactly 100 mL. Pipet 4 mL of this solution, add ethanol(95) to make exactly 100 mL, and use this solution as the standard solution. Perform the test of the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy using ethanol(95) as a control solution, and determine the absorbances, A_T and A_S, at a wavelength of 231 nm.

Amount (mg) of ethyl loflazepate ($C_{18}H_{14}ClFN_2O_3$)
= Amount (mg) of ethyl loflazepate RS × (A_T / A_S) × 0.4

Packaging and storage Preserve in tight containers.

Ethylene Oxide
산화에틸렌



Ethylene Oxide C_2H_4O : 44.05
Ethylene Oxide, [*75-21-8*]

Ethylene Oxide contains NLT 99.0% and NMT 101.0% of ethylene oxide (C_2H_4O).

Description Ethylene Oxide occurs as a colorless and clear liquid at 0 to 5 ℃.
It has a weak ether odor when vaporized.
It is very soluble in water, ethanol(95), acetone or ether at 0 to 5 ℃.

Identification To 1 mL of Ethylene Oxide, previously

cooled to 0 to 5 ℃, add 1 mL of water, 2 drops of phenolphthalein TS and 4 mL of sodium chloride solution (1 in 5), and allow to stand for 5 minutes; the solution exhibits a reddish purple color.

Purity (1) ***Aldehyde*—**In a 250-mL Erlenmeyer flask, add about 100 mL of water and cool to 0 to 5 ℃ in iced water. To this, add 10 mL of 0.2 mol/L sodium bisulfite and allow to stand for 30 minutes in iced water. Titrate with 0.05 mol/L iodine VS, previously cooled to 0 to 5 ℃ (indicator: 2 mL of starch TS). However, the endpoint of titration is when the blue color persists for 1 minute. Perform a blank test in the same manner and make any necessary correction (NMT 0.03% of acetaldehyde).

$$\text{Content (\%) of aldehyde} = \frac{(B - A) \times 0.0022}{10 \times G} \times 100$$

A: Consumed amount (mL) of 0.05 mol/L iodine VS
B: Amount (mL) of 0.05 mol/L iodine VS consumed for the blank test
G: Specific gravity of ethylene oxide at 0 to 5 ℃

(2) ***Chloride*—**Perform the test with 4.0 mL of Ethylene Oxide, previously cooled to 0 to 5 ℃, as directed under the Chloride. Prepare the control solution with 1.0 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.01%).

Water NMT 0.05% (20.0 mL of Ethylene Oxide previously cooled to 0 to 5 ℃, volumetric titration, direct titration).
The above test should be performed at 0 to 5 ℃.

Acidity Evaporate 68.0 mL of Ethylene Oxide, previously cooled to 0 to 5 ℃, to the volume of about 50 mL in a fume chamber to eliminate carbon dioxide. Titrate with 0.1 mol/L sodium hydroxide VS (indicator: 3 to 4 drops of phenolphthalein TS) (NMT 0.005% as acetic acid).

Residue on evaporation Evaporate 20 mL of Ethylene Oxide, previously cooled to 0 to 5 ℃, in a crucible, previously measured in the mass, in a fume chamber and dry at 105 ± 2 ℃ for 1 hour. Place in a desiccator, allow to stand for 30 minutes, cool to the room temperature, and measure the mass (NMT 0.03%).

$$\text{Residue (\%) on evaporation} = \frac{A - B - C}{20 \times G} \times 100$$

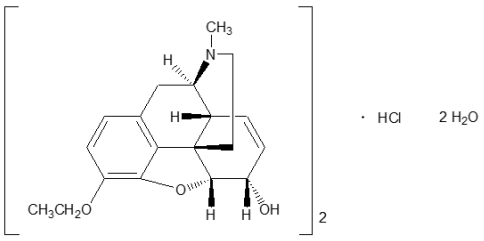
A: Mass (g) of the crucible measured after placing the sample in it and heating
B: Mass (g) of the crucible
C: Mean mass (g) of the blank test mass difference
G: Specific gravity of ethylene oxide at 0 to 5 ℃

Assay Connect and fix Ethylene Oxide to a connector, attach the needle valve for flow rate control, and allow to stand for NLT 30 minutes. Slowly open the needle valve for flow rate control, exhaust the Ethylene Oxide into a container containing water, and control bubbles so that 3 to 4 bubbles appear per second. Introduce the gas to the gas collector for 2 minutes, inject the conversion valve for 2 seconds, and perform the test as directed under the Gas Chromatography according to the following conditions.

Operating conditions
Detector: A thermal conductivity detector (TCD)
Column: A column about 4 mm in internal diameter and about 3 m in length, packed with 80- to 100-mesh divinylbenzene-ethylene glycol-dimethylacrylate copolymer for gas chromatography.
Column temperature: 120 ℃
Detector temperature: 225 ℃
Carrier gas: Helium
Flow rate: Between 40 mL/min and 50 mL/min.

Packaging and storage Preserve in tight containers.

Ethylmorphine Hydrochloride Hydrate
에틸모르핀염산염수화물



Ethylmorphine Hydrochloride
$C_{19}H_{23}NO_3 \cdot HCl \cdot 2H_2O$: 385.88
(4*R*,4a*R*,7*S*,7a*R*,12b*S*)-9-Ethoxy-3-methyl-2,4,4a,7,7a,13-hexahydro-1*H*-4,12-methanobenzofuro[3,2-e]isoquinoline-7-ol hydrochloride dihydrate [*6746-59-4*]

Ethylmorphine Hydrochloride Hydrate contains NLT 98.0% and NMT 101.0% of ethylmorphine hydrochloride ($C_{19}H_{23}NO_3 \cdot HCl$: 349.85), calculated on the anhydrous basis.

Description Ethylmorphine Hydrochloride Hydrate occurs as white to pale yellow crystals or a crystalline powder.
It is very soluble in methanol or acetic acid(100), freely soluble in water, soluble in ethanol(95), sparingly soluble in acetic anhydride and practically insoluble in ether.
It is affected by light.

Melting point—About 123 ℃ (with decomposition).

Identification (1) Determine the absorption spectra of aqueous solutions of Ethylmorphine Hydrochloride Hydrate and ethylmorphine hydrochloride RS (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy;

both spectra exhibit similar intensities of absorption at the same wavelength.

(2) Determine the infrared spectra of Ethylmorphine Hydrochloride Hydrate and ethylmorphine hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Ethylmorphine Hydrochloride Hydrate (1 in 50) responds to the Qualitative Analysis (2) for chloride.

Optical rotation $[\alpha]_D^{20}$: Between -103° and -106° (0.4 g calculated on the anhydrous basis, water, 20 mL, 100 mm).

pH Dissolve 0.10 g of Ethylmorphine Hydrochloride Hydrate in 10 mL of water; the pH of this solution is between 4.0 and 6.0.

Purity ***Related substances***—Dissolve 0.20 g of Ethylmorphine Hydrochloride Hydrate in 10 mL of diluted ethanol (1 in 2) and use this solution as the test solution. Pipet 0.5 mL of this solution, add diluted ethanol (1 in 2) to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of ethanol(99.5), toluene, acetone and ammonia water(28) (14 : 14 : 7 : 1) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Water Between 8.0% and 10.0% (0.25 g, volumetric titration, direct titration).

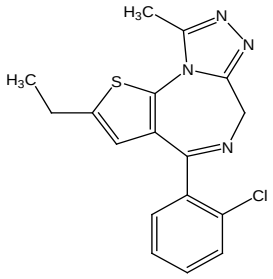
Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately about 0.5 g of Ethylmorphine Hydrochloride Hydrate, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 34.985 mg of $C_{19}H_{23}NO_3 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Etizolam
에티졸람



Etizolam $C_{17}H_{15}ClN_4S$: 342.85
7-(2-Chlorophenyl)-4-ethyl-13-methyl-3-thia-1,8,11,12-tetraazatricyclo[8.3.0.02,6}]trideca-2(6),4,7,10,12-pentaene [*40054-69-1*]

Etizolam contains NLT 98.5% and NMT 101.0% of etizolam ($C_{17}H_{15}ClN_4S$).

Description Etizolam occurs as a white to pale yellowish white crystalline powder.
It is soluble in ethanol(99.5), sparingly soluble in acetonitrile or acetic anhydride, and practically insoluble in water.

Identification (1) Determine the absorption spectra of the solutions of Etizolam and etizolam RS in ethanol(99.5) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Etizolam and etizolam RS as directed in potassium bromide disk method under the Mid-infrared Absorption Spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 146 and 149 ℃.

Purity (1) ***Heavy metals*** Proceed with 2.0 g of Etizolam according to Method 2 and perform the test Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances*** Dissolve 20 mg of Etizolam in 50 mL of acetonitrile, and use this solution as the test solution. Take exactly 1.0 mL of this solution and add acetonitrile to make exactly 20 mL. Pipet 1 mL of this solution, add acetonitrile to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution as directed in the automatic integration method; each peak area other than that of etizolam from the test solution is not greater than the peak area of etizolam from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: Dissolve 1.36 g of potassium dihydrogen phosphate in water to make 1000 mL, and add diluted phosphoric acid (1 in 10) to adjust the pH to 3.5. To 550 mL of this solution, add 450 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of etizolam is about 6 minutes.

System suitability

Test for required detectability: Pipet 2 mL of the standard solution and add acetonitrile to make exactly 20 mL. Confirm that the peak area of etizolam obtained from 10 μL of this solution is equivalent to 8 to 12% of the peak area of etizolam from the standard solution.

System performance: Dissolve 0.02 g each of Epizolam and ethylparaben in the mobile phase to make 50 mL. To 1 mL of this solution, add the mobile phase to make 50 mL. Proceed with 10 μL of this solution according to the above conditions; ethylparaben and etizolam are eluted in this order with the resolution being NLT 3.0.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of etizolam is NMT 2.0%.

Time span of measurement: About 5 times the retention time of etizolam after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 °C, 3 hours).

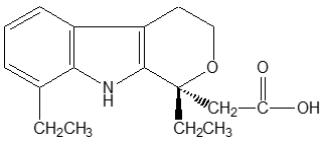
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Etizolam, previously dried, dissolve in 70 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). The endpoint of the titration is the second inflection point. Perform a blank test in the same way and make a necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 17.14 mg of $C_{17}H_{15}ClN_4S$

Packaging and storage Preserve in light-resistant, tight containers.

Etodolac
에토돌락



and enantiomer

Etodolac $C_{17}H_{21}NO_3$: 287.35
2-(1,8-Diethyl-4,9-dihydro-3H-pyrano[3,4-b]indol-1-yl)acetic acid [*41340-25-4*]

Etodolac contains NLT 98.0% and NMT 102.0% of etodolac ($C_{17}H_{21}NO_3$), calculated on the anhydrous basis.

Description Etodolac occurs as white to pale yellow crystals or a crystalline powder.
It is freely soluble in methanol or ethanol(99.5) and practically insoluble in water.
A solution of Etodolac in methanol (1 in 50) shows no optical rotation.

Melting point—About 147 °C (with decomposition).

Identification (1) Determine the absorption spectra of solutions of Etodolac and etodolac RS in ethanol(99.5) (1 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Etodolac and etodolac RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Chloride***—Dissolve about 0.5 g of Etodolac in 30 mL of methanol, add water to make 50 mL, and use this solution as the test solution. Prepare the control solution by adding 30 mL of methanol and water to 0.42 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.03%).

(2) ***Heavy metals***—Proceed with 1.0 g of Etodolac according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Methanol and ethanol***—Dissolve about 0.5 g of Etodolac, weighed accurately, in 5.0 mL of the internal standard solution, and use this solution as the test solution. Separately, pipet 5 mL each of methanol and ethanol(95), add *N*,*N*-dimethylformamide to make exactly 200 mL. Pipet 5.0 mL of this solution, add *N*,*N*-dimethylformamide to make exactly 100 mL, and use this solution as the standard stock solution. Pipet 10.0 mL of the standard stock solution, add 5.0 mL of the internal standard, dilute with *N*,*N*-dimethylformamide to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak areas of methanol and ethanol in Etodolac to that of the internal standard for the test solution and the standard solution,

respectively. The contents of methanol and ethanol is NMT 0.1%, respectively.

$$\text{Content (\%) of methanol or ethanol} = 500 \times \frac{C}{W} \times \frac{Q_T}{Q_S}$$

C: Concentration (mg/mL) of ethanol or methanol in the standard solution

W: Weight (mg) of Etodolac in the test solution

Internal standard solution—Dissolve a suitable quantity of 2-propanol in *N*,*N*-dimethylformamide to make a solution with a concentration of 2.5 μL/mL. Pipet 5.0 mL of this solution, and dilute this solution with *N*,*N*-dimethylformamide to make exactly 100 mL.

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A fused silica capillary column 0.32 mm in internal diameter and 25 m in length, coated with a 5 μm film of 1% vinyl–5% phenylmethylpolysiloxane for gas chromatography.

Carrier gas: Helium

Flow rate: 50 mL/min

Sample injection port temperature: 200 ℃

Detector temperature: 300 ℃.

Column temperature: Maintain the temperature of 45 ℃ for 5 minutes, then raise to 280 ℃ at the rate of 30 ℃ per minute, and maintain at 280 ℃ for 27 minutes.

System suitability

System performance: Proceed with 1 μL of the standard solution under the above operating conditions; methanol, ethanol, and 2-propanol are eluted in this order with the resolution between their peaks being NLT 1.0.

(4) ***Related substances***—Dissolve 25 mg of Etodolac, weighted accurately, in acetonitrile to make exactly 250 mL, and use this solution as the test solution. Perform the test with 20 μL of the test solution as directed under the Liquid Chromatography according to the following conditions. Each peak area of any peak other than the major peak from the test solution is NMT 0.5% to the total area of all peaks, and the total area is NMT 2.0%.

$$\text{Content (\%) of related substances} = 100 \times \frac{A_T}{A_S}$$

A_T: Each peak area of the peaks other than the principle peak

A_S: Total area of all peaks

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 to 10 μm in particle diameter).

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows. For the first 5 minutes, use mixture of 60% solution A and 40% solution B as the mobile phase. For the next 30 minutes, change the mixture ratio as linear gradient to finally make mixture of 20% solution A and 80% solution B. Adjust mobile phase to 40% of solution B before injection of the test solution and the standard solution, and keep re-equilibrium.

Mobile phase A: Mix 0.6 mL of phosphoric acid with 100 mL of water.

Mobile phase B: Mix 0.6 mL of phosphoric acid with 100 mL of acetonitrile.

Flow rate: 1 mL/min

System suitability

System performance: Dissolve suitable amount each of etodolac related substance I RS and etodolac RS in acetonitrile to make solutions containing 10 μg of etodolac related substance I RS and 0.2 mg of etodolac RS per mL, respectively. Proceed with 20 μL of this solution as directed under the above operating conditions; etodolac related substance I and etodolac are eluted in this order with the resolution between their peaks being NLT 3.0.

System repeatability: Repeat the test 6 times with 20 μL each of the solution according to the above conditions; the relative standard deviation of the ratio of the peak area is NMT 3%.

Water NMT 0.5% (2 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.23 g of Etodolac, dissolve in 60 mL of methanol, and titrate with 0.1 mol/L tetrabutylammonium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L tetrabutylammonium hydroxide VS = 28.735 mg of $C_{17}H_{21}NO_3$

Packaging and storage Preserve in tight containers.

Etodolac Tablets
에토돌락 정

Etodolac Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of etodolac ($C_{17}H_{21}NO_3$: 287.36).

Method of preparation Prepare as directed under Tablets, with Etodolac.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Dissolution Perform the test with 1 tablet of Etodolac Tablets at 100 revolutions per minute according to Method 1 under the Dissolution, using 1000 mL of pH 6.8 phosphate buffer solution as the dissolution medium. Take 20 mL of the dissolved solution 30 minutes after starting the test, and filter through a membrane filter with a pore size of NMT 0.8 μm. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 25 mg of etodolac RS, dissolve in the dissolution medium to make exactly 100 mL, pipet 5 mL of this solution, and add the dissolution medium to make exactly 50 mL. Use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy at the absorbance maximum wavelength of about 274 nm, using the dissolution medium as a control solution.
The acceptable dissolution criterion is NLT 80% of Etodolac Tablets dissolved in 30 minutes.

Dissolution rate (%) of the labeled amount of etodolac ($C_{17}H_{21}NO_3$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{100}{C}$$

W_S: Amount (mg) of etodolac RS
C: Labeled amount (mg) of etodolac ($C_{17}H_{21}NO_3$) in 1 tablet

Uniformity of dosage units It meets the requirements when the Content uniformity test is performed according to the following procedure. Take 1 tablet of Etodolac Tablets, add 10 mL of phosphate buffer solution, and shake to mix until disintegration. Then, add phosphate buffer solution to make exactly 100 mL, and centrifuge. Take χ mL of the clear supernatant, add phosphate buffer solution to obtain V mL of a solution having known concentration of about 25 μg of etodolac ($C_{17}H_{21}NO_3$) per mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg of the etodolac RS, and dissolve in phosphate buffer solution to make exactly 100 mL. Pipet 10 mL of this solution, add phosphate buffer solution to make 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy at the absorbance maximum wavelength at about 274 nm.

Amount (mg) of etodolac ($C_{17}H_{21}NO_3$)

$$= \text{Amount (mg) of etodolac RS} \times \frac{A_T}{A_S} \times \frac{V}{10} \times \frac{1}{x}$$

Assay Weigh accurately the mass of NLT 20 tablets of Etodolac Tablets, and powder. Weigh accurately an amount, equivalent to about 0.1 g of etodolac ($C_{17}H_{21}NO_3$), add 30 mL of the mobile phase, shake to mix for 15 minutes, and sonicate for 5 minutes to mix. After cooling, add 50 mL of the mobile phase to make exactly 50 mL. Allow to stand for 10 minutes, then take 10.0 mL of this solution, add the mobile phase to make exactly 100 mL, and filter. Use the filtrate as the test solution. Separately, weigh accurately about 20 mg of etodolac RS, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of etodolac in each solution.

Amount (mg) of etodolac ($C_{17}H_{21}NO_3$)

$$= \text{Amount (mg) of etodolac RS} \times \frac{A_T}{A_S} \times 5$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 274 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile, water, and phosphoric acid (500 : 500 : 0.25).

Flow rate: 1.5 mL/min

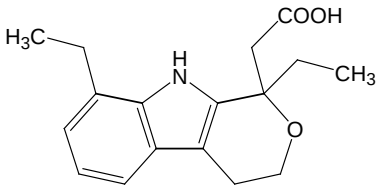
System suitability

System performance: Dissolve an appropriate amount of etodolac related substance I RS and etodolac RS in acetonitrile to make a solution containing 10 μg of etodolac related substance I RS and 0.2 mg of etodolac RS per mL. Proceed with 20 μL of this solution as directed under the above conditions; etodolac related substance I and etodolac are eluted in this order with the resolution being NLT 3.0.

System repeatability: Repeat the test 6 times with 20 μL each of the solution according to the above conditions; the relative standard deviation of the peak area is NMT 3%.

Packaging and storage Preserve in tight containers.

Etodolac Micronized
미분화에토돌락



Etodolac Micronized $C_{17}H_{21}NO_3$: 287.36
(1*S*)-1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid, [*87249-11-4*]

Etodolac Micronized contains NLT 97.0% and NMT 101.0% of etodolac ($C_{17}H_{21}NO_3$), calculated on the anhydrous basis.

Description Etodolac Micronized occurs as a white fine crystalline powder.
It is very soluble in polyethylene glycol 400, freely soluble in ethanol, methanol or chloroform and practically insoluble in water.

Melting point—Between 145 and 148 ℃.

Identification (1) Perform the test with Etodolac Micronized as directed in article (2) of the Purity; the spots obtained from the test solution and the standard solution show the same R_f value and color.

(2) Determine the infrared spectra of Etodolac Micronized and etodolac RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Etodolac Micronized as directed under Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Weigh accurately about 0.1 g of Etodolac Micronized, add acetone to make 100 mL, and use this solution as the test solution. Separately, weigh accurately 0.10 g of etodolac RS, dissolve in acetone to make 100 mL, and use this solution as the standard solution. To 25.0 mL of the standard solution, add acetone to make 100 mL, and use this solution as the diluted standard solution. Perform the test with the test solution, the standard solution and the diluted standard solution as directed under the Thin Layer Chromatography. Immerse a plate made of silica gel for thin-layer chromatography (with florescent agent) in a solution prepared by dissolving 0.5 g of ascorbic acid in a mixture of water and ethanol (1 in 5) to make 100 mL, and air-dry the plate. Apply 25 μL each of the test solution and the standard solution and 2 μL of the diluted standard solution on the plate. Develop the plate with a mixture of toluene, acetic acid and ethanol (70 : 50 : 30) as the developing solvent to a distance of 16 cm to 18 cm, and air-dry the plate for 30 minutes. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not greater or more intense than the spot from the diluted standard solution.

Water NMT 0.5%.

Residue on ignition NMT 0.1% (1.0 g).

Particle size Place a small amount of Etodolac Micronized on a microscope slide, add 1 to 2 drops of mineral oil, mix well, and disperse. Then, cover it with a coverslip and measure the particle size with a microscope with a magnification of 40 to 400 times. Measure the size of all particles in the micrometer range of particle size measurement, and repeat the test more than three times; the average particle size should be NMT 8 μm, and the percentage of the number of particles NMT 20 μm should be NLT 95%.

Assay Weigh accurately about 0.1 g of Etodolac Micronized and dissolve in methanol to make 100.0 mL. Pipet 1.0 mL of this solution and add methanol to make 50.0 mL. Use this solution as the test solution. Separately, weigh accurately 0.1 g of etodolac RS and proceed in the same manner as in the preparation of the test solution. Use the resulting solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution according to the following conditions as directed under the Liquid Chromatography, and determine the peak areas, A_T and A_S, of etodolac in each solution.

$$\text{Amount (mg) of etodolac } (C_{17}H_{21}NO_3) = \text{Amount (mg) of etodolac RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of buffer solution, methanol and acetonitrile (68 : 19 : 13).

Flow rate: 1.0 mL/min

Buffer solution—To 0.5 mol/L potassium dihydrogen phosphate, add 200 mL of water to make 1000 mL.

Packaging and storage Preserve in tight containers.

Etodolac Micronized Capsules
미분화에토돌락 캡슐

Etodolac Micronized Capsules contain NLT 90.0% and NMT 110.0% the labeled amount of etodolac ($C_{10}H_{21}NO_3$: 287.36).

Method of preparation Prepare as directed under Capsules, with Etodolac Micronized.

Identification The retention times of the major peaks

from the test solution and standard solution obtained under the Assay are the same.

Dissolution Perform the test with 1 capsule of Etodolac Micronized Capsules at 100 revolutions per minute according to Method 1, using 900 mL of phosphate buffer solution (pH 7.5) as the dissolution medium. Take the dissolved solution 45 minutes after the start of the dissolution, filter, take 4.0 mL of the filtrate, and add phosphate buffer solution (pH 7.5) to make 25.0 mL. Use this solution as the test solution. Separately, weigh accurately about 0.1 g of etodolac RS, dissolve in phosphate buffer solution (pH 7.5), make the same concentration as the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, at 278 nm as directed under the Ultraviolet-visible Spectroscopy, using phosphate buffer solution (pH 7.5) as the control solution. It meets the requirements if the dissolution rate in 45 minutes is NLT 75%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the contents of NLT 20 capsules of Etodolac Micronized Capsules and powder. Weigh an amount equivalent to about 50 mg of etodolac ($C_{17}H_{21}NO_3$), add 0.1 mol/L sodium hydroxide to make 100 mL, sonicate for 30 minutes, and centrifuge. Take 1.0 mL of the clear supernatant, add the mobile phase to make 50.0 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of etodolac RS, add 0.1 mol/L sodium hydroxide to make 100.0 mL. Take an appropriate amount of this solution to obtain a solution having known concentration of 10 μg per mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of etodolac, A_T and A_S, respectively.

$$\text{Amount (mg) of etodolac } (C_{17}H_{21}NO_3) = \text{Amount (mg) of etodolac RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Mobile phase: A mixture of phosphate buffer (pH 4.75) and acetonitrile buffer (55 : 45).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Etodolac Micronized Tablets
미분화에토돌락 정

Etodolac Micronized Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of etodolac ($C_{17}H_{21}NO_3$: 287.36).

Method of preparation Prepare as directed under Tablets, with Etodolac Micronized.

Identification The major peaks obtained from the test solution and the standard solution under the Assay are the same in the retention time.

Dissolution Perform the test with 1 tablet of Etodolac Micronized Tablets at 100 revolutions per minute according to Method 1 under the Dissolution, using 900 mL of phosphate buffer solution, pH 7.5, as the dissolution medium. Take the dissolved solution 45 minutes after starting of the dissolution test, filter, take 4.0 mL of the filtrate, add phosphate buffer solution, pH 7.5, to make 25.0 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of etodolac RS, dissolve in phosphate buffer solution, pH 7.5, to make it the same concentration as the test solution, and this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution at a wavelength of 278 nm as directed under the Ultraviolet-visible Spectroscopy, using phosphate buffer solution, pH 7.5, as the control solution. Meets the requirements if the dissolution rate of Etodolac Micronized Tablets for 45 minutes is NLT 75%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately NLT 20 tablets of Etodolac Micronized Tablets, and powder. Weigh accurately a portion of this powder, equivalent to about 50 mg of etodolac ($C_{17}H_{21}NO_3$), add 0.1 mol/L sodium hydroxide solution to make 100.0 mL, sonicate for 30 minutes, and centrifuge. Take 1.0 mL of the clear supernatant, add the mobile phase to make 50.0 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of etodolac RS, and dissolve in 0.1 mol/L hydrochloric acid to make 100.0 mL. Take an appropriate amount of this solution, prepare a solution containing 10 μg per mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution according to the following conditions as directed under the Liquid Chromatography, and determine the peak areas, A_T and A_S, of etodolac for each solution.

$$\text{Amount (mg) of etodolac } (C_{17}H_{21}NO_3) = \text{Amount (mg) of etodolac RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

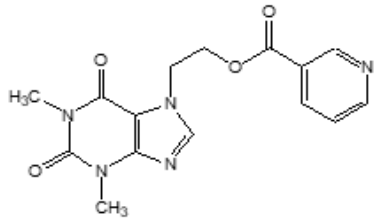
Mobile phase: A mixture of phosphate buffer solution, pH 4.75, and acetonitrile (55 : 45).

Flow rate: 1.0 mL/min

Phosphate buffer solution, pH 4.75—Add water to 100 mL of 0.5 mol/L potassium dihydrogen phosphate solution to make 1000 mL, and adjust the pH to 4.75 with potassium hydroxide solution.

Packaging and storage Preserve in tight containers.

Etofylline Nicotinate
에토필린니코티네이트



Etofylline Nicotinate $C_{15}H_{15}N_5O_4$: 329.31

2-(1,2,3,6-Tetrahydro-1,3-dimethyl-2,6-dioxo-7*H*-purin-7-yl)ethyl 3-pyridinecarboxylic acid ester, [*13425-39-3*]

Etofylline Nicotinate, when dried, contains NLT 99.0% and NMT 101.0% of etofylline nicotinate ($C_{15}H_{15}N_5O_4$).

Description Etofylline Nicotinate occurs as a white crystalline powder, is odorless and has a bitter taste.

Identification (1) Add 10 drops of 3% hydrogen peroxide and 3 drops of hydrochloric acid to 10 mg of Etofylline Nicotinate, mix well, and evaporate to dryness. Add a few drops of 10% ammonia water to the residue on evaporation; it exhibits dark red color.

(2) Determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy with a solution of Etofylline Nicotinate in hydrochloric acid (1 in 10000); it exhibits a maximum at about 268 nm.

Melting point Between 151 and 152 ℃.

Purity (1) ***Clarity and color of solution***—Weigh 2.0 g of Etofylline Nicotinate in 10 mL of chloroform; the resulting solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Etofylline Nicotinate as directed under Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

Loss on drying 0.5% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Etofylline Nicotinate, previously dried, dissolve in 50 mL of acetic acid(100) for non-aqueous titration, and titrate with 0.1 mol/L perchloric acid VS as directed in the potentiometric titration under the Titrimetry. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 16.47 mg of $C_{15}H_{15}N_5O_4$

Packaging and storage Preserve in tight containers.

Etofylline Nicotinate Injection
에토필린니코티네이트 주사액

Etofylline Nicotinate Injection is an aqueous injection and contains NLT 95.0% and NMT 105.0% of etofylline nicotinate ($C_{15}H_{15}N_5O_4$: 329.31).

Method of preparation Prepare as directed under Injections, with Etofylline Nicotinate.

Identification (1) To an amount of Etofylline Nicotinate Injection equivalent to 10 mg of etofylline nicotinate, add 10 drops of 3% hydrogen peroxide and 3 drops of hydrochloric acid, shake to mix, evaporate in an evaporating dish until a reddish brown residue forms, and add a few drops of 10% ammonia water; the solution exhibits a dark red color.

(2) Take an amount of Etofylline Nicotinate Injection equivalent to 25 mg of etofylline nicotinate according to the labeled amount, extract in 100 mL of chloroform, and add chloroform to 10 mL of the extract to make 100.0 mL. Use this solution as the test solution. Separately, dissolve 10 mg of etofylline nicotinate RS in 100 mL of chloroform and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform and methanol (9 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly a phosphomolybdic acid ethanol solution on the plate, dry at 120 ℃ and apply iodine vapor to the plate; the R_f values and colors of spots obtained from the test solution and the standard solution are the same.

(3) Take an amount of Etofylline Nicotinate Injection, equivalent to 10 mg of etofylline nicotinate, add 0.05 mol/L hydrochloric acid to make exactly 100 mL, and filter. Take 10 mL of the filtrate, add 0.05 mol/L hy-

drochloric acid to make 100.0 mL, and measure the absorbance spectrum as directed under Ultraviolet-visible Spectroscopy; it exhibits a maximum around 268 nm.

Sterility Meets the requirements.

Bacterial endotoxins Less than 3 EU per mg of etofylline nicotinate.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

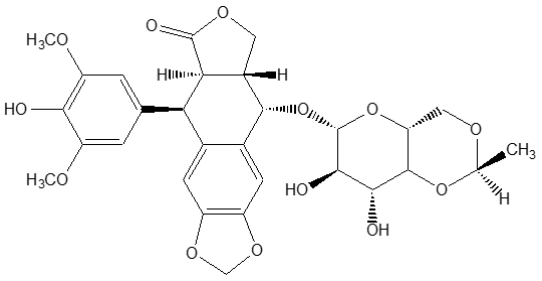
Extractable volume of injections Meets the requirements.

Assay Take an amount of Etofylline Nicotinate Injection equivalent to 0.1 g of etofylline nicotinate ($C_{15}H_{15}N_5O_4$) according to the labeled amount, place in a 125 mL separatory funnel, then extract 3 times with 30 mL of chloroform each time. Combine the chloroform extract and filter with cotton wool to make 100 mL. Pipet 3 mL of this solution and evaporate the chloroform to dryness completely on a steam bath. Add 0.05 mol/L hydrochloric acid to the residue and shake to dissolve to make exactly 500 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of etofylline nicotinate RS, previously dried at 105 °C for 2 hours, and dissolve in 0.05 mol/L hydrochloric acid TS to make exactly 100 mL. Pipet 3 mL of this solution, add 0.05 mol/L hydrochloric acid TS to make exactly 500 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution at the wavelength of 268 nm as directed under the Ultraviolet-visible Spectroscopy, using 0.05 mol/L hydrochloric acid as a control solution.

Amount (mg) of etofylline nicotinate ($C_{15}H_{15}N_5O_4$)
= Amount (mg) of etofylline nicotinate RS × (A_T / A_S)

Packaging and storage Preserve in hermetic containers.

Etoposide
에토포시드



Etoposide $C_{29}H_{32}O_{13}$: 588.56
(5*S*,5a*R*,8a*R*,9*R*)-5-[[(2*R*,4a*R*,6*R*,7*R*,8*R*,8a*S*)-7,8-Dihydroxy-2-methyl-4,4a,6,7,8,8a-hexahydropyrano[3,2-d][1,3]dioxin-6-yl]oxy]-9-(4-hydroxy-3,5-dimethoxyphenyl)-5a,6,8a,9-tetrahydro-5H-[2]benzofuro[6,5-f][1,3]benzodioxol-8-one [*33419-42-0*]

Etoposide contains NLT 98.0% and NMT 102.0% of etoposide ($C_{29}H_{32}O_{13}$), calculated on the anhydrous basis.

Description Etoposide occurs as white crystals or a crystalline powder.
It is sparingly soluble in methanol, slightly soluble in ethanol(99.5), and very slightly in water.

Melting point—About 260 °C.

Identification (1) Determine the absorption spectra of Etoposide and etoposide RS in methanol (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Etoposide and etoposide RS as directed in the paste method under Infrared Spectrophotometry: both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -100° and -105° (0.1 g, calculated on the anhydrous basis, methanol, 20 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed about 2.0 g of Etoposide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Dissolve 50 mg of Etoposide in 10 mL of methanol, add the mobile phase to make 50 mL, and use this solution as the test solution. Pipet 2 mL of this solution, add the mobile phase to it make exactly 200 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area by the automatic integration method: the area of any peak other than etoposide obtained with the test solution is not greater than 1/5 times the peak area of etoposide obtained with the standard solution. The total area of all peaks other than the peak of etoposide obtained with the test solution is not greater than 1/2 times the peak area of etoposide obtained with the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

System performance: Proceed as directed under the system suitability under the Assay.

Test for required detectability: Weigh accurately 1

mL of the standard solution and add the mobile phase to make exactly 10 mL. Confirm that the peak area of Etoposide obtained from 50 μL of this solution is within the range between 7% and 13% of the peak area of Etoposide in the standard solution.

System repeatability: Repeat the test 6 times with 50 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area for Etoposide is NMT 2.0%.

Time span of measurement: About 3 times the retention time of etoposide after the solvent peak.

Water NMT 4.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 25 mg each of Etoposide and etoposide RS (previously determined the water), dissolve separately in and dilute with methanol to make exactly 25 mL each. Pipet 10 mL each of these solutions, add exactly 5 mL of the internal standard solution and the mobile phase to make exactly 50 mL and use these solutions as the test solution and standard solution, respectively. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and measure the ratio of the peak area of etoposide to that of the internal standard, Q_T and Q_S.

$$\text{Amount (mg) of Etoposide } (C_{29}H_{32}O_{13}) = \text{Amount (mg) of etoposide RS, as calculated on the anhydrous basis} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of 2,6-dichlorophenol in methanol (3 in 2500).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 290 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with phenylsilyl silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: Dissolve 6.44 g of sodium sulfate decahydrate in diluted acetic acid(100) (1 in 100) to make 1000 mL, and add 250 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of etoposide is about 20 minutes.

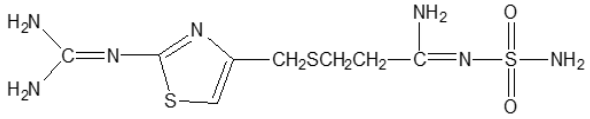
System suitability

System performance: Dissolve 10 mg of Etoposide in 2 mL of methanol, add 8 mL of the mobile phase, and mix well. Add 0.1 mL of diluted acetic acid(100) (1 in 25) and 0.1 mL of phenolphthalein TS, and add sodium hydroxide TS until the color of the solution changes to faintly red. After allowing to stand for 15 minutes, add 0.1 mL of diluted acetic acid(100)(1 in 25). Proceed with 10 μL of this solution under the above operating conditions; the resolution between the peak having the relative retention time of about 1.3 with respect to etoposide is NLT 3.0.

System repeatability: Repeat the test 6 times with 50 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area for Etoposide is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Famotidine
파모티딘



Famotidine $C_8H_{15}N_7O_2S_3$: 337.45
3-[({2-[(Diaminomethylidene)amino]-1,3-thiazol-4-yl}methyl)sulfanyl]-*N'*-sulfamoylpropanimidamide
[*76824-35-6*]

Famotidine, when dried, contains NLT 98.5% and NMT 101.0% of famotidine ($C_8H_{15}N_7O_2S_3$).

Description Famotidine occurs as white to yellowish white crystals.
It is freely soluble in acetic acid(100), slightly soluble in ethanol(95), very slightly soluble in water.
It dissolves in 0.5 mol/L hydrochloric acid TS.
It is gradually colored by light.

Melting point—About 164 °C (with decomposition).

Identification (1) Determine the absorption spectra of solutions of Famotidine and famotidine RS in 0.05 mol/L potassium dihydrogen phosphate TS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Famotidine and famotidine RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Famotidine in 10 mL of 0.5 mol/L hydrochloric acid TS; the solution is clear and colorless to pale yellow.

(2) ***Heavy metals***—Proceed with 2.0 g of Famotidine according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 0.20 g of Famotidine in 10 mL of acetic acid(100), and use this solu-

tion as the test solution. Pipet 1 mL of this solution, and add acetic acid(100) to make exactly 100 mL. Pipet 1 mL, 2 mL and 3 mL of this solution, and add acetic acid(100) to make exactly 100 mL each, and use these solutions as the standard solutions (1), (2) and (3). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution, the standard solution (1), the standard solution (2), the standard solution (3) on the plate made of silica gel for thin-layer chromatography (5 μm to 7 μm in particle diameter, with fluorescent indicator). Then, dry with the aid of a current of nitrogen. Next, develop the plate using a mixture of ethyl acetate, methanol, toluene and ammonia water(28) (40 : 25 : 20 : 2) as the developing solvent to a distance of about 8 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot and the spot of the starting point obtained from the test solution are not more intense than the spots from the standard solution (3). The total intensity of the spots other than the principal spot and the spot of the starting point obtained from the test solution are NMT 0.5%, as compared to intensities of the spots obtained from the standard solutions (1) and (2).

Loss on drying NMT 0.5% (1 g, in vacuum, phosphorus pentoxide, 80 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Famotidine, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of perchloric acid VS
= 16.873 mg of $C_8H_{15}N_7O_2S_3$

Packaging and storage Preserve in light-resistant, tight containers.

Famotidine for Injection
주사용 파모티딘

Famotidine for injection is a preparation for injection, which is dissolved before use. Famotidine for injection contains NLT 94.0% and NLT 106.0% of the labeled amount of famotidine ($C_8H_{15}N_7O_2S_3$: 337.45).

Method of preparation Prepare as directed under Injections, with Famotidine.

Description Famotidine for injection occurs as a porous mass or a powder.

Identification Weigh an amount of Famotidine for injection, equivalent to 10 mg of famotidine according to the labeled amount, dissolve in 50 mL of 0.05 mol/L potassium dihydrogen phosphate TS, then to 5 mL of the resulting solution, add 0.05 mol/L potassium dihydrogen phosphate TS to make 50 mL. Determine the absorption spectra of this solution as directed under Ultraviolet-visible Spectroscopy; it exhibits a maximum absorption between 263 nm and 267 nm.

pH Dissolve an amount of Famotidine for injection equivalent to 20 mg (potency) of famotidine, and dissolve in 1 mL of water; the pH of this solution is between 4.9 and 5.5.

Purity (1) ***Clarity and color of solution***—Weigh an amount of Famotidine for injection equivalent to about 20 mg of famotidine according to the labeled amount, and dissolved in 1 mL of water; the solution is clear and colorless.

(2) ***Related substances***—Take a number of Famotidine for injection, equivalent to about 0.1 g of famotidine (C8H15N7O2S3), dissolve each content in water, wash the inside of the container with water, combine the solutions of the contents with the washings, add water to the combined solution to make exactly 100 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of these solutions by the automatic integration method: the total area of the peaks other than the major peak from the test solution is not larger than the major peak from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase, flow rate and system performance, proceed as directed in the operating conditions under the Assay.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of famotidine obtained from 5 μL of the standard solution is between 5 mm and 10 mm.

System suitability

System performance: Proceed as directed under the system suitability under the Assay.

Test for required detectability: Pipet 2 mL of the standard solution, and add water to make exactly 20 mL. Confirm that the peak area of famotidine obtained from 5 μL of this solution is 8% to 12% of the peak area of famotidine obtained from the standard solution.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of famotidine is NMT 2.0%.

Time span of measurement: About 2 times the retention time of famotidine after the solvent peak.

Water NMT 1.5% (0.1 g, coulometric titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 15 EU per mg of Famotidine for Injection.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Take a number of Famotidine for injection equivalent to about 0.1 g of famotidine ($C_8H_{15}N_7O_2S_3$), dissolve the contents in water, wash each container with water, add the washings to the initial fluid, and add water to make exactly 100 mL. Pipet 5 mL of this solution, add 5.0 mL of the internal standard solution, add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of famotidine RS (previously dried at 80 ℃ for 4 hours in a phosphorus pentoxide desiccator) and dissolve in the mobile phase to make exactly 50 mL. Pipet 5 mL of this solution, add 5.0 mL of the internal standard solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of famotidine to the internal standard, respectively.

$$\text{Amount (mg) of famotidine } (C_8H_{15}N_7O_2S_3) = \text{Amount (mg) of famotidine RS} \times \frac{Q_T}{Q_S} \times 2$$

Internal standard solution—To 5 mL of a solution of methyl *p*-hydroxybenzoate in methanol (1 in 500), add water to make 50 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 2 g of sodium 1-heptanesulfonate in 900 mL of water, add acetic acid(100) to adjust the pH to 3.0, and add water to make 1000 mL. To this solution, add 240 mL of acetonitrile and 40 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of famotidine is about 6 minutes.

System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; famotidine and the internal standard are eluted in this order with the resolution being NLT 11.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution according to the above conditions; the relative standard deviation of ratios of the peak area of famotidine to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in hermetic containers.

Famotidine Tablets
파모티딘 정

Famotidine Tablets contain NLT 94.0% and NMT 106.0% of the labeled amount of famotidine ($C_8H_{15}N_7O_2S_3$: 337.45).

Method of preparation Prepare as directed under Tablets, with Famotidine.

Identification Weigh an amount of Famotidine Tablets, previously powdered, equivalent to 10 mg of famotidine according to the labeled amount, add 50 mL of 0.05 mol/L potassium dihydrogen phosphate TS, shake well to mix, and then centrifuge. To 5 mL of the clear supernatant, add 0.05 mol/L potassium dihydrogen phosphate TS to make 50 mL, and determine the absorption spectrum of the solution as directed under Ultraviolet-visible Spectroscopy; it exhibits a maximum absorption between 263 nm and 267 nm.

Purity ***Related substances***—Take NLT 10 Famotidine Tablets, add 200 mL of diluent, and disintegrate by shaking well to mix. To this solution, add 200 mL of methanol, mix at 300 revolutions per minute for 1 hour, add diluent to make exactly 1000 mL, and then filter. Pipet an amount of this solution equivalent to 10 mg of famotidine, add diluent to make 100 mL, and use this solution as the test solution. Separately, weigh accurately 10 mg of famotidine RS, add 20 mL of methanol, sonicate for 5 minutes, and then add diluent to make exactly 100 mL. Use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method, and calculate the amount of each related substance in the test solution; the famotidine related substance I {3-[2-(diaminomethyleneamino)-1,3-thiazol-4-yl methylsulfonyl]phenyl}-*N*-sulfamoyl-propanamide} is NMT 1.0%, and famotidine related substance II {3-[2-(diaminomethyleneamino)-1,3-thiazol-4-yl methylthio]propanoic acid}, famotidine related substance III {3-[2-(diaminomethyleneamino)-1,3-thiazol-4-yl methylthio]-*N*-sulfamoyl-propanamide}, and famotidine related

substances IV {3-[2-(diaminomethyleneamino)-1,3-thiazol-4-yl methylthio]-propanamide} are NMT 0.5%, and the total amount of related substances is NMT 1.5%. However, the peak area of famotidine related substance IV is obtained by dividing the area determined with the automatic integration method by the correction factor 1.3.

$$\text{Content (\%) of related substances} = 100 \times \frac{C_S}{C \times N} \times \frac{A_i}{A_S}$$

C_S: Concentration (mg/mL) of famotidine in the standard solution

C: Labeled amount (g) of famotidine in 1 tablet

N: Number of tablets used in the preparation of the test solution

A_T: Peak area of each related substance in the test solution

A_S: Peak area of famotidine in the standard solution

Diluent—Dissolve 6.8 g of potassium dihydrogen phosphate in 750 mL of water, adjust pH with 1 mol/L potassium hydroxide to 6.0, and add water to make 1000 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 275 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: A mixture of buffer solution and acetonitrile (93 : 7).

Flow rate: About 1.4 mL/min

System suitability

Test for required detectability: To 10 mg of famotidine, add 1 mL of 0.1 mol/L hydrochloric acid, heat at 80 ℃ for 30 minutes, and then cool to room temperature. Then, add 2 mL of 0.1 mol/L sodium hydroxide TS, heat at 80 ℃ for 30 minutes, then cool to room temperature, and then neutralize with 1 mL of 0.1 mol/L hydrochloric acid. Add diluent to make 50 mL. Pipet 10 mL of this solution, transfer into a solution of 5 mg of famotidine dissolved in 8 mL of methanol, then add diluent to make 50 mL. Take 25 mL of this solution, add diluent to make 50 mL, and use this solution as the system suitability stock solution. Take 1 to 1.5 mL of this solution, add 1 drop of hydrogen peroxide TS, and use this solution as the system suitability solution. Proceed with 50 μL of this solution according to the above conditions; the relative retention time of famotidine related substances I, II, III, and IV to the retention time of the famotidine peak are 0.4, 0.7, 0.8, and 1.2, respectively.

System performance: Proceed with 50 μL of the system suitability solution according to the above conditions; the resolutions between famotidine related substance III and famotidine, and between famotidine and famotidine related substance IV, are NLT 1.3, respectively, and the mass distribution ratio of the famotidine peak is NLT 2.0.

System repeatability: Repeat the test 6 times with 50 μL each of the standard solution according to the above conditions; the relative standard deviation is NMT 2.0%.

Buffer solution—Dissolve 13.6 g of sodium acetate trihydrate in 750 mL of water, add 1 mL of triethylamine, adjust the pH to 6.0 with acetic acid(100), and then add water to make 1000 mL.

Dissolution Perform the test with 1 tablet of Famotidine Tablets at 50 revolutions per minute according to Method 2, using 900 mL of pH 4.5 0.1 mol/L phosphate buffer solution as the dissolution medium. Take 20 mL of the dissolved solution 30 minutes after starting the test, and filter through a membrane filter with a pore size of NMT 0.8 μm. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately 20 mg of Famotidine RS, add buffer solution to make exactly 100 mL. Pipet 5.0 mL of this solution, add the buffer solution to make exactly 50 mL, and use this solution as the standard solution. Determine the absorbances, AT and AS, of the test solution and the standard solution at the absorbance maximum wavelength near 265 nm as directed under Ultraviolet-visible Spectrophotometry.

It meets the requirements if the dissolution rate of Famotidine Tablets in 30 minutes is NLT 75%.

$$\text{Dissolution rate (\%) of the labeled amount of famotidine } (C_8H_{15}N_7O_2S_3) = \text{Amount (mg) of famotidine RS} \times \frac{Q_T}{Q_S} \times \frac{90}{C}$$

C: Labeled amount (mg) of famotidine ($C_8H_{15}N_7O_2S_3$) in 1 tablet

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following method.

Take 1 tablet of Famotidine Tablets, add 2 mL of water, shake to disintegrate. Add methanol, shake well to mix, then add methanol to make exactly V mL of a solution containing about 0.2 mg of famotidine ($C_8H_{15}N_7O_2S_3$) per mL, and centrifuge. Pipet 10 mL of the clear supernatant, add 2.0 mL of the internal standard solution, add the mobile phase to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of famotidine RS, previously dried in a phosphorus pentoxide desiccator in vacuum at 50 ℃ for 4 hours, and dissolve in methanol to make exactly 100 mL. Pipet 10 mL of this solution, add 2.0 mL of the internal standard solution, add the mobile phase to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard

solution as directed under Liquid Chromatography according to the operating conditions described in the Assay and calculate the ratios, QT and QS, of the peak area of famotidine to that of the internal standard.

$$\text{Amount (mg) of famotidine } (C_8H_{15}N_7O_2S_3) = \text{Amount (mg) of famotidine RS} \times \frac{Q_T}{Q_S} \times \frac{V}{500}$$

Internal standard solution—To 5 mL of a solution of methyl *p*-hydroxybenzoate in methanol (1 in 500), add water to make 50 mL.

Assay Take a certain number of Famotidine Tablets equivalent to 0.2 g of famotidine ($C_8H_{15}N_7O_2S_3$), add 50 mL of water, and disintegrate by shaking well to mix. Next, add 100 mL of methanol, shake well to mix, then add methanol to make exactly 200 mL, and centrifuge. Pipet 5 mL of the clear supernatant, add exactly 5 mL of the internal standard solution, add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of famotidine RS, previously dried in a phosphorus pentoxide desiccator in vacuum at 80 ℃ for 4 hours, and dissolve in methanol to make exactly 100 mL. Pipet 5 mL of this solution, add exactly 5 mL of the internal standard solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of famotidine to the peak area of the internal standard, respectively.

$$\text{Amount (mg) of famotidine } (C_8H_{15}N_7O_2S_3) = \text{Amount (mg) of famotidine RS} \times \frac{Q_T}{Q_S} \times 2$$

Internal standard solution—To 5 mL of a solution of methyl *p*-hydroxybenzoate in methanol (1 in 500), add water to make 50 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: Dissolve 2 g of sodium 1-heptanesulfonate in 900 mL of water, add acetic acid(100) to adjust the pH to 3.0, and add water to make 1000 mL. To this solution, add 240 mL of acetonitrile and 40 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of famotidine is about 6 minutes.

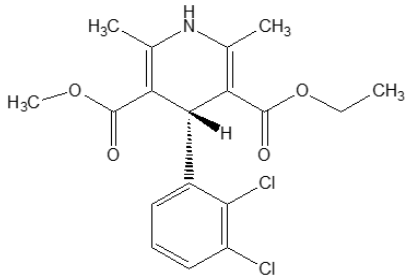
System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; famotidine and the internal standard are eluted in this order with the resolution being NLT 11.

System repeatability: Repeat the test 6 times with 5 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area of famotidine is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Felodipine
펠로디핀



and enantiomer

Felodipine $C_{18}H_{19}Cl_2NO_4$: 384.25

3-Ethyl 5-methyl 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate [*72509-76-3*]

Felodipine contains NLT 98.0% and NMT 101.0% of felodipine ($C_{18}H_{19}Cl_2NO_4$), calculated on the dried basis.

Description Felodipine occurs as a pale yellow to yellow crystalline powder.

It is freely soluble in acetone or ethanol(95), slightly soluble in heptane, and practically insoluble in water.

Identification (1) Determine the infrared spectra of Felodipine and felodipine RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Felodipine in methanol to make 50 mL, perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy using methanol as a control solution, and determine the absorbance at the wavelength of 440 nm with a layer length of 5 cm; it is NMT 0.2.

(2) ***Heavy metals***—Proceed with 1.0 g of Felodipine according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—With 40 μL of the test solution prepared according to the Assay, perform the test

as directed under the Liquid Chromatography according to the following conditions, and determine the peak area from the test solution; each peak area other than the major peak from the test solution is NMT 1.0%, and the sum of peak areas of these peaks is NMT 1.5% relative to the major peak area.

$$\text{Content (\%) of related substances} = 100 \times \frac{A_\text{i}}{A_\text{S}}$$

A_T: Each peak area other than the major peak
A_S: Total area of all peaks

Operating conditions

Proceed as directed under the operating conditions under the Assay.

Time span of measurement: NLT 2 times the retention time of felodipine.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 30 mg each of Felodipine and felodipine RS, dissolve each in the mobile phase to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Prepare the test solution and the standard solution before use. Perform the test with 40 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of felodipine in each solution.

$$\text{Amount (mg) of felodipine } (C_{18}H_{19}ClNO_4) = \text{Amount (mg) of felodipine RS} \times \frac{A_\text{T}}{A_\text{S}}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of phosphate buffer solution, acetonitrile and methanol (2 : 2 : 1).

Flow rate: 1 mL/min

System suitability

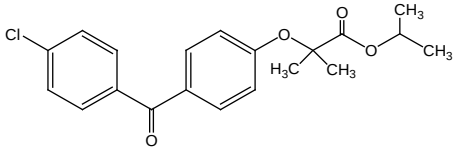
System performance: Dissolve 0.15 g of felodipine in a mixture of 25 mL of t-butyl alcohol and 25 mL of 1 mol/L perchloric acid, add 10 mL of 0.1 mol/L cerium ferric sulfate TS, allow to stand for 15 minutes, and add 3.5 mL of 10 mol/L sodium hydroxide TS. Neutralize with 2 mol/L sodium hydroxide TS. Transfer this mixture into a separatory funnel, add 25 mL of dichloromethane, shake, and take the lower layer. Evaporate the lower layer to dryness on a steam bath with the aid of a current of nitrogen. Dissolve 10 mg of the residue (felodipine oxide) and 5 mg of felodipine RS in the mobile phase to make 100 mL. Take 1.0 mL of this solution, and add the mobile phase to make 100 mL. Proceed with 20 μL of this solution according to the above conditions; felodipine oxide and felodipine are eluted in this order with the resolution not being less than 2.5. Proceed with 40 μL of the standard solution according to the above conditions; the symmetry factor of the felodipine peak is NMT 1.5.

Detection sensitivity: Adjust the detection sensitivity so that the height of the two peaks obtained from the solution in the system performance is NLT 20% of the full scale.

Phosphate buffer solution—Dissolve 6.9 g of sodium dihydrogen phosphate dihydrate in 400 mL of water, add 8 mL of 1 mol/L phosphoric acid, and add water to make 1000 mL.

Packaging and storage Preserve in light-resistant, tight containers.

Fenofibrate
페노피브레이트



Fenofibrate $C_{20}H_{21}ClO_4$: 360.83
Propan-2-yl 2-{4-[(4-chlorophenyl)carbonyl] phenoxy}-2-methylpropanoate [*49562-28-9*]

Fenofibrate contains NLT 98.5% and NMT 101.0% of fenofibrate ($C_{20}H_{21}ClO_4$), calculated on the dried basis.

Description Fenofibrate occurs as a white crystalline powder.
It is very soluble in dichloromethane, slightly soluble in ethanol(95), and practically insoluble in water.

Identification Determine the infrared spectra of Fenofibrate and fenofibrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 79 and 82 ℃.

Purity (1) ***Clarity and color of solution*—**Dissolve 0.50 g of Fenofibrate in acetone to make exactly 10 mL; the resulting solution is clear.

(2) ***Acid*—**Dissolve 1.0 g of Fenofibrate in 50 mL of ethanol previously neutralized with 0.2 mL of phenolphthalein TS. To this solution, add dropwise 0.1 mol/L sodium hydroxide solution until the resulting solution

exhibits a pink color; the consumed amount is NMT 0.2 mL.

(3) ***Chloride*—**To 5.0 g of Fenofibrate, add 25 mL of water, heat at 50 °C for 10 minutes, cool, and filter. To 5 mL of the filtrate, add 6 mL of dilute nitric acid and water to make 50 mL, and perform the test. Prepare the control solution by adding 6 mL of dilute nitric acid, 0.30 mL of 0.01 mol/L hydrochloric acid, and water to make 50 mL (NMT 0.01%).

(4) ***Sulfate*—**To 5.0 g of Fenofibrate, add 25 mL of water, heat at 50 °C for 10 minutes, cool, and filter. To 10 mL of the filtrate, add 1 mL of dilute hydrochloric acid and water to make 50 mL. Prepare the control solution by adding 1 mL of dilute hydrochloric acid, 0.42 mL of 0.005 mol/L sulfuric acid, and water to make 50 mL (NMT 0.01%).

(5) ***Heavy metals***—Proceed with 1.0 g of Fenofibrate and perform the test as directed under Method 2. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 20 ppm).

(6) ***Related substances*—**Dissolve about 100 mg of Fenofibrate in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Pipet 1 mL of this solution, and add the mobile phase to make exactly 100 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of each solution according to the automatic integration method and determine the amount of each related substance; fenofibrate related substance I with the relative retention time of 0.3 for fenofibrate obtained from the test solution and fenofibrate related substance II with the relative retention time of 0.4 are NMT 0.1%, and fenofibrate related substance III with the relative retention time of 1.3 is NMT 0.1%. Any other individual unidentified related substances are NMT 0.1%, and the total related substances are NMT 0.5%. However, exclude any peaks smaller than 0.05%.

$$\text{Content (\%) of related substances} = \frac{A_T}{A_S} \times rf \times \frac{1}{10}$$

A_T: Peak area of each related substance obtained from the test solution

A_S: Peak area of fenofibrate obtained from the standard solution

rf: The correction factor for each related substance for fenofibrate peak

Fenofibrate related substance I: 0.78
Fenofibrate related substance II: 1.02
Fenofibrate related substance III: 1.27
Other related substances: 1.00

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 286 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and water (7 : 3) (adjust the pH with phosphoric acid).

Flow rate: 1.0 mL/min

System suitability

Test for required detectability: Pipet 5 mL of the standard solution, and add the mobile phase to make exactly 10 mL. Proceed with 20 μL of this solution according to the above conditions; confirm that the signal-to-noise ratio of the torsemide peak is NLT 10.

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the symmetry factor of the fenofibrate peak is between 0.8 and 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of fenofibrate is NMT 10.0%.

Loss on drying NMT 0.5% (0.5 g, 60 °C, in vacuum, constant mass).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 25 mg each of Fenofibrate and fenofibrate RS, dissolve in the mobile phase to make exactly 25 mL, and use these solutions as the test solution and the standard solution (1), respectively. Also, weigh 10.0 mg of fenofibrate RS, 10.0 mg of fenofibrate related substance I RS, 10.0 mg of fenofibrate related substance II RS, and 20.0 mg of fenofibrate related substance III RS, and dissolve in the mobile phase to make exactly 100 mL. To 1.0 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution (2). Perform the test with 5 μL each of the test solution and the standard solution (1) as directed under the Liquid Chromatography according to the operating conditions for testing related substances, and determine the peak areas, A_T and A_S, of fenofibrate in each solution.

$$\text{Amount (mg) of fenofibrate } (C_{20}H_{21}ClO_4) = \text{Amount (mg) of fenofibrate RS} \times \frac{A_T}{A_S}$$

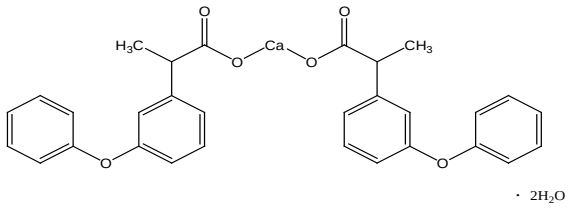
System suitability

Detection sensitivity: Adjust the sensitivity so that the peak heights obtained by performing the test with 5 μL of standard solution (2) according to the above conditions are NLT 50% of the full scale of the data collection device.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution (1) according to the above conditions; the relative standard deviation of the peak area of fenofibrate is NMT 1.0%.

Packaging and storage Preserve in light-resistant, well-closed containers.

Fenoprofen Calcium Dihydrate
페노프로펜칼슘수화물



Fenoprofen Calcium $C_{30}H_{26}CaO_6 \cdot 2H_2O$: 558.63
Calcium 2-(3-phenoxyphenyl)propanoate dihydrate [*152864-45-4*]

Fenoprofen Calcium Dihydrate contains NLT 97.0% and NMT 103.0% of fenoprofen calcium ($C_{30}H_{26}CaO_6$: 522.60), calculated on the anhydrous basis.

Description Fenoprofen Calcium Dihydrate occurs as a white crystalline powder.
It is slightly soluble in n-hexanol, methanol, or water, and practically insoluble in chloroform.

Identification (1) Mix 1 g of Fenoprofen Calcium Dihydrate with 50 mL of acetic acid(31), heat, filter, and add 2mL of ammonium oxalate TS to the filtrate; a white precipitate develops, and dissolve the precipitate in 3 mol/L hydrochloric acid TS.

(2) Determine the infrared spectra of Fenoprofen Calcium Dihydrate and fenoprofen calcium dihydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Calcium***—Weigh accurately about 0.75 g of Fenoprofen Calcium Dihydrate, add ethanol(95), and dissolve by heating if necessary. Add ethanol(95) to make exactly 50 mL, and use this solution as the test solution. Put 70 mL of water, 2 mL of sodium hydroxide solution (1 in 10) and 0.3 g of hydroxynaphthol in a 150-mL beaker to mix, add about 1 mL of the test solution, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS until the resulting solution exhibits a blue color. To this solution, add 10.0 mL of the test solution, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS until the resulting solution exhibits a blue color (between 7.3% and 8.0%, calculated on the anhydrous basis).

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.004 mg of Ca

(2) ***Heavy metals***—Proceed with 2.0 g of Fenoprofen Calcium Dihydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Weigh accurately about 0.2 g of Fenoprofen Calcium Dihydrate, dissolve in a mixture of water and acetonitrile (1 : 1) to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of fenoprofen calcium dihydrate RS and dissolve in a mixture of water and acetonitrile (1 : 1) to make exactly 100 mL. To 5.0 mL of this solution, add a mixture of water and acetonitrile (1 : 1) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, determine each peak area from each solution by the automatic integration method, and calculate the amount of each related substance; the amount of each related substance is NMT amount 0.5%, and the total amount of related substances is NMT 2.0%.

$$\text{Content (\%) of related substances} = 10000 \times \frac{C}{W} \times \frac{A_i}{A_S}$$

C: Concentration (mg/mL) of fenoprofen calcium in the standard solution

W: Amount (mg) of Fenoprofen Calcium Dihydrate taken from the test solution

A_i: Peak area of each related substance obtained from the test solution

A_S: Peak area of fenoprofen obtained from the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: A mixture of water and acetic acid(31) (98 : 2).

Mobile phase B: A mixture of acetonitrile and acetic acid(31) (98 : 2).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0	70	30
0 - 3	70	30
3 - 41	70 → 10	30 → 90
41 - 42	10	90
42 - 43	10 → 70	90 → 30

43 - 55	70	30

Flow rate: 1.5 mL/min

System suitability

System performance: Dissolve 2 mg of 3-phenoxybenzoic acid and 2 mg of fenoprofen calcium dihydrate RS in a mixture of water and acetonitrile (1 : 1) to make 100 mL. Proceed with 20 μL of this solution according to the above conditions; the relative retention times of 3-phenoxybenzoic acid peak and fenoprofen peak are 0.89 and 1.0, respectively, the resolution between these peaks is NLT 9.0, and the symmetry factor of the fenoprofen peak is NMT 2.0. Proceed with 20 μL of the standard solution according to the above conditions; the symmetry factor of the fenoprofen peak is NMT 2.0.

System repeatability: Repeat the test 5 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of temazepam is NMT 2.0%.

Water Between 5.0% and 8.0% (1 g, volumetric titration, direct titration).

Assay Weigh accurately about 70 mg each of Fenoprofen Calcium Dihydrate and fenoprofen calcium dihydrate RS, add 0.5 mL of 0.5 mol/L hydrochloric acid TS and 2 mL of acetone, dissolve in a mixture of methanol and water (7 : 3) to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak areas, A_T and A_S, of fenoprofen in each solution.

$$\text{Amount (mg) of fenoprofen calcium } [(C_{15}H_{13}O_3)_2Ca] = 100 \times C \times \frac{A_T}{A_S}$$

C: Amount (mg) of fenoprofen calcium in fenoprofen calcium dihydrate RS, calculated on the anhydrous basis

Operating conditions

Detector: An ultraviolet absorption photometer (272 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile, water, and phosphoric acid (50 : 49.6 : 0.4).

Flow rate: 2 mL/min

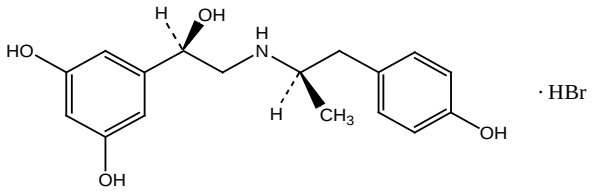
System suitability

System performance: Dissolve 5 mg of fenoprofen calcium dihydrate RS and 5 mg of gemfibrozil in a mixture of methanol and water (7 : 3) to make 5 mL. Proceed with 20 μL of this solution according to the above conditions; the relative retention times of fenoprofen peak and gemfibrozil peak are about 0.5 and 1.0, respectively, and the resolution between these peaks is NLT 8. Also, proceed with 20 μL of the standard solution according to the above conditions; the number of theoretical plate obtained from the fenoprofen peak is NLT 3000.

System repeatability: Repeat the test 5 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of fenoprofen is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Fenoterol Hydrobromide
페노테롤브롬화수소산염



and enantiomer

$C_{17}H_{21}NO_4 \cdot HBr$: 384.27

5-[1-Hydroxy-2-[1-(4-hydroxyphenyl)propan-2-ylamino]ethyl]benzene-1,3-diolhydrobromide [*1944-12-3*]

Fenoterol Hydrobromide contains NLT 99.0% and NMT 101.0% of fenoterol hydrobromide ($C_{17}H_{21}NO_4 \cdot HBr$), calculated on the dried basis.

Description Fenoterol Hydrobromide occurs as a white crystalline powder.
It is soluble in water or ethanol(95).

Identification (1) Determine the infrared spectra of Fenoterol Hydrobromide and fenoterol hydrobromide RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Fenoterol Hydrobromide (1 in 100) responds to the Qualitative Analysis (1) for bromide.

pH Dissolve 2.0 g of Fenoterol Hydrobromide in water to make exactly 50 mL; the pH of this solution is between 4.2 and 5.2.

Purity (1) ***Clarity and color of solution***—Dissolve 2.0 g of Fenoterol Hydrobromide in water to make exactly 50 mL; the resulting solution is clear and colorless.

(2) ***Iron***—Proceed with 1.0 g of Fenoterol Hydrobromide according to Method 3 and perform the test as directed under Method A. Prepare the control solution

with 0.5 mL of iron standard solution (NMT 5 ppm).

(3) ***Phenone***—Dissolve 2.0 g of Fenoterol Hydrobromide in water to make 50 mL. Determine the absorbance of this solution at the wavelength of 330 nm as directed under the Ultraviolet-visible Spectroscopy; it is NMT 0.42 (NMT 0.2%).

(4) ***Isomer***—Dissolve 25.0 mg each of Fenoterol Hydrobromide and fenoterol hydrobromide RS in water to make exactly 10 mL, and use these solutions as the test solution and the standard solution, respectively. Prepare the test solution and the standard solution before use. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Calculate the amount of isomer by determining the heights, (H_T) and (H_S), of the peak eluting immediately after the major peak obtained from the test solution; it is NMT 4.0%.

$$\text{Content (\%) of isomer} = \text{Content (\%) of isomer indicated on the reference standards} \times \frac{H_T}{H_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: To 10 mL of 0.9 w/v% potassium dihydrogen phosphate, add 690 mL of 2.4 w/v% dibasic sodium phosphate 12-hydrate solution, mix, and add phosphoric acid to adjust the pH to 8.5. Add 300 mL of methanol, and mix.

Flow rate: 1.0 mL/minute. Adjust the retention time of the major peak to be NMT 20 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution under the above conditions; adjust the sensitivity so that the peak height of the isomer eluting immediately after the major peak is NLT 10% of the full scale. The height of the valley between the major peak and the isomer peak obtained from the standard solution is NMT 4% of the full scale.

Loss on drying NMT 0.5% (1 g, 105 ℃, constant mass).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.6 g of Fenoterol Hydrobromide, dissolve in 50 mL of water, add 5 mL of dilute nitric acid and 25.0 mL of 0.1 mol/L silver nitrate solution, and titrate with 0.1 mol/L ammonium thiocyanate VS while shaking to mix until the resulting solution exhibits an orange color (indicator: 2 mL of ammonium iron(III) sulfate TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L silver nitrate VS
= 38.43 mg of $C_{17}H_{21}NO_4$

Packaging and storage Preserve in light-resistant, well-closed containers.

Fenoterol Hydrobromide Tablets
페노테롤브롬화수소산염 정

Fenoterol Hydrobromide Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of fenoterol hydrobromide ($C_{17}H_{21}NO_4 \cdot HBr$: 384.27).

Method of preparation Prepare as directed under Tablets, with Fenoterol Hydrobromide.

Identification Weigh an amount of Fenoterol Hydrobromide Tablets, equivalent to about 50 mg of fenoterol hydrobromide according to the labeled amount, extract with 5 mL of water, then filter, and use this solution as the test solution. Weigh 50 mg of fenoterol hydrobromide RS, add water to make 5 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of 2-butanol, formic acid and water (75 : 15 : 10), and air-dry the plate. Spray evenly a diazobenzenesulfonic acid TS on the plate, and heat at 105 ℃ for 10 minutes; the R_f values and colors of the spots from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 tablet of Fenoterol Hydrobromide Tablets at 50 revolutions per minute according to Method 2, using 900 mL of water as the dissolution medium. Take the medium 15 minutes after starting the test, and filter. Discard the first 10 mL of the filtrate, pipet V mL of the subsequent filtrate, add water to make V' mL of a solution containing about 2 μg of fenoterol hydrobromide ($C_{17}H_{21}NO_4 \cdot HBr$) per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 20 mg of fenoterol hydrobromide RS, and dissolve in water to make 100 mL. Pipet 1 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 100 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of fenoterol hydrobromide in each solution. The dissolution rate in 15 minutes is NLT 80%.

Dissolution rate (%) of the labeled amount of fenoterol hydrobromide ($C_{17}H_{21}NO_4$)

$$= W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 9$$

W_S: Amount (mg) of fenoterol hydrobromide RS
C: Labeled amount (mg) of fenoterol hydrobromide ($C_{17}H_{21}NO_4$) in 1 tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 276 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: A mixture of pH 3.2 buffer solution and acetonitrile (100 : 27).

Flow rate: 1.0 mL/min

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Fenoterol Hydrobromide Tablets, and powder. Weigh accurately an amount equivalent to about 2.5 mg of fenoterol hydrobromide ($C_{17}H_{21}NO_4$·HBr), add water to make exactly 100 mL, then filter, and use the filtrate as the test solution. Separately, weigh accurately about 25 mg of fenoterol hydrobromide RS, and add water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and determine the peak areas, A_T and A_S, of fenoterol hydrobromide in each solution.

Amount (mg) of fenoterol hydrobromide ($C_{17}H_{21}NO_4$·HBr)
$= \text{Amount (mg) of fenoterol hydrobromide RS} \times \frac{A_T}{A_S} \times \frac{1}{10}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 276 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: A mixture of pH 3.2 buffer solution and acetonitrile (100 : 27).

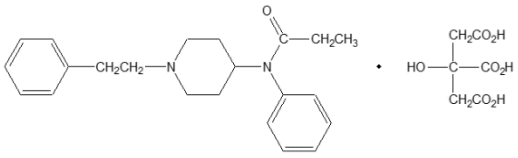
Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of fenoterol hydrobromide is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Fentanyl Citrate
펜타닐시트르산염



$C_{22}H_{28}N_2O \cdot C_6H_8O_7$: 528.59
2-Hydroxypropane-1,2,3-tricarboxylic acid ; *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide [*990-73-8*]

Fentanyl Citrate contains NLT 98.0% and NMT 101.0% of fentanyl citrate ($C_{22}H_{28}N_2O \cdot C_6H_8O_7$), calculated on the dried basis.

Description Fentanyl Citrate occurs as white crystals or a crystalline powder.
It is freely soluble in methanol or acetic acid(100), sparingly soluble in water or ethanol(95), and very slightly soluble in ether.

Identification (1) Dissolve 50 mg each of Fentanyl Citrate and fentanyl citrate RS in 10 mL of 0.1 mol/L hydrochloric acid TS and ethanol(95) to make 100 mL. Determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Fentanyl Citrate and fentanyl citrate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Fentanyl Citrate (1 in 100) responds to the Qualitative Analysis (1) for citrate.

Melting point Between 150 and 154 ℃.

pH Dissolve 0.10 g of Fentanyl Citrate in 10 mL of water; the pH of this solution is between 3.0 and 5.0.

Purity (1) ***Heavy metals***—Proceed with 0.5 g of Fentanyl Citrate according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 0.10 g of Fentanyl Citrate in 5 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel

for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, water and acetic acid(31) (3 : 1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly Dragendorff's TS for spraying on the plate; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (0.2 g, in vacuum, silica gel, 60 ℃, 2 hours).

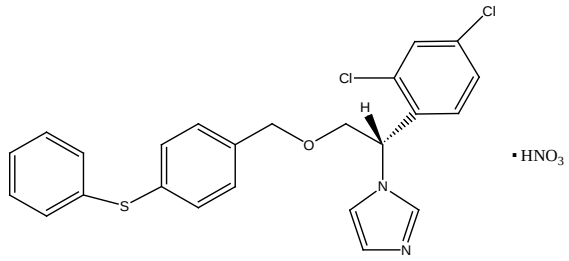
Residue on ignition NMT 0.2% (0.5 g).

Assay Weigh accurately about 75 mg of Fentanyl Citrate, dissolve in 50 mL of acetic acid(100), and titrate with 0.02 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.02 mol/L perchloric acid VS
= 10.572 mg of $C_{22}H_{28}N_2O \cdot C_6H_8O_7$

Packaging and storage Preserve in light-resistant, tight containers.

Fenticonazole Nitrate
펜티코나졸질산염



and enantiomer

$C_{24}H_{20}Cl_2N_2OS \cdot HNO_3$: 518.41
1-{2-(2,4-Dichlorophenyl)-2-[4-(phenylthio) benzyloxy]ethyl}-1*H*-imidazole nitrate [*73151-29-8*]

Fenticonazole Nitrate contains NLT 99.0% and NMT 101.0% of fenticonazole nitrate ($C_{24}H_{20}Cl_2N_2OS \cdot HNO_3$), calculated on the dried basis.

Description Fenticonazole Nitrate occurs as a white crystalline powder.
It is freely soluble in methanol or *N*,*N*-dimethylformamide, sparingly soluble in ethanol(95), and practically insoluble in water.

Identification (1) Determine the absorption spectra of solutions of Fenticonazole Nitrate and fenticonazole nitrate RS in ethanol(95) (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Fenticonazole Nitrate and fenticonazole nitrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Weigh an amount of Fenticonazole Nitrate, equivalent to 1 mg of nitrate ions, add a mixture of 0.1 mL of nitrobenzene and 0.2 mL of sulfuric acid, allow to stand for 5 minutes, and cool with iced water. Add gently 5 mL of water while stirring, add 5 mL of 10 mol/L sodium hydroxide TS and 5 mL of acetone, shake to mix, and allow to stand; the upper layer exhibits an intense purple color.

Optical rotation $[\alpha]_D^{20}$: Between -0.10° and + 0.10° (0.1 g, methanol, 10 mL, 100 mm).

Melting point Between 134 and 137 ℃.

Purity (1) ***Toluene***—Weigh exactly 0.2 g of Fenticonazole Nitrate, transfer into a 10 mL vial, disperse with exactly 5 mL of water, and use this solution as the test solution. Separately, mix 4.0 mg of toluene with water to make 1000 mL. Transfer 5 mL of this solution into a 10 mL vial, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions. Use a headspace sample injection apparatus. Determine the amount of toluene according to the standard addition method; it is NMT 100 ppm.

Operating conditions
Detector: A flame ionization detector
Column: A tube about 0.32 mm in internal diameter and about 25 m in length, coated with poly(cyanopropyl)(7)phenyl(7)methyl(86)siloxane for gas chromatography with a thickness of 1.2 μm.
Headspace conditions: Equilibrium temperature of 90 ℃, equilibrium time of 1 hour.
Column temperature: 80 ℃
Injection port temperature: 180 ℃
Detector temperature: 220 ℃
Carrier gas: Helium
Split ratio: About 1 : 25.
Column head pressure: 40 kPa
Injection volume: Maintain each liquid at 90 ℃ for 1 hour, and inject 1 mL in the form of vapor into the column.

(2) ***Related substances***—Weigh accurately 25.0 mg of Fenticonazole Nitrate, add the mobile phase to make exactly 25 mL, and use this solution as the test solution. To 1.0 mL of the test solution, add the mobile phase to make exactly 200 mL, and use this solution as the standard solution (1). To 10.0 mL of the standard solution (1), add the mobile phase to make exactly 25 mL, and use this solution as the standard solution (2). Pipet 1.0 mL of the

standard solution (1), add the mobile phase to make exactly 10 mL, and use this solution as the standard solution (3). To 5.0 mL of the test solution, add 5 mg of fenticonazole related substance I RS {(*RS*)-1-[2-(2,4-dichlorophenyl)-2-hydroxyethyl]-3-[4-(phenylsulfanyl)benzyl]imidazolium nitrate}, and dissolve in the mobile phase to make exactly 100 mL. To 2.0 mL of this solution, add 2.0 mL of the mobile phase to make exactly 10 mL, and use this solution as the standard solution (4). Perform the test with 10 μL each of the test solution and the standard solution (1) as directed under the Liquid Chromatography according to the following operating conditions, and determine the areas of each peak according to the automatic integration method; the peak area other than the major peak and nitric acid ion peak (corresponding to the void volume of column) obtained from test solution is NMT the major peak area obtained from the standard solution (2) (0.2%), and the total area of these peaks is NMT the major peak area obtained from standard solution (1) (0.5%). However, exclude any peak having an area smaller than the major peak area obtained from the standard solution (3).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 229 nm).

Column: A stainless steel column, about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 - 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and phosphate buffer solution (70 : 30).

Flow rate: 1.0 mL/min

System suitability

Inject 10 μL of the standard solution (2), and adjust the sensitivity so that the peak height of fenticonazole is at least 10% of the full scale of the data collection device. Inject 10 μL each of the standard solution (3) and the standard solution (4) separately. In the chromatogram obtained from the standard solution (4), the resolution between fenticonazole related substance I and fenticonazole is NLT 2, and in the chromatogram obtained from the standard solution (3), a signal-to-noise ratio is NLT 5.

Phosphate buffer solution—Dissolve 3.4 g of potassium dihydrogen phosphate in 900 mL of water, adjust pH with phosphoric acid to 3.0, and add water to make 1000 mL.

Loss on drying NMT 0.5% (1 g, in vacuum, 60 ℃, constant mass).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.45 g of Fenticonazole Nitrate, dissolve with 50 mL of a mixture of 2-butanone and acetic acid(100) (1 : 1), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 51.84 mg of $C_{24}H_{20}Cl_2N_2OS \cdot HNO_3$

Packaging and storage Preserve in light-resistant, well-closed containers.

Ferric Hydroxide Polymaltose Complex
폴리말토오스수산화제이철착염

Ferric Hydroxide Polymaltose Complex contains NLT 24.0% and NMT 32.0% of iron (Fe: 55.85).

Description Ferric Hydroxide Polymaltose Complex occurs as a brown amorphous powder and is odorless.
It is soluble in water and insoluble in organic solvents.

Identification (1) ***Ionized iron***—Weigh an amount of Ferric Hydroxide Polymaltose Complex, equivalent to 5 g of iron according to the labeled amount, add 80 mL of water, dissolve at 70 ℃ for 1 hour while shaking, add water to make 100 mL, and filter the solution. Use the filtrate as the test solution. To the solution of 1 mL of the test solution in 4 mL of water, add 1 mL of 2 mol/L ammonia TS, and mix; a brown precipitate does not form.

(2) ***Iron***—Mix with 1 mL of the test solution of (1), 20 mL of water and 5 mL of hydrochloric acid, and heat on a steam bath for 5 minutes. After cooling, neutralize with excess 25% ammonia water, and filter. Wash the produced ferric hydroxide precipitate with water, dissolve the precipitate in a small amount of 2 mol/L hydrochloric acid, and add water to make 20 mL. To this solution, add 1 mL of hydroxylamine hydrochloride TS, allow to stand for 30 minutes, and add *o*-phenanthroline ethanol solution (1 in 50); the resulting solution exhibits an dark red color.

(3) ***Polymaltose***—To 1 mL of the test solution of (1), add 4 mL of water and 0.5 mL of hydrochloric acid, heat on a steam bath for 5 minutes, cool rapidly, add 2 mL of 25% ammonia water and 5 mL of freshly prepared hydrogen sulfide TS, and mix. Remove excess hydrogen sulfide by boiling, cool, and filter. To 5 mL of the filtrate, add 1 mL of hydrochloric acid, heat on a steam bath for 15 minutes, and cool immediately. Add 4 mL of 20% sodium hydroxide solution and 5 mL of Fehling's TS, mix, boil for 1 minute, and cool immediately; a red Cu_2O precipitate forms.

pH Weigh an amount of Ferric Hydroxide Polymaltose Complex, equivalent to 5 g of iron according to the labeled amount, add 80 mL of water, dissolve at 70 ℃ for 1 hour while shaking, and add water to make 100 mL; the pH of the filtrate is between 5.5 and 7.5.

Purity (1) ***Polymaltose***—Between 25.0% and 50.0% Weigh an amount of Ferric Hydroxide Polymaltose Complex, equivalent to 5 g of iron, add 80 mL of water,

dissolve at 70 ℃ for 1 hour while shaking, add water at 20 ℃ to make 100 mL, and filter. To 2.0 mL of this solution, add water to make 100 mL. To 20 mL of this solution, add water to make 100 mL, and use this solution as the test solution. Separately, transfer 0.10 g of the anhydrous glucose into a 100-mL volumetric flask, and add water to make 100 mL. Take 20 mL of this solution, add water to make 100 mL, and use it as the standard solution. Prepare 6 stoppered test tubes, separately add 1 mL of water for 2 test tubes, 1 mL of the test solution for 2 test tubes, and 1 mL of the standard solution for 2 test tubes. Add 10 mg of anthrone solution to each tube, mix well, and close the stopper. After warming on a steam bath for exactly 10 minutes, take it out, and cool. Next, shake for 5 minutes to mix, perform the test as directed under the Ultraviolet-visible Spectroscopy using water as the control solution, and determine the absorbances, A_T and A_S, at the absorbance maximum wavelength of between 600 nm and 605 nm from the test solution and the standard solution.

$$\text{Amount (mg) of polymaltose} = \frac{A_T \times 100\ (mg) \times 162}{A_S \times 180}$$

(2) ***Sodium chloride***—NMT 6.0%. Transfer 10.0 mL of the test solution of (1) into a 100-mL beaker, add 60 mL of water and 0.2 mL of nitric acid, shake well, and titrate with 0.1 mol/L silver nitrate VS using the potentiometric titration. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L silver nitrate VS
= 5.850 mg of NaC1

Loss on drying NMT 5.0% (1 g, in vacuum, 20 ℃, phosphorus pentoxide, 2 hours).

Assay After mixing 10 g of Ferric Hydroxide Polymaltose Complex well, weigh accurately 0.3 g of the mixed drug, transfer into a 200-mL beaker, add 10 mL of hydrochloric acid, and heat on a steam bath for 1 to 2 minutes while shaking to mix. After the solution is completely dissolved, take it out, and allow to stand for 5 minutes. Add 100 mL of water and 10 mL of acetic acid(100), and adjust the pH to between 2.2 and 2.5 with 30% sodium hydroxide solution. Add 2.5 mL of 2% pyrocatechol sodium salt solution as the indicator, titrate with freshly prepared 0.1 mol/L ethylenediaminetetraacetic acid disodium salt VS at between 40 and 50 ℃ until the green color of the solution turns yellow. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 5.585 mg of Fe

Packaging and storage Preserve in tight containers.

Ferric Hydroxide Polymaltose Complex Solution
폴리말토오스수산화제이철착염 액

Ferric Hydroxide Polymaltose Complex Solution contains NLT 95.0% and NMT 105.0% of the labeled amount of iron (Fe: 55.85) in the ferric hydroxide polymaltose complex.

Method of preparation Prepare as directed under Liquids, with Ferric Hydroxide Polymaltose Complex.

Identification Take 0.25 mL of Ferric Hydroxide Polymaltose Complex Solution, add 1 mL of 4 mol/L sulfuric acid, and heat until it becomes transparent yellow. Add 0.1 mol/L potassium ferrocyanide TS; the resulting solution exhibits a blue color.

pH Between 5.0 and 7.0.

Purity To 0.25 mL of Ferric Hydroxide Polymaltose Complex Solution, add 4 mL of water and 1 mL of 2 mol/L ammonia TS, and shake to mix; a brown precipitate ($Fe(OH)_3$) does not form.

Assay Take 5.0 mL of Ferric Hydroxide Polymaltose Complex Solution, add 10 mL of hydrochloric acid, shake well to mix, and heat until the solution becomes yellow. Add 100 mL of water and 10 mL of acetic acid(100), and adjust the pH to between 2.2 and 2.5 with 30% sodium hydroxide solution. Add 0.2 mL of hydrogen peroxide, immediately add 2.5 mL of 2% pyrocatechol sodium salt solution, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS while maintaining the temperature at 40 to 50 ℃. The endpoint of the titration is when the color of this solution changes from green to yellow. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.7925 mg of Fe

Packaging and storage Preserve in tight containers.

Ferric Hydroxide Polymaltose Complex and Folic Acid Tablets
폴리말토오스수산화제이철착염·폴산 정

Ferric Hydroxide Polymaltose Complex and Folic Acid Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of iron (Fe: 55.85) and NLT 90.0% and NMT 150.0% of folic acid ($C_{19}H_{19}N_7O_6$: 441.40).

Method of preparation Prepare as directed under Tablets, with Ferric Hydroxide Polymaltose Complex and Folic Acid.

Identification (1) ***Ferric hydroxide polymaltose complex*—**Perform the test with Ferric Hydroxide Polymaltose Complex and Folic Acid Tablets as directed under the Analysis for Minerals.

(2) ***Folic acid*—**Perform the test with Ferric Hydroxide Polymaltose Complex and Folic Acid Tablets as directed under the Analysis for Vitamins.

Disintegration Meets the requirements.

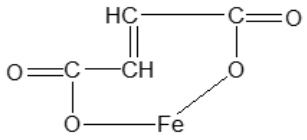
Uniformity of dosage units Meets the requirements.

Assay (1) ***Ferric hydroxide polymaltose complex*—**Weigh accurately the mass of NLT 20 Ferric Hydroxide Polymaltose Complex and Folic Acid Tablets, then powder, and perform the test as directed under the Analysis for Minerals.

(2) ***Folic acid*—**Weigh accurately the mass of NLT 20 Ferric Hydroxide Polymaltose Complex and Folic Acid Tablets, and perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in tight containers.

Ferrous Fumarate
푸마르산철



Ferrous fumarate $C_4H_2FeO_4$: 169.90
Iron(II) (*E*)-but-2-enedioate [*141-01-5*]

Ferrous fumarate, when dried, contains NLT 97.0% and NMT 101.0% of ferrous fumarate ($C_4H_2FeO_4$).

Description Ferrous fumarate occurs as an orange to reddish brown powder and is odorless.
It is slightly soluble in water and very slightly soluble in ethanol(95).
The solubility of Ferrous Fumarate in dilute hydrochloric acid is decreased by separation of fumarate.

Identification (1) Add 25 mL of diluted hydrochloric acid (1 in 2) to 1.5 g of Ferrous fumarate, add water to make 50 mL, and heat until the solution completely dissolves. After cooling, filter using a glass filter, wash the precipitate with diluted hydrochloric acid (3 in 100), and dry at 105 ℃. Determine the infrared spectra of this precipitate and fumarate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

(2) The filtrate obtained in (1) responds to the Qualitative Analysis for ferrous salt.

Purity (1) ***Sulfate*—**Put 1.0 g of Ferrous Fumarate in a 250-mL beaker, add 100 mL of water, and heat on a steam bath while adding hydrochloric acid dropwise until the solution completely dissolves (about 2 mL of hydrochloric acid is consumed). Filter, if necessary, and add water to the filtrate to make 100 mL. Heat this solution to boiling, add 10 mL of barium chloride TS, heat for 2 hours on a steam bath, put a lid, and allow to stand for 16 hours. If crystals of ferrous fumarate form, dissolve by heating the solution on a steam bath. Filter the solution with filter paper for assay, add ammonium sulfide TS to the filtrate, and wash with warm water until the black precipitate is no longer produced. Transfer the residue into a crucible, previously weighed along with the filter paper, carbonize the filter paper without burning, and ignite the crucible and its contents at 600 ℃ to a constant mass. 1 mg of the residue corresponds to 0.412 mg of sulfate (SO_4) (NMT 0.2%).

(2) ***Arsenic***—Put 2.0 g of Ferrous Fumarate in a beaker and add 10 mL of water and 10 mL of sulfuric acid. Heat the fumaric acid and precipitate completely, cool, add 20 mL of water, and filter in a 50-mL volumetric flask. Wash the precipitate with water, combine the washings in a volumetric flask, and add water to the gauge line to mix. Use 25.0 mL of this solution as the test solution and perform the test. Prepare the control solution with 3.0 mL of arsenic standard solution (NMT 3 ppm).

(3) ***Ferric ion*—**Weigh accurately about 2.0 g of Ferrous Fumarate, put in a 250-mL Erlenmeyer flask with a stopper, add 25 mL of water and 4 mL of hydrochloric acid, and heat on a hot plate until it completely dissolves. Stopper and cool to room temperature. Add 3 g of potassium iodide, stopper, shake to mix, and allow to stand for 5 minutes in the dark. Remove the stopper, add 75 mL of water, then titrate with 0.1 mol/L sodium thiosulfate solution (indicator : 3 mL of starch TS). NMT 7.16 of 0.1 mol/L sodium thiosulfate is consumed (NMT 2.0%).

(4) ***Mercury*—**Proceed with the following procedure using a light-resistant container. Weigh accurately about 1 g of Ferrous Fumarate, add 30 mL of diluted nitric acid (1 in 10), and dissolve while heating on a steam bath. Cool quickly in an ice bath and filter using a filter washed with pre-diluted nitric acid (1 in 10) and water. To the filtrate, add 20 mL of sodium citrate solution (1 in 4) and 1 mL of hydroxylamine hydrochloride TS, and use this solution as the test solution. Separately, prepare the control solution with 3.0 mL of mercury standard solution, 30 mL of diluted nitric acid (1 in 4), 5 mL of sodium citrate solution (1 in 4) and 1 mL of hydroxylamine hydrochloride. Add ammonia TS to the control solution to adjust the pH to 1.8, and adjust the pH of the test solution to 1.8 with sulfuric acid, and transfer each to a separatory funnel. Perform the test with the test solution and the control solution as directed below. Extract 2 times using

5 mL of dithizone solution for extraction and then 5 mL of chloroform, and transfer the chloroform extract to another separatory funnel. To the extract, add 10 mL of diluted hydrochloric acid (1 in 2), shake to mix, allow to stand, and then discard the chloroform layer. Wash the acid-extract with 3 mL of chloroform and discard the washings. Add 0.1 mL of ethylenediaminetetraacetic acid disodium salt solution (1 in 50) and 2 mL of 6 mol/L acetic acid, mix, and slowly add 5 mL of ammonia TS. Close the lid of the separatory funnel, cool it under running cold water, open the lid, and transfer the contents into a beaker. Adjust the pH of the test solution and the control solution to 1.8 in the same way as the above, and transfer them to separatory funnels again. Add 5.0 mL of diluted dithizone solution for extraction, shake vigorously to mix, and allow to stand. Compare the color of the chloroform layers of the test solution and the control solution using a diluted dithizone solution for extraction as a control solution; the color obtained from the test solution is not more intense than that from the control solution (NMT 3 ppm).

Mercury standard stock solution—Transfer 135.4 mg of mercury(II) chloride to a 100-mL volumetric flask, dissolve in 0.5 mol/L sulfuric acid TS, fill to the gauge line, and mix. This solution contains 0.1 g of mercury (Hg) in 100 mL.

Mercury standard solution—Take 1.0 mL of the mercury standard stock solution immediately before use, put in a 1000-mL volumetric flask, add 0.5 mol/L sulfuric acid TS, fill up to the gauge line, and mix. 1 mL of this solution contains 1 μg of mercury (Hg).

Diluted dithizone solution for extraction—Dilute 5 mL of dithizone solution for extraction with 25 mL of chloroform before use.

(5) ***Lead***—Put 1.0 g of Ferrous Fumarate in a 50-mL beaker, add 6 mL of nitric acid and 10 mL of perchloric acid, cover with a watch glass, and heat to evaporate until completely dry. Cool, then dissolve the residue by adding 10 mL of 9 mol/L hydrochloric acid, and then use about 10 mL of water to transfer to a 50-mL volumetric flask. Add 20 mL of ascorbic acid-sodium iodide TS and 5.0 mL of trioctylphosphine oxide solution, shake for 30 seconds to mix, and allow to stand to separate. Then, add water so that the organic solvent layer reaches the neck portion of the flask, shake to mix again, and allow to stand to separate. Use the organic solvent layer as the test solution. Separately, take 5mL of lead standard solution, and add water to make exactly 100 mL. Pipet 2 mL of this solution and put in a 50-mL beaker. To this beaker and a beaker for blank test, add 6 mL of nitric acid and 10 mL of perchloric acid, and heat to evaporate to dryness. Cool, dissolve the residue in 10 mL of 9 mol/L hydrochloric acid, and use about 10 mL of water to transfer to 50-mL flasks, respectively. To each flask, add 20 mL of ascorbic acid-sodium iodide TS and 5.0 mL of trioctylphosphine oxide solution, shake for 30 seconds to mix, and allow to stand to separate. Then add water so that the organic solvent layer reaches the neck portion of the flask, shake to mix again, allow to stand to separate. Use the organic solvent layers as the standard solution(2.0 μg/mL) and the blank test solution, respectively. Perform the test with the test solution and the standard solution as directed under Atomic Absorption Spectroscopy according to the following conditions; the absorbance of the test solution is not greater than that of the standard solution (NMT 0.001%). Use 4-methyl-2-pentanone to adjust absorbance to 0; the absorbance of the blank test solution is NMT 20% of the difference between the absorbance of the standard solution and the absorbance of the blank test solution.

Gas: Air–acetylene
Lamp: Lead hollow-cathode lamp
Wavelength: 283.3 nm

Trioctylphosphine oxdie solution—Dissolve 5.0 g of trioctylphosphine oxide in 4-methyl-2-pentanone to make 100 mL.

(6) ***Cadmium***—Weigh 2.0 g of Ferrous Fumarate and dissolve in 10 mL of hydrochloric acid and 80 mL of water, and heat gently as needed. After cooling, filter as needed, add water to make 100 mL, and use this solution as the test solution. Separately, pipet 2.0 mL of cadmium standard solution, add hydrochloric acid to make exactly 10 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solutions as directed under Atomic Absorption Spectroscopy according to the following conditions; the absorbance of the test solution is NMT that of the standard solution (NMT 10 ppm).

Gas: Air–acetylene
Lamp: Cadmium hollow-cathode lamp
Wavelength: 228.8 nm

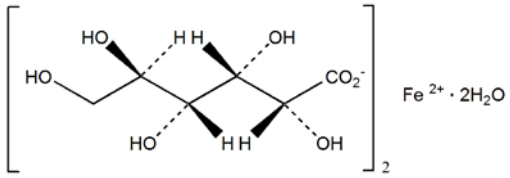
Loss on drying NMT 1.5% (1 g, 105 ℃, 16 hours).

Assay Weigh accurately about 0.15 g of Ferrous Fumarate, previously dried, add 7.5 mL of dilute sulfuric acid, dissolve by heating and cool, then add 25 mL of water, and immediately titrate with 0.1 mol/L cerium sulfate VS (indicator : 0.1 mL of ferroin TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L cerium sulfate VS
= 16.990 mg of $C_4H_2FeO_4$

Packaging and storage Preserve in well-closed containers.

Ferrous Gluconate Hydrate
글루콘산제일철수화물



Ferrous Gluconate $C_{12}H_{22}FeO_{14}\cdot 2H_2O$: 482.17
Iron(2+);(2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanoate; dihydrate [*6047-12-7*]

Ferrous Gluconate Hydrate contains NLT 97.0% and NMT 102.0% of ferrous gluconate ($C_{12}H_{22}FeO_{14}$: 446.14), calculated on the dried basis.

Description Ferrous Gluconate Hydrate occurs as a yellowish gray or light yellowish green fine powder or granule with a faint odor of burning sugar.
1.0 g of Ferrous Gluconate Hydrate dissolves in 10 mL of warm water and is practically insoluble in ethanol(95).
Its aqueous solution (1 in 20) is acidic.

Identification (1) Weigh 10 mg of Ferrous Gluconate Hydrate and dissolve in 10 mL of water to use it as the test solution. If necessary, warm it in a 60 °C water bath. Separately, dissolve 10 mg of ferrous gluconate hydrate RS in 10 mL of water and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethanol(95), water. ammonia water(28) and ethyl acetate (50 : 30 : 10 : 10) as a developing solvent to a distance of about 15 cm, dry the plate at 110 ℃ for 20 minutes, and cool it. Dissolve 2.5 g of ammonium heptamolybdate tetrahydrate in 50 mL of 1 mol/L sulfuric acid, add 1.0 g of cerium sulfate, shake to dissolve, and add 1 mol/L sulfuric acid to make 100 mL. Spray this solution evenly on the plate and heat at 110 ° C for 10 minutes; the color and R_f values of the spots obtained from the test and standard solutions are the same.

(2) Add potassium hexacyanoferrate(III) TS to the aqueous solution of Ferrous Gluconate Hydrate (1 in 200); a dark blue precipitate is formed.

Purity (1) ***Chloride***—Proceed with 1.0 g of Ferrous Gluconate Hydrate and perform the test. Prepare the control solution with 1.0 mL of 0.02 mol/L hydrochloric acid (NMT 0.07%).

(2) ***Sulfate***—Proceed with 1.0 g of Ferrous Gluconate Hydrate and perform the test. Prepare the control solution with 1.0 mL of 0.01 mol/L sulfuric acid (NMT 0.1%).

(3) ***Oxalic acid***—Dissolve 1.0 g of Ferrous Gluconate Hydrate in 10 mL of water, add 2 mL of hydrochloric acid, extract each with 50 mL and 20 mL of ether, and combine all the extracts. To the combined extracts, add 10 mL of water and evaporate ether on a steam bath. Add 1 drop of 6 mol/L acetic acid and 1 mL of calcium acetate hydrate solution (1 in 20); the solution does not become turbid within 5 minutes.

(4) ***Lead***—Weigh 1.0 g of Ferrous Gluconate Hydrate, put it in 50-mL volumetric flask, add 10 mL of 9 mol/L hydrochloric acid, about 10 mL of water, 20 mL of ascorbic acid-sodium iodide TS, and 5 mL of 4-methyl-2-pentanone solution of trioctylphosphine oxide (5 in 100), shake for 30 seconds, and allow to stand until the layers separate. Next, add water to the neck of the volumetric flask, shake it again, and allow it to stand. Take the organic solvent layer and use it as the test solution. Separately, put exactly 5.0 mL of lead nitrate standard stock solution into a volumetric flask, dilute with water to make 100 mL, transfer exactly 2.0 mL of this solution into a volumetric flask, and then prepare the standard solution in the same way as the test solution. Perform the test with the test solution and the standard solution as directed under the Atomic Absorption Spectroscopy according to the following conditions; the absorbance of the test solution is less than that of the standard solution (NMT 0.001%).

Gas: Air–acetylene
Lamp: Lead hollow-cathode lamp
Wavelength: 283.8 nm

(5) ***Mercury***—Proceed with the following procedure using a light-resistant container. Weigh accurately about 1 g of Ferrous Gluconate Hydrate, add 30 mL of diluted nitric acid (1 in 10), and dissolve while heating on a steam bath. Cool quickly in an ice bath and filter using a filter washed with pre-diluted nitric acid (1 in 10) and water. To the filtrate, add 20 mL of sodium citrate solution (1 in 4) and 1 mL of hydroxylamine hydrochloride TS and use this solution as the test solution. Separately, prepare the control solution with 3.0 mL of mercury standard solution, 30 mL of diluted nitric acid (1 in 4), 5 mL of sodium citrate solution (1 in 4) and 1 mL of hydroxylamine hydrochloride. Put the test solution and the control solution each into a separatory funnel, adjust the pH to 1.8 using sulfuric acid, extract twice with 5 mL of dithizone solution for extraction and then with 5 mL of chloroform, and transfer the chloroform extract to another separatory funnel. To the extract, add 10 mL of diluted hydrochloric acid (1 in 2), shake to mix, allow to stand, and then discard the chloroform layer. Wash the acid-extract with 3 mL of chloroform and discard the solution used for washing. Add 0.1 mL of ethylenediaminetetraacetic acid disodium salt solution (1 in 50) and 2 mL of 6 mol/L acetic acid, mix, and slowly add 5 mL of ammonia TS. Close the lid of the separatory funnel, cool it under running cold water, open the lid, and transfer the contents into a beaker. Adjust the pH of the test solution and the control solution to 1.8 in the same way as the above, and transfer them to separatory funnels again. Add 5.0 mL of diluted dithizone solution for extraction, shake

vigorously, and allow to stand. Compare the color of the chloroform layers of the test solution and the control solution using a diluted dithizone solution for extraction as a control solution; the color obtained from the test solution is not more intense than that from the control solution (NMT 3 ppm).

Mercury standard stock solution—Transfer 135.4 mg of mercury(II) chloride into a 100-mL volumetric flask, dissolve in 0.5 mol/L sulfuric acid TS, fill up to the gauge line, and mix. This solution contains 0.1 g of mercury (Hg) in 100 mL.

Mercury standard solution—Before use, take 1.0 mL of the mercury standard stock solution, put it in a 1000-mL volumetric flask, add 0.5 mol/L sulfuric acid TS, fill up to the gauge line, and mix. 1 mL of this solution contains 1 μg of mercury (Hg).

Before using diluted dithizone solution for extraction, dilute 5 mL of dithizone solution for extraction with 25 mL of chloroform.

(6) ***Ferric ion***—Weigh accurately about 5 g of Ferrous Gluconate Hydrate and dissolve it in a mixture of 100 mL of water and 10 mL of hydrochloric acid, and add 3.0 g of potassium iodide. Shake well to mix and allow to stand in the dark place for 5 minutes. Then, titrate any free iodine with 0.1 mol/L sodium thiosulfate VS (indicator: 3 mL of starch TS). Perform a blank test in the same manner and make any necessary correction (NMT 2.0%).

Each mL of 0.1 mol/L sodium thiosulfate VS
= 5.585 mg of Fe^{+3}

(7) ***Arsenic***—Weigh 1.0 g of Ferrous Gluconate Hydrate, put it in 100 mL round bottom flask, add 40 mL of 4.5 mol/L sulfuric acid and 2 mL of potassium bromide solution (3 in 10), and connect it to a distillation device equipped with an ice water cooler. Heat the test sample to dissolve and start distillation. Perform the test using 25 mL of the distillate as the test solution (NMT 3 ppm).

(8) ***Reducing sugars***—Weigh 0.5 g of Ferrous Gluconate Hydrate, dissolve it in 10 mL of water, slightly warm it up, and add 1 mL of ammonia TS to make it alkaline. Precipitate iron through hydrogen sulfide in this solution, allow to stand for 30 minutes, filter, and wash the precipitate twice with 5 mL of water. Then, combine the filtrate and the solution used for washing, make the combined solution acidic with hydrochloric acid, and add another 2 mL of dilute hydrochloric acid. Boil this solution until the steam does not turn the lead acetate paper black, and if necessary, boil further to concentrate to about 10 mL. After cooling, add 5 mL of sodium carbonate TS and 20 mL of water, filter, wash the residue with water, combine the filtrate and the solution used for washing, add water to make the combined solution to exactly 100 mL. To 5mL of this solution, add 2 mL of Ferring's TS, and boil for 1 minute; a red precipitate is not formed within 1 minute.

Loss on drying Between 6.5% and 10.0% (1 g, 105 ℃, 16 hours).

Assay Weigh accurately about 1.5 g of Ferrous Gluconate Hydrate, put it in a 300-mL Erlenmeyer flask, and dissolve in a mixture of 75 mL of water and 15 mL of dilute sulfuric acid. Add 0.25 g of zinc powder, stopper the flask with a Bunsen valve, and allow to stand at room temperature for 20 minutes or until the solution becomes colorless. Filter the solution through a filtering crucible (Gooch crucible) containing an asbestos mat coated with a thin layer of zinc dust, and wash the crucible and the contents with 10 mL of dilute sulfuric acid and then with 10 mL of water. To the filtrate, add 1,10-phenanthroline monohydrate TS, and immediately titrate the filtrate with 0.1 mol/L cerium sulfate VS in a suction flask. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L cerium sulfate solution
= 44.61 mg of $C_{12}H_{22}FeO_{14}$

Packaging and storage Preserve in tight containers.

Ferrous Gluconate Tablets
글루콘산제일철 정

Ferrous Gluconate Tablets contains NLT 93.0% and NMT 107.0% of the labeled amount of ferrous gluconate hydrate ($C_{12}H_{22}FeO_{14}\cdot 2H_2O$: 482.17).

Method of preparation Prepare Ferrous Gluconate Tablets as directed under Tablets, with Ferrous Gluconate Hydrate.

Identification Powder Ferrous Gluconate Tablets, weigh an appropriate amount of the powder, equivalent to 1 g of ferrous gluconate hydrate, according to the labeled amount, dissolve in 100 mL of water, and filter. Take an appropriate amount of the filtrate, add water, dilute it to the corresponding concentration, and perform the test as directed under the Identification for Ferrous Gluconate Hydrate.

Dissolution Perform the test with 1 tablet of Ferrous Gluconate Tablets at 150 revolutions per minute according to Method 1 under the dissolution using 900 mL of dissolution medium 1. Take the dissolved solution 80 minutes after the start of the dissolution, filter it, and use the filtrate as the test solution. If necessary, dilute the test solution to a suitable concentration using the dissolution medium. Separately, weigh accurately an appropriate amount of ferrous gluconate hydrate RS, dissolve in the

dissolution medium, and prepare the standard solution containing the same concentration of iron as the test solution. Determine the absorbances of the test solution and the standard solution according to the following conditions, as directed under the Atomic Absorption Spectroscopy, and calculate the content of iron using the calibration curve obtained from the absorbance of the standard solution.

Gas: Air–acetylene
Lamp: Iron hollow-cathode lamp
Wavelength: 248.3 nm

It meets the requirements when the dissolution rate of Ferrous Gluconate Tablets in 80 minutes is NLT 80%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately NLT 20 tablet of Ferrous Gluconate Tablets and powder them. Weigh accurately an appropriate amount of the powder equivalent to about 1.5 g of ferrous gluconate hydrate ($C_{12}H_{22}FeO_{14}\cdot 2H_2O$), put in a 300-mL Erlenmeyer flask, dissolve in a mixture of 75 mL of water and 15 mL of dilute sulfuric acid, and hereinafter proceed as directed under the Assay of Ferrous Gluconate Hydrate.

Each mL of 0.1 mol/L cerium sulfate VS
= 48.22 mg of $C_{12}H_{22}FeO_{14}\cdot 2H_2O$

Packaging and storage Preserve in tight containers.

Ferrous Sulfate Hydrate
황산철수화물

Ferrous Sulfate $FeSO_4\cdot 7H_2O$: 278.02
Iron(2+) sulfate heptahydrate [*7782-63-0*]

Ferrous Sulfate Hydrate contains NLT 98.0% and NMT 104.0% of ferrous sulfate hydrate ($FeSO_4\cdot 7H_2O$).

Description Ferrous Sulfate Hydrate occurs as pale green crystals or a crystalline powder. It is odorless and astringent.
It is freely soluble in water and practically insoluble in ether.
It easily effloresces in dry air, and its crystal surface changes to yellowish brown in the humid air.

Identification An aqueous solution of Ferrous Sulfate Hydrate (1 in 10) responds to the Qualitative Analysis for ferrous salt and sulfate.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Ferrous Sulfate Hydrate in 20 mL of water and 1 mL of dilute sulfuric acid; the resulting solution is clear.

(2) ***Acid***—To 5.0 g of powdered Ferrous Sulfate Hydrate, add 50 mL of ethanol(95), shake for 2 minutes, and filter. To 25 mL of the filtrate, add 50 mL of water, 3 drops of bromothymol blue TS, and 0.5 mL of dilute sodium hydroxide TS; the resulting solution exhibits a blue color.

(3) ***Mercury***—Perform the test using a light-resistant container. Weigh accurately about 1 g of Ferrous Sulfate Hydrate, add 30 mL of diluted nitric acid (1 in 10), and dissolve while heating on a steam bath. Cool quickly in an ice bath and filter using a filter washed with pre-diluted nitric acid (1 in 10) and water. To the filtrate, add 20 mL of sodium citrate solution (1 in 4) and 1 mL of hydroxylamine hydrochloride TS, and use this solution as the test solution. Separately, prepare the control solution with 3.0 mL of mercury standard solution, 30 mL of diluted nitric acid (1 in 4), 5 mL of sodium citrate solution (1 in 4), and 1 mL of hydroxylamine hydrochloride. To the control solution, add ammonia TS to adjust the pH to 1.8. To the test solution, add sulfuric acid to adjust the pH to 1.8. Transfer each solution into two separation funnels. Perform the test with the test solution and the control solution as follows. Extract 2 times each with 5 mL of extracting dithizone solution and 5 mL of chloroform, transfer chloroform extract into another separation funnel. To the extract, add 10 mL of diluted hydrochloric acid (1 in 2), shake to mix, allow to stand, and then discard the chloroform layer. Wash the acid extract with 3 mL of chloroform and discard the solution used for washing. Add 0.1 mL of ethylenediaminetetraacetic acid disodium salt solution (1 in 50) and 2 mL of 6 mol/L acetic acid, mix, and slowly add 5 mL of ammonia TS. Close the lid of the separatory funnel, cool it under running cold water, open the lid, and transfer the contents into a beaker. Adjust the pH of the test solution and the control solution to 1.8 in the same way as the above, and transfer them to separatory funnels again. Add 5.0 mL of diluted dithizone solution for extraction, shake vigorously, and allow to stand. Compare the color of the chloroform layers of the test solution and the control solution using a diluted dithizone solution for extraction as a control solution; the color obtained from the test solution is not more intense than that from the control solution (NMT 3 ppm).

Mercury standard stock solution—Transfer 135.4 mg of mercury(II) chloride into a 100-mL volumetric flask, dissolve in 0.5 mol/L sulfuric acid TS, fill up to the gauge line, and mix. This solution contains 0.1 g of mercury (Hg) in 100 mL.

Mercury standard solution—Before use, take 1.0 mL of the mercury standard stock solution, transfer into a 1000-mL volumetric flask, add 0.5 mol/L sulfuric acid TS, fill up to the gauge line, and mix. 1 mL of this solution contains 1 μg of mercury (Hg).

Diluted dithizone solution for extraction—Before use, dilute 5 mL of dithizone solution for extraction with 25 mL of chloroform.

(4) ***Lead***—Transfer about 1.0 g of Ferrous Sulfate

Hydrate into a 50-mL volumetric flask, add 10 mL of 9 mol/L hydrochloric acid, about 10 mL of water, 20 mL of ascorbic acid-sodium iodide TS, and 5 mL of a solution of 4-methyl-2-pentanone solution in trioctylphosphine oxide (5 in 100), shake for 30 seconds, and allow to stand until the layers separate. Next, add water to the neck of the volumetric flask, shake it again, and allow to stand. Take the organic solvent layer and use this solution as the test solution. Separately, transfer exactly 5.0 mL of lead nitrate standard stock solution into a volumetric flask, dilute with water to make 100 mL, transfer exactly 2.0 mL of this solution into a volumetric flask, and proceed in the same manner as the test solution. Use this solution as the standard solution. Determine the absorbances of the test solution and the standard solution according to the following conditions, as directed under Ultraviolet-visible Spectrophotometry; the absorbance of the solution obtained from the test solution is not greater than that from the standard solution.

Gas: Air–acetylene
Lamp: Lead hollow-cathode lamp
Wavelength: 283.8 nm

(5) ***Arsenic***—Prepare the test solution with 1.0 g of Ferrous Sulfate Hydrate, according to Method 1, and perform the test (NMT 2 ppm).

Assay Weigh accurately about 0.7 g of Ferrous Sulfate Hydrate, add 20 mL of water, 20 mL of dilute sulfuric acid TS, and 2 mL of phosphoric acid, and titrate immediately with 0.02 mol/L potassium permanganate VS.

Each mL of 0.02 mol/L potassium permanganate VS
= 27.80 mg of $FeSO_4 \cdot 7H_2O$

Packaging and storage Preserve in tight containers.

Dried Ferrous Sulfate, Folic Acid, Cyanocobalamin and DL-Serine Capsules
건조황산제일철·폴산·시아노코발라민·DL-세린 캡슐

Dried Ferrous Sulfate, Folic Acid, Cyanocobalamin and DL-Serine Capsules contain ferrous sulfate ($FeSO_4$: 151.90) equivalent to NLT 90.0% and NMT 110.0% of the labeled amount, folic acid ($C_{19}H_{19}N_7O_6$: 441.40) and cyanocobalamin ($C_{63}N_{88}Co_{14}O_{14}P$: 1355.37) equivalent to NLT 90.0% and NMT 150.0% of the labeled amount, and DL-serine ($C_3H_7NO_3$: 105.10) NLT 90.0% and NMT 130.0% of the labeled amount.

Method of preparation Prepare as directed under Capsules, with Dried Ferrous Sulfate, Folic Acid, Cyanocobalamin and DL-Serine.

Identification (1) ***Ferrous sulfate***—Weigh an amount of the contents of Dried Ferrous Sulfate, Folic Acid, Cyanocobalamin and DL-Serine Capsules, equivalent to 0.25 g of ferrous sulfate according to the labeled amount, add water and hydrochloric acid to acidify, and add water again to make 50 mL; the solution responds to the Qualitative Analysis for ferrous salt and sulfate.

(2) ***Folic acid***—Perform the test with the contents of 5 capsules of Dried Ferrous Sulfate, Folic Acid, Cyanocobalamin and DL-Serine Capsules as directed under the Analysis for Vitamins.

(3) ***Cyanocobalamin***—Perform the test with the contents of 5 capsules of Dried Ferrous Sulfate, Folic Acid, Cyanocobalamin and DL-Serine Capsules as directed under the Analysis for Vitamins.

(4) ***DL-serine***—Add the contents of 5 capsules of Dried Ferrous Sulfate, Folic Acid, Cyanocobalamin and DL-Serine Capsules to a G4 glass filter, and wash several times with petroleum ether until the fat of the residue is completely removed. Carefully dry the residue at 65 ℃, dissolve in 50 mL of water, and use this solution as the test solution. Separately, dissolve 0.13 g of DL-serine RS in 100 mL of water, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescence indicator for thin-layer chromatography. Next, develop the plate with a mixture of methanol and water (70 : 30) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray ninhydrin-ethanol solution evenly on the plate, and heat at 100 ℃ for 10 minutes; the R_f values of the spots obtained from the test and standard solutions are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Ferrous sulfate***—Weigh accurately the mass of the contents of NLT 20 capsules of Dried Ferrous Sulfate, Folic Acid, Cyanocobalamin and DL-Serine Capsules. Weigh accurately about 0.4 g of ferrous sulfate ($FeSO_4$), dissolve in a mixture of 20 mL of dilute sulfuric acid and 80 mL of freshly boiled and cooled water, and filter. Wash the beaker and the residue on the filter paper with a small amount of the mixture of 20 mL of dilute sulfuric acid and 80 mL of freshly boiled and cooled water, combine the washings with the filtrate, and immediately titrate with 0.1 mol/L cerium sulfate VS (indicator: *o*-Phenanthroline TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L cerium sulfate VS
= 15.190 mg of $FeSO_4$

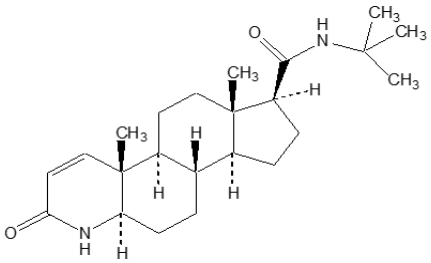
(2) ***Folic acid and cyanocobalamin***—Weigh accurately the mass of the contents of NLT 20 tablets of Dried Ferrous Sulfate, Folic Acid, Cyanocobalamin and DL-

Serine Capsules and perform the test as directed under the Analysis for Vitamins.

(3) ***DL-serine*—**Weigh accurately the mass of the contents of NLT 20 tablets of Dried Ferrous Sulfate, Folic Acid, Cyanocobalamin and DL-Serine Capsules and perform the test as directed under the Identification and Assay for Amino Acids.

Packaging and storage Preserve in well-closed containers.

Finasteride
피나스테리드



Finasteride $C_{23}H_{36}N_2O_2$: 372.54
(1*S*,3a*S*,3b*S*,5a*R*,9a*R*,9b*S*,11a*S*)-*N*-*tert*-Butyl-9a, 11a-dimethyl-7-oxo-1,2,3,3a,3b,4,5,5a,6,9b,10,11-dodecahydroindeno[5,4-f]quinoline-1-carboxamide
[*98319-26-7*]

Finasteride contains NLT 98.5% and NMT 101.0% of finasteride ($C_{23}H_{36}N_2O_2$: 372.55), calculated on the anhydrous basis.

Description Finasteride occurs as a white or grayish white crystalline solid.
It is freely soluble in ethanol(95) or chloroform, and very slightly soluble in water.

Melting point—About 257 °C.

Identification (1) Determine the infrared spectra of Finasteride and finasteride RS, as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Optical rotation $[\alpha]_{405\text{nm}}^{25}$: Between -56.0° and -60.0° (0.1 g calculated on the anhydrous basis, methanol, 10 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Finasteride according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances*—**Weigh accurately 0.1 g of Finasteride, dissolve in a mixture of acetonitrile and water (1 : 1) to make exactly 100 mL, and use this solution as the test solution. Perform the test with 15 μL of the test solution as directed under the Liquid Chromatography according to the following conditions, determine the peak areas according to the automatic integration method, and calculate the amount of each related substance; it is NMT 0.5%, and total amount of all related substances is NMT 1.0%.

$$\text{Content (\%) of each related substance} = 100 \times \frac{A_\text{i}}{A_\text{S}}$$

A_i: Peak area of each related substance
A_S: Total area of peaks obtained from the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (4 μm in particle diameter).

Mobile phase: A mixture of water, tetrahydrofuran and acetonitrile (8 : 1 : 1).

Column temperature: A constant temperature of about 60 °C.

Flow rate: About 1.5 mL/min.

System suitability

System performance: Weight 10 mg of finasteride TS, dissolve in a mixture of water and acetonitrile (1 : 1) to make 10 mL. Proceed with 15 μL of this solution according to the above conditions; the number of theoretical plates and the symmetry factor of the peak of finasteride are NLT 10000 plates and NMT 1.3, respectively.

Water NMT 0.3% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 20 mg each of Finasteride and finasteride RS, dissolve in a mixture of water and acetonitrile (1 in 1) to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of finasteride, A_T and A_S, from each solution.

$$\text{Amount (mg) of finasteride } (C_{23}H_{36}N_2O_2) = \text{Amount (mg) of finasteride RS} \times \frac{A_\text{T}}{A_\text{S}}$$

Operating conditions

Detector: An ultraviolet absorption photometer

(wavelength: 215 nm).

Column: A stainless steel column about 3.0 mm in internal diameter and 30 cm in length, packed with octylsilyl silica gel for liquid chromatography (3 μm in particle diameter).

Mobile phase: A mixture of water and tetrahydrofuran (4 : 1).

Flow rate: About 3 mL/min.

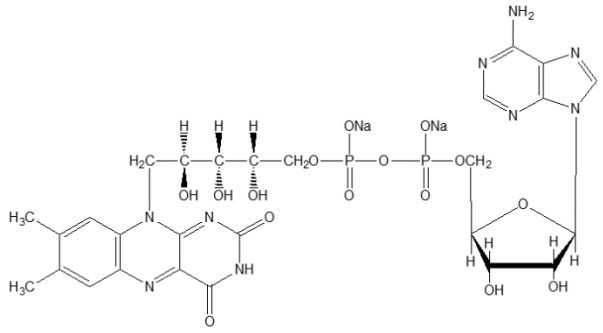
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the number of theoretical plates and the symmetry factor of the peak of finasteride are NLT 1800 plates and NMT 1.3, respectively.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Flavin Adenine Dinucleotide Sodium
플라빈아데닌디뉴클레오티드나트륨



Flavin Adenine Dinucleotide Sodium

$C_{27}H_{31}N_9Na_2O_{15}P_2$: 829.51

Disodium adenosine 5'-(3-{D-ribo-5-[7,8-dimethyl-2,4-dioxo-3,4-dihydrobenzo[g]pteridin-10(2*H*)-yl]-2,3,4-trihydroxypentyl} dihydrogen diphosphate) [*84366-81-4*]

Flavin Adenine Dinucleotide Sodium contains NLT 93.0% and NMT 101.% of flavin adenine dinucleotide sodium ($C_{27}H_{31}N_9Na_2O_{15}P_2$), calculated on the anhydrous basis.

Description Flavin Adenine Dinucleotide Sodium occurs as an orange yellow to pale yellowish brown powder. It is odorless or has a slightly characteristic odor and has a slightly bitter taste.

It is freely soluble in water and practically insoluble in methanol, ethanol(95), ethylene glycol or ether.

It is hygroscopic.

It is decomposed by light.

Identification (1) An aqueous solution of Flavin Adenine Dinucleotide Sodium (1 in 100000) is pale yellowish green and has an intense yellowish green fluorescence. To 5 mL of the solution, add 20mg of sodium hydrosulfite; the color and fluorescence of the solution disappear, but reappear slowly upon shaking the mixture in air. This fluorescence disappears upon the addition of dilute hydrochloric acid or sodium hydroxide TS dropwise.

(2) Determine the infrared absorption spectrum of Flavin Adenine Dinucleotide Sodium and flavin adenine dinucleotide sodium RS as directed in the potassium bromide disk method under Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) Take 0.1g of Flavin Adenine Dinucleotide Sodium, add 10 mL of nitric acid, evaporate on a steam bath to dryness, and ignite. Boil the residue with 10 mL of diluted nitric acid (1 in 50) for 5 minutes. Cool, then neutralize with ammonia TS and filter as needed; the solution responds to the Qualitative Analysis for sodium salt and Qualitative Analysis (1) and (3) for phosphate.

Optical rotation $[\alpha]_D^{20}$: Between -21.0° and -25.5° (0.3g calculated on the anhydrous basis, water, 20 mL, 100 mm).

pH Dissolve 1.0 g of Flavin Adenine Dinucleotide Sodium in 100 mL of water; the pH of the solution is between 5.5 and 6.5.

Purity (1) ***Clarity and color of solution*—**Dissolve 0.20 g of Flavin Adenine Dinucleotide Sodium in 10 mL of water; the resulting solution is clear and yellow.

(2) ***Free phosphoric acid***—Weigh accurately about 20 mg of Flavin Adenine Dinucleotide Sodium, dissolve in 10 mL of water, and use this solution as the test solution. Separately, pipet 2 mL of phosphoric acid RS, add 10 mL of water, and use this solution as the standard solution. Add 2 mL of diluted perchloric acid (100 in 117) to each of the test solution and the standard solution, add 1 mL of ammonium molybdate TS and 2 mL of 2,4-diaminophenol hydrochloride TS, shake to mix, add water to make exactly 25 mL, and allow to stand for 30 minutes at 20 ± 1 ℃. With these solutions and the control solution prepared with 2 mL of water in the same way, perform the test according to Ultraviolet-visible Spectroscopy. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at wavelength 730 nm; the amount of free phosphoric acid is NMT 0.25%.

$$\text{Content (\%) of free phosphoric acid } (H_3PO_4) = \frac{A_T}{A_S} \times \frac{1}{W} \times 5.16$$

W: Amount (mg) of Riboflavin Sodium Phosphate calculated on the anhydrous basis

(3) ***Heavy metals***—Weigh 1.0 g of Flavin Adenine Dinucleotide Sodium according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead

standard solution (NMT 20 ppm).

(4) ***Arsenic***—Proceed with 2.0g of Flavin Adenine Dinucleotide Sodium according to Method 3 and perform the test (NMT 1 ppm).

(5) ***Related substances*—**Dissolve about 0.10 g of Flavin Adenine Dinucleotide Sodium in 200 mL of the mobile phase and use this solution as the test solution. Perform the test with 20 μL of the test solution as directed under the Liquid Chromatography according to the following conditions. Measure the peak area A of flavin adenine dinucleotide sodium and the total area S of the other peaks; S/(A + S) is NMT 0.10.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 260 nm).

Follow the operating conditions under Assay 1) Procedure (B) for the column, column temperature, mobile phase, flow rate and time span of measurement.

System suitability

Test system performance as directed in System suitability under Assay 1) Procedure B).

Test for required detectability: Pipet 2 mL of the test solution, add the mobile phase to make exactly 20 mL, and use this solution as the system suitability solution. Confirm that the peak area of flavin adenine dinucleotide sodium obtained from 20 μL of this solution is equivalent to between 8% and 12% of the peak area of flavin adenine dinucleotide sodium obtained from the standard solution.

System repeatability: Repeat the test 6 times with 20 μL each of the system suitability solution according to the above conditions; the relative standard deviation of the peak areas of flavin adenine dinucleotide sodium is NMT 1.0%.

Water Put 50 mL of a mixture of methanol for water determination and ethylene glycol for water determination (1:1) in a dry flask for titration and titrate with a test solution for water determination to the endpoint. Weigh accurately about 0.1 g of Flavin Adenine Dinucleotide Sodium, quickly transfer into the titration flask, add a certain amount of the excess test solution for water determination, stir to mix for 10 minutes, and perform the test; the water content is NMT 10.0%.

Assay (1) ***Procedure***—(i) Total amount of flavin: Perform the procedure using light-resistant containers. Separately, weigh accurately about 0.1 g of Flavin Adenine Dinucleotide Sodium and dissolve in water to make exactly 200 mL. Pipet 5 mL of this solution, add 5 mL of zinc chloride TS, heat for 30 minutes on a steam bath, and cool. Then add water to make exactly 100 mL, and use this solution as the standard solution. Separately, weigh accurately about 50 mg of riboflavin RS (previously dried at 105 ℃ for 2 hours), dissolve in 200 mL of diluted acetic acid(100) (1 in 100) by warming, cool, and add water to make exactly 500 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. With the test solution and the standard solution, perform the test as directed under the Ultraviolet-visible Spectroscopy using water as the control solution, and determine the absorbances, A_T and A_S, at the wavelength of 450 nm.

$$\text{Total amount (mg) of flavin} = \text{Amount (mg) of riboflavin RS} \times \frac{A_T}{A_S} \times \frac{4}{5}$$

(ii) Peak area ratio of flavin adenine nucleotide: Weigh accurately about 0.1 g of Flavin Adenine Dinucleotide Sodium, dissolve in water to make exactly 200 mL, and use this solution as the test solution. Perform the test with 5 μL of the test solution as directed under the Liquid Chromatography according to the following conditions. Measure the respective peak areas using the automatic integration method, and determine the peak area *A* of flavin adenine dinucleotide sodium and the sum of the other peak areas S.

$$\text{Peak area ratio of flavin adenine dinucleotide sodium} = \frac{1.08A}{1.08A + S}$$

Operating conditions

Detector: A visible absorption photometer (wavelength: 450 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm to 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of potassium dihydrogen phosphate solution (17 in 500) and methanol (4 : 1).

Flow rate: Adjust the flow rate so that the retention time of flavin adenine dinucleotide sodium is about 10 minutes.

System suitability

Test for required detectability: Pipet 2 mL of the test solution, add water to make exactly 20 mL, and use this solution as the system suitability solution. Weigh accurately 2 mL of this solution and make 20 mL. Confirm that the peak area of flavin adenine dinucleotide sodium obtained from 5 μL of this solution is equivalent to between 8% and 12% of the peak area of flavin adenine dinucleotide sodium obtained from the standard solution.

System performance: Dissolve 20 mg each of Flavin Adenine Dinucleotide Sodium and sodium riboflavinphosphate in 100 mL of water. Proceed with 5 μL of this solution according to the above conditions; flavin adenine dinucleotide sodium and riboflavin phosphate are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 5 μL each of the system suitability solution according to the above conditions; the relative standard deviation of the peak areas of flavin adenine dinucleotide sodium is

NMT 1.0%.

Time span of measurement: About 4.5 times the retention time of flavin adenine dinucleotide sodium.

(2) ***Calculation formula***

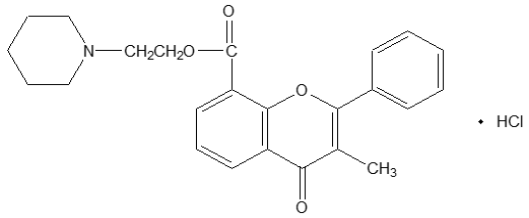
Amount (mg) of flavin adenine dinucleotide sodium ($C_{27}H_{31}N_9Na_2O_{15}P_2$)
$= f_T \times f_R \times 2.2040$

f_T: Total amount (mg) of flavin in Flavin Adenine Dinucleotide Sodium obtained from the Procedure (i)

f_R: Peak area ratio of flavin adenine nucleotide in Flavin Adenine Dinucleotide Sodium obtained from the Procedure (ii)

Packaging and storage Preserve in light-resistant, tight containers.

Flavoxate Hydrochloride
플라복세이트염산염



$C_{24}H_{25}NO_4 \cdot HCl$: 427.92

2-(1-Piperidyl)ethyl 3-methyl-4-oxo-2-phenyl-chromene-8-carboxylate hydrochloride [*3717-88-2*]

Flavoxate Hydrochloride, when dried, contains NLT 99.0% and NMT 101.0% of propranolol hydrochloride ($C_{24}H_{25}NO_4 \cdot HCl$).

Description Flavoxate Hydrochloride occurs as white crystals or a crystalline powder.
It is sparingly soluble in acetic acid(100) or chloroform, slightly soluble in water or ethanol(95), and practically insoluble in acetonitrile or ether.

Identification (1) Determine the absorption spectra of the solutions of Flavoxate Hydrochloride and flavoxate hydrochloride RS in 0.01 mol/L hydrochloric acid TS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Flavoxate Hydrochloride and flavoxate hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy, respectively; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Flavoxate Hydrochloride (1 in 100) responds to the Qualitative Analysis for chloride.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Flavoxate Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Proceed with 2.0 g of Flavoxate Hydrochloride according to Method 4, and perform the test (NMT 1 ppm).

(3) ***Related substances***—Dissolve 80 mg of Flavoxate Hydrochloride in 10 mL of chloroform and use this solution as the test solution. Pipet 1 mL of this solution and add chloroform to make exactly 20 mL. Pipet 1 mL of this solution, add chloroform to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, water and acetic acid(100) (3 : 1 : 1) as the developing solvent to a distance of about 12 cm and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than those from the standard solution.

Loss on drying NMT 1.0% (1 g, in vacuum, silica gel, 2 hours).

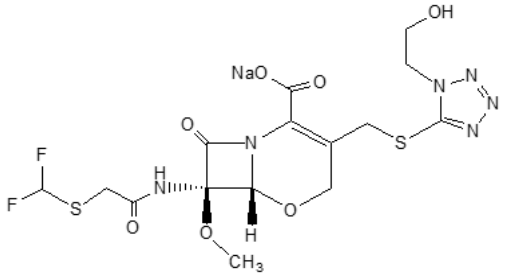
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.6 g of Flavoxate Hydrochloride, previously dried, add 10 mL of acetic acid(100) and 40 mL of acetonitrile, and dissolve. Add 50 mL of acetic anhydride and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 42.79 mg of $C_{24}H_{25}NO_4 \cdot HCl$

Packaging and storage Preserve in tight containers.

Flomoxef Sodium
플로목세프나트륨



Flomoxef Sodium $C_{15}H_{17}F_2N_6NaO_7S_2$: 518.45
Sodium (6*R*,7*R*)-7-[[2-(difluoromethylsulfanyl)acetyl]amino]-3-[[1-(2-hydroxyethyl)tetrazol-5-yl]sulfanylmethyl]-7-methoxy-8-oxo-5-oxa-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate
[*92823-03-5*]

Flomoxef Sodium contains NLT 870 μg (potency) and NMT 985 μg (potency) of flomoxef ($C_{15}H_{18}F_2N_6O_7S_2$: 496.47) per mg, calculated on the anhydrous basis.

Description Flomoxef Sodium occurs as a white to pale yellowish white crystalline powder.
It is very soluble in water, freely soluble in methanol, and sparingly soluble in ethanol(99.5).

Identification (1) Weigh about 0.01 g of Flomoxef Sodium and decompose as directed under the Oxygen Flask Combustion, using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as the absorbent. To 2 mL of this test solution, add 1.5 mL of a mixture of alizarin complexone TS, acetic acid, potassium acetate buffer solution (pH 4.3) and cerium(III) nitrate TS (1 : 1 : 1); the solution exhibits a bluish purple color.

(2) Determine the absorption spectra of each aqueous solution of Flomoxef Sodium and flomoxef sodium RS (3 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Flomoxef Sodium and flomoxef sodium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) Determine the ^1H spectrum of a solution of Flomoxef Sodium in deuterium oxide for nuclear magnetic resonance spectroscopy (1 in 10) as directed under the Nuclear Magnetic Resonance Spectroscopy, using sodium 3-trimethylsilylpropanesulfonate as the internal reference compound; the acquired spectrum exhibits a singlet A at around δ 3.5 ppm, a singlet or sharp multiplet B at around δ 3.7 ppm and a singlet C at around δ 5.2 ppm. The ratio of the integrated intensity of these signals, A : B : C, is about 3 : 2 : 1.

(5) Flomoxef Sodium responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between -8° and -13° (1 g calculated on the anhydrous basis, a mixture of water and ethanol(99.5) (4 : 1), 50 mL, 100 mm).

pH Dissolve 0.5 g (potency) of Flomoxef Sodium in 5 mL of water; the pH of the solution is between 4.0 and 5.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Flomoxef Sodium in 10 mL of water; the resulting solution is colorless to pale yellow and clear.

(2) ***Heavy metals***—Place about 1.0 g of Flomoxef Sodium in a quartz crucible, proceed according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—To 1.0 g of Flomoxef Sodium, add 5 mL of sulfuric acid and 5 mL of nitric acid and heat carefully. Continue heating, adding 2 mL of nitric acid occasionally until the solution is colorless to pale yellow. After cooling, add 10 mL of ammonium oxalate TS and concentrate the solution from 2 mL to 3 mL by heating until white fumes evolve. After cooling, add water to make 10 mL and perform the test using this solution as the test solution; the color of the solution is not more intense than the reference color.

Reference color: Proceed to prepare a solution in the same manner as the test solution without Flomoxef Sodium, transfer 10 mL of this solution to the bottle of the generator apparatus, add exactly 2 mL of arsenic standard solution, and proceed in the same manner as the test solution (NMT 2 ppm).

(4) ***1-(2-hydroxyethyl)-1H-tetrazol-5-thiol***—Use the test solution prepared under the Assay as the test solution. Separately, weigh accurately about 20 mg of 1-(2-hydroxyethyl)-1*H*-tetrazol-5-thiol and dissolve in water to make exactly 100 mL. Pipet 5 mL of this solution, add exactly 25 mL of the internal standard solution and water to make 50 mL and use this solution as the standard solution. Perform the test with each 5 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and calculate the ratios, Q_T and Q_S, of the peak area of 1-(2-hydroxyethyl)-1*H*-tetrazol-5-thiol to that of the internal standard. The amount of 1-(2-hydroxyethyl)-1*H*-tetrazol-5-thiol is NMT 1.0% of Flomoxef Sodium, calculated on the anhydrous basis.

$$\text{Amount (mg) of 1-(2-hydroxyethyl)-1}H\text{-tetrazol-5-thiol } (C_3H_6N_4OS) = \text{Potency (mg) of 1-(2-hydroxyethyl)-1}H\text{-tetrazol-5-thiol} \times \frac{Q_T}{Q_S} \times \frac{1}{10}$$

Internal standard solution—*m*-cresol solution (3 in 1000).

Operating conditions

Proceed as directed under the operating conditions under the Assay.

System suitability Proceed as directed under the system suitability under the Assay.

Water NMT 1.5% (0.5 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in sterile

preparations (excluding in case of a manufacturing process of a sterile preparation with a terminal sterilization process). Use a diluent containing 0.1% polysorbate 80 as the rinsing fluid.
Bacterial endotoxins Less than 0.025 EU/mg (potency) of flomoxef, when used in a sterile preparation.

Assay Weigh accurately each 50 mg (potency) of Flomoxef Sodium and flomoxef sodium RS, dissolve in the internal standard solution to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 5 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and calculate the ratios, Q_T and Q_S, of the peak area of flomoxef to that of the internal standard for the test solution and the standard solution, respectively.

$$\text{Amount [μg (potency)] of flomoxef } (C_{15}H_{18}F_2N_6O_7S_2) = \text{Potency (μg) of flomoxef trimethylammonium RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—*m*-cresol solution (3 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength 246 nm).

Column: A stainless steel column, about 4 mm in internal diameter and 20 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 6.94 g of potassium dihydrogen phosphate, 3.22 g of disodium hydrogen phosphate dodecahydrate and 1.60 g of tetra-n-butylammonium bromide in water to make 1000 mL. Add 250 mL of methanol to 750 mL of this solution.

Flow rate: Adjust the flow rate so that the retention time of flomoxef is about 9 minutes.

System suitability

System performance: Perform the test with 5 μL of the standard solution according to the above operating conditions; flomoxef and the internal standard are eluted in this order, and the peak resolution is NLT 10.

System repeatability: Repeat the test 3 times with 5 μL of the standard solution under the above operating conditions; the relative standard deviation of the ratio of the peak area of flomoxef to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers (at below 5 °C).

Flomoxef Sodium for Injection
주사용 플로목세프나트륨

Flomoxef Sodium for Injection is an injection to be dissolved before use and contains NLT 90.0% and NLT 110.0% of the labeled amount of flomoxef ($C_{15}H_{18}F_2N_6O_7S_2$: 496.47).

Method of preparation Prepare as directed under Injections, with Flomoxef Sodium.

Description Flomoxef Sodium for Injection occurs as a hard, white to pale yellowish white mass or a powder.

Identification Perform the test with Flomoxef Sodium for Injection as directed under the Identification (3) under Flomoxef Sodium.

pH Dissolve an amount of Flomoxef Sodium for Injection, equivalent to 0.5 g (potency) of flomoxef sodium, in 5 mL of water; the pH of this solution is between 4.0 and 5.5.

Purity (1) ***Clarity and color of solution***—Dissolve an amount of Flomoxef Sodium for Injection equivalent to 1.0 g (potency) of flomoxef sodium according to the labeled amount, in 10 mL of water; the solution is clear and colorless to pale yellow.

(2) ***1-(2-hydroxyethyl)-1H-tetrazole-5-thiol***—Use the test solution obtained in Assay as the test solution. Separately, weigh accurately about 20 mg of 1-(2-hydroxyethyl)-1*H*-tetrazol-5-thiol and dissolve in water to make exactly 100 mL. Pipet 5 mL of this solution, add exactly 25 mL of the internal standard solution and water to make 50 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratio, Q_T and Q_S, of 1-2(hydroxyethyl)-1*H*-tetrazole-5-thiol to the peak area of the internal standard. The amount of 1-(2-hydroxyethyl)-1*H*-tetrazole-5-thiol is NMT 10 mg per g (potency) of Flomoxef Sodium for Injection.

$$\text{Amount (mg) of 1-2(2-hydroxyethyl)-1}H\text{-tetrazole-5-thiol } (C_3H_6N_4OS) = \text{Potency (mg) of 1-(2-hydroxyethyl)-1}H\text{-tetrazol-5-thiol} \times \frac{Q_T}{Q_S} \times \frac{1}{10}$$

Internal standard solution—m-Cresol solution (3 in 1000).

Operating conditions

Perform the test according to the operating conditions as directed under the Assay under Flomoxef Sodium.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution, and add water to make exactly 20 mL. Confirm that the peak area of 1-methyl-1*H*-tetrazole-5-thiol obtained from 5 μL of this solution is 3.5% to 6.5% of the peak area of 1-methyl-1*H*-tetrazole-5-thiol obtained from 5 μL of the standard solution.

System performance: Proceed with 5 μL of the standard solution according to the above conditions; 1-(2-hydroxyethyl)-1*H*-tetrazol-5-thiol and the internal standard are eluted in this order with the resolution being NLT 20.

System repeatability: Repeat the test 3 times with 5 μL each of the standard solution (1) according to the above conditions; the relative standard deviation of the peak area of 1-methyl-1*H*-tetrazole-5-thiol is NMT 1.0%.

Water NMT 1.5% (0.5 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.025 EU per mg (potency) of flomoxef.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

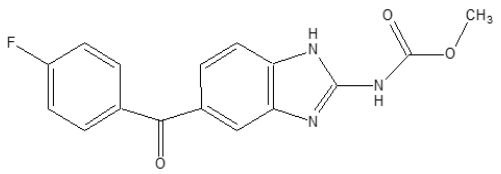
Assay Take NLT 10 units of Flomoxef Sodium for Injection, weigh accurately the mass of the contents, and determine the average weight of the contents. Thinly spread about 1 g of the contents on a petri dish, and allow it to stand in a humidistat with a saturated solution of magnesium bromide, protected from light, to bring the water to equilibrium. Measure the water content of 0.1 g of the content as directed under Water. Weigh accurately an amount of Flomoxef Sodium for Injection, equivalent to about 50 mg (potency) of flomoxef sodium, dissolve in exactly 50 mL of the internal standard solution, and add water to make 100 mL. Use this solution as the test solution. Separately, weigh accurately about 50 mg (potency) of flomoxef triethylammonium RS, dissolve in exactly 50 mL of the internal standard solution, add water to make 100 mL, and use this solution as the standard solution. Perform the test as directed under the Assay of Flomoxef Sodium.

$$\text{Potency (μg) of flomoxef } (C_{15}H_{18}F_2N_6O_7S_2) = \text{Potency (μg) of flomoxef triethylammonium RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—*m*-cresol solution (3 in 1000).

Packaging and storage Preserve in hermetic containers. Plastic containers for aqueous injections may be used.

Flubendazole
플루벤다졸



Flubendazole $C_{16}H_{12}FN_3O_3$: 313.28
Methyl *N*-[6-(4-fluorobenzoyl)-1*H*-benzimidazol-2-yl]carbamate [*31430-15-6*]

Flubendazole contains NLT 99.0% and NMT 101.0% of flubendazole ($C_{16}H_{12}FN_3O_3$), calculated on the dried basis.

Description Flubendazole occurs as a white powder.
It is practically insoluble in water, dichloromethane or ethanol(95).
It shows crystalline polymorphism.

Identification Determine the infrared spectra of Flubendazole and flubendazole RS as directed in the potassium bromide disk method under Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity ***Related substances***—Dissolve 0.10 g of Flubendazole in *N*,*N*-dimethylformamide to make exactly 100 mL, and use this solution as the test solution. To 1.0 mL of the test solution, add *N*,*N*-dimethylformamide to make exactly 100 mL. To 5.0 mL of this solution, add *N*,*N*-dimethylformamide to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. The area of peaks of the related substances, each of which the relative retention time to flubendazole is between 1.2 and 1.3, is not greater than the major peak area from the standard solution (0.25%), and the total area of peaks other than the major peak from the test solution is not greater than 6 times the major peak area from the standard solution (1.5%). However, exclude any peak having an area smaller than 0.2 times the major peak area obtained from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 250 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 10 cm in length, packed with base-deactivated octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: Dissolve 7.5 g of ammonium acetate in water to make 1000 mL.

Mobile phase B: Acetonitrile

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 15	90 → 75	10 → 25
15 - 30	75 → 45	25 → 55
30 - 32	45 → 10	55 → 90
32 - 37	10	90
37 - 38	10 → 90	90 → 10
38 - 42	90	10

Flow rate: 1.2 mL/min

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.25 g of Flubendazole, dissolve in 3 mL of formic acid, add 50 mL of a mixture of 2-butanone and acetic acid(100) (7 : 1), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid
= 31.330 mg of $C_{16}H_{12}FN_3O_3$

Packaging and storage Preserve in light-resistant, well-closed containers.

Flubendazole Suspension
플루벤다졸 현탁액

Flubendazole Suspension contains NLT 90.0% and NMT 105.0% of the labeled amount of flubendazole ($C_{16}H_{12}FN_3O_3$: 313.28).

Method of preparation Prepare as directed under Suspensions, with Flubendazole.

Identification (1) Shake Flubendazole Suspension well to mix, take an amount of Flubendazole Suspension, equivalent to 25 mg of flubendazole. Add it to 10 mL of formic acid, shake well to mix, and add isopropanol to make 25 mL. Filter and use the filtrate as the test solution. Separately, weigh 25 mg of flubendazole RS, dissolve in 10 mL of formic acid, add isopropanol to make 25 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescence indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform, methanol and ammonia water(28) (45 : 4 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Expose the plate under ultraviolet light (main wavelength: 254 nm) or spray Dragendorff's TS onto the plate; the R_f values and colors of the spots from the test solution and the standard solution are the same.

(2) Determine the absorption spectra of the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelength.

pH Between 4.5 and 6.5.

Assay Shake Flubendazole Suspension well to mix, and pipet an amount of Flubendazole Suspension, equivalent to 50 mg of flubendazole ($C_{16}H_{12}FN_3O_3$). Add it to 10 mL of formic acid, shake well to mix, add isopropanol to make exactly 100 mL, and filter. Discard the first 10 mL of the filtrate, pipet 10 mL of the subsequent filtrate, add isopropanol to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of flubendazole RS, dissolve in 10 mL of formic acid, and add isopropanol to make exactly 100 mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution at the wavelength of 310 nm as directed under the Ultraviolet-visible Spectroscopy, using isopropanol as a control solution.

Amount (mg) of flubendazole ($C_{16}H_{12}FN_3O_3$)
= Amount (mg) of flubendazole RS × (A_T / A_S)

Packaging and storage Preserve in tight containers.

Flubendazole Tablets
플루벤다졸 정

Flubendazole Tablets contain NMT 95.0% and NLT 105.0% of the labeled amount of flubendazole ($C_{16}H_{12}FN_3O_3$: 313.28).

Method of preparation Prepare as directed under Tablets, with Flubendazole.

Identification (1) Weigh an amount of Flubendazole Tablets, equivalent to 20 mg of flubendazole according to the labeled amount, dissolve with 2 mL of formic acid, and add chloroform to make 25 mL. Filter this solution, and use the filtrate as the test solution. Separately, weigh 20 mg of flubendazole RS, dissolve with 2 mL of formic

acid, add chloroform to make 25 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate in a mixture of chloroform, methanol and formic acid (18 : 1 : 1) to a distance of about 15 cm and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots from the test solution and the standard solution are the same in R_f value.

(2) Perform the test as directed under the Assay; the test solution shows the maximum absorbance at the same wavelength as the standard solution.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Flubendazole Tablets, and powder them. Weigh accurately an amount of the powder equivalent to about 0.1 g of flubendazole ($C_{16}H_{12}FN_3O_3$), add 10 mL of formic acid, dissolve by warming on a steam bath for 15 minutes, and add isopropanol to make exactly 100 mL. Filter this solution, take exactly 1 mL of the filtrate, add isopropanol to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of flubendazole RS, proceed in the same manner with the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution at the wavelength of 311 nm as directed under the Ultraviolet-visible Spectroscopy, using 10% formic acid-isopropanol as a control solution.

Amount (mg) of flubendazole ($C_{16}H_{12}FN_3O_3$)
= Amount (mg) of flubendazole RS × (A_T / A_S)

Packaging and storage Preserve in well-closed containers.

Fluconazole Capsules
플루코나졸 캡슐

Fluconazole Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of fluconazole ($C_{13}H_{12}F_2N_6$: 306.27).

Method of preparation Prepare as directed under Capsules, with Fluconazole.

Identification Weigh an amount of contents equivalent to about 50 mg of fluconazole according to the labeled amount of Fluconazole Capsules, dissolve in 5 mL of methanol, centrifuge, and use the clear supernatant as the test solution. Separately, dissolve about 50 mg of fluconazole RS in 5 mL of methanol and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescence indicator for thin-layer chromatography. Develop the plate with a mixture of dichloromethane, methanol and ammonia (80 : 20 : 1) as the developing solvent, and air-dry the plate. Next, develop the plate with a mixture of ethyl acetate, isopropanol and ammonia (72 : 28 : 1) as the developing solvent, and air-dry the plate. Spray evenly hexachloroplatinic(IV) acid-potassium iodide TS on the plate and examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values of the spots obtained from the test solution and the standard solution are the same.

Uniformity of dosage units Meets the requirements.

Dissolution Perform the test with 1 capsule of Fluconazole Capsules at 100 revolutions per minute according to Method 2 under the Dissolution, using 500 mL of 0.1 mol/L hydrochloric acid with a sinker. Take 20 mL of the dissolved solution after 30 minutes from starting the test and filter. Discard the first 1 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 40 mg of fluconazole RS, transfer to a 250-mL volumetric flask, add 0.1 mol/L hydrochloric acid to make 250 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 261 nm as directed under the Ultraviolet-visible Spectroscopy. Meets the requirements if the dissolution rate of Fluconazole Capsules in 30 minutes is NLT 80%.

Dissolution rate (%) with respect to the labeled amount of fluconazole ($C_{13}H_{12}F_2N_6$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 200$$

W_S: Amount (mg) of fluconazole RS
C: Labeled amount (mg) of fluconazole ($C_{13}H_{12}F_2N_6$) in 1 capsule

Assay Weigh accurately the mass of NLT 20 capsules of Fluconazole Capsules. Weigh accurately an amount equivalent to about 50 mg of fluconazole ($C_{13}H_{12}F_2N_6$) and add the mobile phase to make 100 mL. Take 10.0 mL of the filtrate, add the mobile phase to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of fluconazole RS and dissolve in the mobile phase to make 100 mL. To 10.0 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of fluconazole in each solution.

Amount (mg) of fluconazole ($C_{13}H_{12}F_2N_6$)
= Amount (mg) of fluconazole RS × $\frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

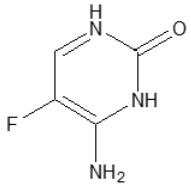
Column: A stainless-steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of water and methanol (75 : 25).

Flow rate: 2 mL/min

Packaging and storage Preserve in well-closed containers.

Flucytosine
플루시토신



Flucytosine $C_4H_4FN_3O$: 129.09
6-Amino-5-fluoropyrimidin-2(1*H*)-one [*2022-85-7*]

Flucytosine, when dried, contains NLT 98.5% and NMT 101.0% of flucytosine ($C_4H_4FN_3O$). It also contains NLT 14.0% and NMT 15.5% of fluorine (F: 19.00).

Description Flucytosine occurs as a white or almost white, crystalline powder and is odorless.
It is sparingly soluble in water, slightly soluble in methanol, acetic acid(100), acetic anhydride or ethanol(95), and practically insoluble in ether.
It dissolves in 0.1 mol/L hydrochloric acid TS.
Dissolve 1.0 g of Flucytosine in 100 mL of water; the pH of the solution is between 5.5 and 7.5.
It is slightly hygroscopic.

Melting point—About 295 °C (with decomposition).

Identification (1) To 5 mL of aqueous solution of Flucytosine (1 in 500), add 0.2 mL of bromine TS; a yellowish brown color of the test solution immediately disappears. Further add 2 mL of barium hydroxide TS; a violet precipitate is formed.

(2) Weigh about 0.1 g of Flucytosine as directed under the Oxygen Flask Combustion, using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as the absorbent; the resulting test solution responds to the Qualitative Analysis (2) for fluoride.

(3) Determine the absorption spectra of solutions of Flucytosine and flucytosine RS in 0.1 mol/L hydrochloric acid TS (1 in 125000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Flucytosine in 100 mL of water; the solution is clear and colorless.

(2) ***Chloride***—To 1.0 g of Flucytosine, add 80 mL of water, and dissolve by heating on a steam bath. After cooling, take 40 mL of this solution, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.20 mL of 0.01 mol/L hydrochloric acid (NMT 0.014%).

(3) ***Fluoride***—Weigh about 0.10 g of Flucytosine and dissolve in 10.0 mL of 0.1 mol/L diluted sodium hydroxide TS (1 in 20). To 5.0 mL of this solution, add 10 mL of a mixture of alizarin complexone TS, acetic acid-potassium acetate buffer solution (pH 4.3) and cerium(III) nitrate TS (1 : 1 : 1), add water again to make exactly 20 mL, allow to stand for 1 hour, and use this solution as the test solution. Separately, add 5.0 mL of 0.01 mol/L diluted sodium hydroxide TS (1 in 20) to 4.0 mL of standard fluorine solution, add 10 mL of a mixture of alizarin complexone TS, acetic acid-potassium acetate buffer solution (pH 4.3) and cerium(III) nitrate TS (1 : 1 : 1), and proceed in the same manner as the test solution. Use this solution as the standard solution. Perform the test with these solutions as directed under the Ultraviolet-visible Spectroscopy using a solution obtained by proceeding with 5.0 mL of 0.01 mol/L diluted sodium hydroxide TS (1 in 20) in the same manner as the blank; the absorbance of the test solution at 600 nm is not greater than that of the standard solution (NMT 0.048%).

(4) ***Heavy metals***—Weigh about 1.0 g of Flucytosine according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(5) ***Arsenic***—Weigh about 1.0 g of Flucytosine according to Method 2 and perform the test (NMT 2 ppm).

(6) ***Related substances***—Dissolve 50.0 mg of Flucytosine in 5 mL of methanol solution (1 in 2) and use this solution as the test solution. Pipet 1 mL of this solution and add methanol solution (1 in 2) to make exactly 25 mL. Pipet 1 mL of this solution and add methanol solution (1 in 2) to make exactly 20 mL. Use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, methanol and water (5 : 3 : 2) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); spots other than the principal spot obtained from the test solution is not more intense than the spots obtained from the standard solution.

Loss on drying NMT 1.0% (1 g, 105 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

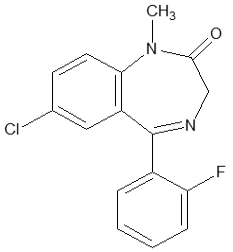
Assay (1) ***Flucytosine***—Weigh accurately about 0.2 g of Flucytosine, previously dried, dissolve in 40 mL of acetic acid(100) and 100 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid
= 12.909 mg of $C_4H_4FN_3O$

(2) ***Fluorine***—Weigh accurately about 10 mg of Flucytosine, previously dried, and perform the test as directed under the Assay of fluorine under the Oxygen Flask Combustion, using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as the absorbent.

Packaging and storage Preserve in light-resistant, tight containers.

Fludiazepam
플루디아제팜



Fludiazepam $C_{16}H_{12}ClN_2O$: 302.73
7-Chloro-5-(2-fluorophenyl)-1-methyl-1*H*-benzo[e][1,4]diazepin-2(3H)-one [*3900-31-0*]

Fludiazepam, when dried, contains NLT 99.0% and NMT 101.0% of fludiazepam ($C_{16}H_{12}ClN_2O$).

Description Fludiazepam occurs as white to pale yellow crystals or crystalline powder.
It is very soluble in chloroform, freely soluble in methanol, ethanol, acetic acid(100) or ether, and practically insoluble in water.

Identification (1) Proceed with 10 mg of Fludiazepam as directed under the Oxygen Flask Combustion, using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as the absorbent; the resulting test solution responds to the Qualitative Analysis (2) for fluoride.

(2) Determine the absorption spectra of solutions of Fludiazepam and fludiazepam RS in methanol (1 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths. Further, determine the absorption spectra of solutions of Fludiazepam and fludiazepam RS in methanol (1 in 20000); both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Fludiazepam and fludiazepam RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) Perform the test with Fludiazepam as directed under the Flame Coloration (2); it exhibits a green color.

Melting point Between 91 and 94 ℃.

Purity (1) ***Chloride***—Dissolve 1.0 g of Fludiazepam in 50 mL of ether, add 50 mL of water, shake to mix, and collect the water layer. Wash the water layer twice each time with 20 mL of ether and filter the water layer. To 20 mL of the filtrate, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid TS (NMT 0.036%).

(2) ***Heavy metals***—Proceed with 2.0 g of Fludiazepam according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 0.10 g of Fludiazepam in 20 mL of chloroform and use this solution as the test solution. Pipet 1 mL of this solution and add chloroform to make exactly 50 mL. Pipet 2 mL of this solution, add chloroform to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform and ethyl acetate (10 : 7) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.3% (1 g, in vacuum, 60 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g, platinum crucible).

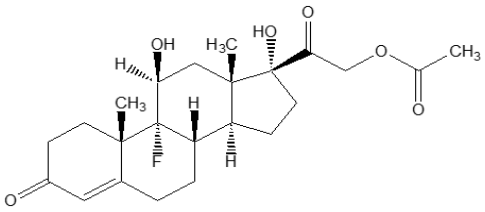
Assay Weigh accurately about 0.5 g of Fludiazepam, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid

= 30.273 mg of $C_{16}H_{12}ClN_2O$

Packaging and storage Preserve in tight containers.

Fludrocortisone Acetate
플루드로코르티손아세테이트



Fludrocortisone Acetate $C_{23}H_{31}FO_6$: 422.49
2-((8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,17*R*)-9-fluoro-11,17-dihydroxy-10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl acetate [*514-36-3*]

Fludrocortisone Acetate contains NLT 97.0% and NMT 103.0% of fludrocortisone acetate ($C_{23}H_{31}FO_6$), calculated on the dried basis.

Description Fludrocortisone Acetate occurs as white to pale yellow crystals or a crystalline powder, which has no odor or slight odor.
It is hygroscopic.
It is sparingly soluble in ethanol(95) or chloroform, slightly soluble in ether, and practically insoluble in water.

Identification Determine the infrared spectra of Fludrocortisone Acetate and fludrocortisone acetate RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +131° and +138° (after drying, 0.1 g, acetone, 20 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 0.5 g of Fludrocortisone Acetate according to Method 2 and perform the test. Prepare the control solution with 1.5 mL of lead standard solution (NMT 30 ppm).

(2) ***Related substances***—Weigh accurately about 20 mg of Fludrocortisone Acetate, dissolve exactly in 10 mL of the mobile phase, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to it make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution according to the automatic integration method; the total area of peaks other than fludrocortisone acetate from the test solution is not greater than 1/4 the peak area of fludrocortisone acetate from the standard solution. The total area of the peaks other than fludrocortisone acetate from the test solution is not greater than 1/ 2 the peak area of fludrocortisone acetate from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6mm in internal diameter and 20 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: A mixture of water and tetrahydrofuran (13 : 7).

Flow rate: Adjust the flow rate so that the retention time of fludrocortisone acetate is about 10 minutes.

System suitability

Test for required detectability: Pipet 5 mL of the standard solution, and add the mobile phase to make exactly 100 mL. Confirm that the peak area of fludrocortisone acetate obtained from 20 μL of this solution is equivalent to 4.0% to 6.0% of the peak area of fludrocortisone acetate obtained from the standard solution.

System performance: Dissolve 2 mg each of Fludrocortisone Acetate and hydrocortisone acetate in the mobile phase to make 50 mL. Proceed with 10 μL of this solution according to the above conditions; hydrocortisone acetate and fludrocortisone acetate are eluted in this order with the resolution being NLT 1.5.

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of fludrocortisone acetate is NMT 2.0%.

Time span of measurement: About 2 times the retention time of fludrocortisone beginning after the solvent peak

Loss on drying NMT 1.0% (1 g, 100 °C, in vacuum, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 25 mg each of Fludrocortisone Acetate and fludrocortisone acetate RS, previously dried in vacuum for 2 hours at 100 ℃, dissolve in chloroform to make exactly 250 mL, pipet 10 mL of the resulting solutions, and add chloroform to make exactly 50 mL. Use these solutions as the test solution and the standard solution. Pipet 10 mL each of the test solution and the standard solution, put them in the 25 mL volumetric flasks, respectively, add 1.0 mL of a solution obtained by dissolving 50 mg of blue tetrazolium in 10 mL of methanol, and shake to mix. Mix with 1.0 mL of a mixture of tetramethylammonium hydroxide TS and methanol (1 : 4), allow to stand for 10 minutes, then add a solution of hydrochloric acid in methanol (1 in 100) to

make exactly 25 mL. With these solutions, perform the test as directed under the Ultraviolet-visible Spectroscopy and determine the absorbances, A_T and A_S, at the absorbance maximum wavelength of around 525 nm, using a solution prepared with 10 mL of chloroform in the same manner as the control solution.

Amount (mg) of Fludrocortisone Acetate ($C_{23}H_{31}FO_6$)
= Amount (mg) of fludrocortisone acetate RS$\times \frac{A_T}{A_S}$

Packaging and storage Preserve in light-resistant, well-closed containers.

Flufenamic Acid Capsules
플루페남산 캡슐

Flufenamic Acid Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of flufenamic acid ($C_{14}H_{10}F_3NO_2$: 281.23).

Method of preparation Prepare as directed under Capsules, with Flufenamic Acid.

Identification Weigh a portion of Flufenamic Acid Capsules, equivalent to 0.3 g of flufenamic acid, extract twice with 30 mL each of ether, combine the ether extracts, and wash with 10 mL of water. Evaporate the ether extracts on a steam bath to dryness, dry the residue at 105 ℃, and perform the following test.

(1) Dissolve 20 mg of the residue in 15 mL of chloroform, and examine under ultraviolet light; it exhibits strong bluish white fluorescence.

(2) Transfer 0.5 mL of chromic acid-sulfuric acid TS to a small test tube, heat on a steam bath for 5 minutes; the side of the test tube is moistened transparently without stickiness. Add 1 to 2 mg of the residue, heat on a steam bath for 5 minutes; the side of the test tube is not moistened and the solution does not flow easily.

(3) With a solution prepared by dissolving 5.0 mg of the residue in 500 mL of a solution of hydrochloric acid in methanol (3.7 in 1000), determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at wavelengths around 287 nm and 344 nm.

Purity ***Related substances*—**Use a solution of the residue in 5% ethanol obtained from the Identification as the test solution, and prepare 0.01% ethanol solution and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography, develop the plate with a mixture of toluene, tetrahydrofuran and acetic acid(100) (90 : 25 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spot from the standard solution.

Disintegration Meets the requirements.

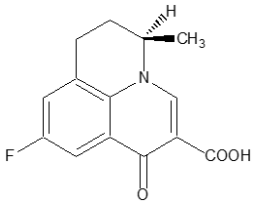
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the contents of NLT 20 capsules of Flufenamic Acid Capsules. Weigh accurately about 0.6 g of flufenamic acid ($C_{14}H_{10}F_3NO_2$), dissolve in 100 mL of ethanol(99.5), previously neutralized with a solution of chromium trioxide in saturated sulfuric acid solution, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: phenol red TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 28.12 mg of $C_{14}H_{10}F_3NO_2$

Packaging and storage Preserve in tight containers.

Flumequine
플루메퀸



and enantiomer

Flumequine $C_{14}H_{12}FNO_3$: 261.25
(*RS*)-9-Fluoro-5-methyl-1-oxo-1,5,6,7-tetrahydropyrido[3,2,1-ij]quinoline-2-carboxylic acid [*42835-25-6*]

Flumequine contains NLT 99.0% and NMT 101.0% of flumequine ($C_{14}H_{12}FNO_3$), calculated on the dried basis.

Description Flumequine occurs as a white fine crystalline powder.
It is sparingly soluble in dichloromethane, very slightly soluble in methanol and practically insoluble in water.
It soluble in dilute sodium hydroxide TS.

Identification (1) Mix 5 mg of Flumequine with 45 mg of magnesium oxide, and incinerate for about 5 minutes until a white residue is obtained. After cooling, add 1 mL of water and 2 drops of phenolphthalein TS to make it colorless, add about 2 mL of dilute hydrochloric acid, filter, and use this solution as the test solution. Mix the

test solution with 0.1 mL of alizarin S TS and 0.1 mL of zirconium nitrate solution, allow to stand for 5 minutes, and compare with the blank test solution proceeded in the same manner as the test solution; the test solution turns red to yellow while the blank test solution remains red.

(2) Determine the infrared spectra of Flumequine and flumequine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 5 mg of Flumequine in dichloromethane to make 10 mL, and use this solution as the test solution. Separately, dissolve 5 mg of flumequine RS in dichloromethane to make 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with fluorescence agent). Develop the plate with a mixture of ethanol(95), water and 9 mol/L ammonia water (90 : 10 : 10) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254nm); the R_f values of the principal spots obtained from the test solution and the standard solution are the same.

Zirconium nitrate solution—Dissolve 0.1 mg of zirconium nitrate in a mixture of 60 mL of hydrochloric acid and 40 mL of water.

9 mol/L ammonia water—Add water to 67 g of 13.5 mol/L ammonia water to make 100 mL.

Optical rotation $[\alpha]_D^{20}$: Between -0.10° and +0.10° (5.0 g, 0.5 mol/L sodium hydroxide TS, 50 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 5.0 g of Flumequine in 0.5 mol/L sodium hydroxide TS to make 50 mL; the solution is clear.

(2) ***Heavy metals***—Proceed with 2.0 g of Flumequine according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 35.0 mg of Flumequine in *N*,*N*-dimethylformamide to make exactly 100 mL, and use this solution as the test solution. Separately, dissolve 5.0 mg of flumequine RS and 5.0 mg of flumequine related substance I RS [(*RS*)-9-fluoro-5-methyl-1-oxo-6,7-dihydro-*1H*,*5H*-benzo[i.j]qunolizine-2-carboxylate (flumequine ethyl ester)] in *N*,*N*-dimethylformamide to make exactly 100 mL. Use this solution as the standard solution (1). To 1.0 mL of the test solution, add *N*,*N*-dimethylformamide to make exactly 200 mL, and use this solution as the standard solution (2). Perform the test with 10 μL each of the blank test solution (dimethylformamide), the test solution, the standard solution (1) and the standard solution (2) as directed under the Liquid Chromatography according to the following conditions. The area of peaks other than the major peak obtained from the test solution is not greater than the major peak area from the standard solution (2) (0.5%) and the total area of peaks other than the major peak obtained from the test solution is not more than twice the major peak area from the standard solution (2) (1.0%). However, exclude the peaks obtained from *N*,*N*-dimethylformamide and any peak with an area less than 0.1 times the major peak area from the standard solution (2).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 250 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of potassium dihydrogen phosphate buffer solution and methanol (51 : 49).

Flow rate: 0.8 mL/min

System suitability

System performance: Proceed with the standard solution (1) according to the above conditions; the retention times of flumequine related substance I and flumequine are about 11 minutes and 13 minutes, respectively, with the resolution between the peaks of flumequine and flumequine related substance I being NLT 2.0.

Potassium dihydrogen phosphate buffer solution—Dissolve 1.36 g of potassium dihydrogen phosphate in water to make 1000 mL.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

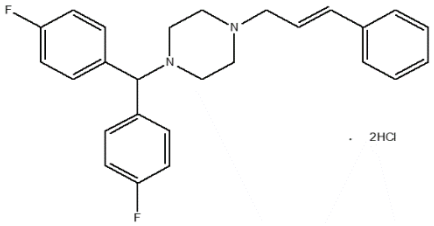
Residue on ignition NMT 0.1% (0.5 g, platinum crucible).

Assay Weigh accurately about 0.5 g of Flumequine, dissolve in 50 mL of *N*,*N*-dimethylformamide, and titrate with 0.1 mol/L tetramethylammonium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L tetrabutylammonium hydroxide
= 26.126 mg of $C_{14}H_{12}FNO_3$

Packaging and storage Preserve in well-closed containers.

Flunarizine Dihydrochloride
플루나리진염산염



Flunarizine Dihydrochloride

$C_{26}H_{26}F_2N_2 \cdot 2HCl$: 477.42

1-[Bis(4-fluorophenyl)methyl]-4-[(2*E*)-3-phenylprop-2-enyl]piperazine dihydrochloride, *[30484-77-6*]

Flunarizine Dihydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of flunarizine dihydrochloride ($C_{26}H_{26}F_2N_2 \cdot 2HCl$) and NLT 7.2% and NMT 8.8% of fluorine (F: 19.00).

Description Flunarizine Dihydrochloride occurs as a white to pale yellowish white powder.
It is soluble in ethanol(95), sparingly soluble in methanol, acetic acid(100) or chloroform, slightly soluble in water or acetic anhydride, and practically insoluble in ether.

Melting point—About 209 °C.

Identification (1) Weigh 15 mg of Flunarizine Dihydrochloride, and prepare the test solution as directed under the Oxygen Flask Combustion using 20 mL of water as the absorbent. The resulting test solution responds to the Qualitative Analysis for fluoride.

(2) Dissolve 10 mg of Flunarizine Dihydrochloride in 10 mL of water, add dilute nitric acid, shake to mix, allow to stand for 5 minutes, and filter. The filtrate responds to the Qualitative Analysis for chloride.

(3) Dissolve 3 mg of Flunarizine Dihydrochloride in 3 mL of citric acid-acetic acid TS, and heat for 10 minutes on a steam bath; the resulting solutions exhibits a reddish purple color.

(4) Determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy using a solution of Flunarizine Dihydrochloride in methanol (1 in 100000); it exhibits a maximum between 252 nm and 256 nm.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Flunarizine Dihydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Weigh 0.4 g of Flunarizine Dihydrochloride, dissolve in methanol to make exactly 10 mL, and use this solution as the test solution. Pipet 1 mL of this solution and add methanol to make exactly 50 mL. Pipet 5 mL of this resulting solution, add methanol to make exactly 50 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of tetrahydrofuran, water, methanol and ammonia water(28) (40 : 30 : 30 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, phosphorus pentoxide, 60 °C, 3 hours).

Residue on ignition NMT 0.1% (1 g, platinum crucible).

Assay (1) ***Flunarizine dihydrochloride***—Weigh accurately about 0.25 g of Flunarizine Dihydrochloride, previously dried, dissolve in 20 mL of acetic acid(100) and 50 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 23.87 mg of $C_{26}H_{26}F_2N_2 \cdot 2HCl$

(2) ***Fluorine***—Weigh accurately about 4 mg of Flunarizine Dihydrochloride, previously dried, and perform the test as directed under the assay of fluorine under the Oxygen Flask Combustion, using 15 mL of water as the absorbent.

Packaging and storage Preserve in light-resistant, tight containers.

Flunarizine Dihydrochloride Capsules
플루나리진염산염 캡슐

Flunarizine Dihydrochloride Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of flunarizine dihydrochloride ($C_{26}H_{26}F_2N_2 \cdot 2HCl$: 477.42).

Method of preparation Prepare as directed under Capsules, with Flunarizine Dihydrochloride.

Identification (1) Weigh an amount of Flunarizine Dihydrochloride Capsules, equivalent to 10 mg of flunarizine dihydrochloride RS, according to the labeled amount. Dissolve in 10 mL of methanol, filter, and use the filtrate as the test solution. Separately, weigh 10 mg of flunarizine dihydrochloride RS, dissolve in 10 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Next, develop the plate with a mixture of *n*-heptane, methanol, ethyl acetate and acetic acid(100) (7 : 1.5 : 1.5 : 0.1) (as the developing solvent) to a distance of about 15 cm, and air-dry the

plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots from the test solution exhibits R_f values and color corresponding to that of the test solution.

(2) Determine the absorption spectra of the test solution and the standard solution from the Assay as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit the same maximum absorption at the same wavelength.

Dissolution Take 1 capsule of Flunarizine Dihydrochloride Capsules and perform the test at 100 revolutions per minute according to Method 2 under the Dissolution, using 600 mL of the first fluid for the Disintegration as the dissolution medium. Take the dissolved solution 45 minutes after staring the test, filter, and use the filtrate as the test solution. Separately, weigh accurately about 25 mg of flunarizine dihydrochloride RS and dissolve in methanol to make exactly 50 mL. Pipet 1 mL of this solution, add the dissolution medium to make exactly 50 mL, and use this solution as the standard solution. With the test solution and the standard solution, perform the test as directed under the Ultraviolet-visible Spectroscopy using the dissolution medium as a control solution, and determine the absorbances, A_T and A_S, at 252 nm. Meets the requirements if the dissolution rate of Flunarizine Dihydrochloride Capsules in 45 minutes is NLT 70%.

Dissolution rate (%) of flunarizine dihydrochloride ($C_{26}H_{26}F_2N_2 \cdot 2HCl$)
= Amount (mg) of flunarizine dihydrochloride RS
$\times (A_T / A_S) \times (1 / C) \times 24$

C: Labeled amount (mg) of flunarizine dihydrochloride in 1 capsule

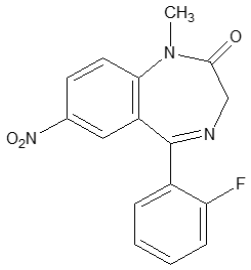
Uniformity of dosage units It meets the requirements when the Content uniformity test is performed according to the following procedure. Perform the test with 1 capsule of Flunarizine Dihydrochloride Capsules as directed under the Assay.

Assay Weigh accurately the mass of the contents of NLT 20 capsules of Flunarizine Dihydrochloride Capsules. Weigh accurately about 10 mg of flunarizine dihydrochloride ($C_{26}H_{26}F_2N_2 \cdot 2HCl$), add 10 mL of 0.1 mol/L hydrochloric acid TS and 40 mL of isopropanol, and dissolve by warming on a steam bath. After cooling, add isopropanol to make exactly 100 mL, and filter through a filter paper. Pipet 10 mL of this solution, add 10 mL of the 0.1 mol/L hydrochloric acid TS, add isopropanol to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of flunarizine dihydrochloride RS, add 20 mL of 0.1 mol/L hydrochloric acid TS and 40 mL of isopropanol, and dissolve by warming on a steam bath. After cooling, add isopropanol to make exactly 100 mL. Pipet 5 mL of this solution and add 10 mL of 0.1 mol/L hydrochloric acid TS. Then, add isopropanol to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and standard solution, respectively, at 252 nm as directed under the Ultraviolet-visible Spectroscopy, using isopropanol as a control solution.

Amount (mg) of flunarizine dihydrochloride ($C_{26}H_{26}F_2N_2 \cdot 2HCl$)
= Amount (mg) of flunarizine dihydrochloride RS
$\times (A_T / A_S) \times 0.5$

Packaging and storage Preserve in well-closed containers.

Flunitrazepam
플루니트라제팜



Flunitrazepam $C_{16}H_{12}FN_3O_3$: 313.28
5-(2-Fluorophenyl)-1-methyl-7-nitro-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one [*1622-62-4*]

Flunitrazepam, when dried, contains NLT 99.0% and NMT 101.0% of flunitrazepam ($C_{16}H_{12}FN_3O_3$).

Description Flunitrazepam occurs as a white to pale yellow crystalline powder.
It is freely soluble in acetic acid(100), soluble in acetic anhydride or acetone, slightly soluble in ethanol(99.5) or ether and practically insoluble in water.

Identification (1) Determine the absorption spectra of solutions of Flunitrazepam and flunitrazepam RS in ethanol(99.5) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Flunitrazepam and flunitrazepam RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 168 and 172 °C.

Purity (1) ***Chloride***—To 1.0 g of Flunitrazepam, add 50 mL of water, allow to stand for 1 hour with occasional shaking, and filter. Take 20 mL of the filtrate, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare

the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid solution (NMT 0.022%).

(2) ***Heavy metals***—Proceed with 2.0 g of Flunitrazepam in a platinum crucible according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 50.0 mg of Flunitrazepam in 10 mL of acetone and use this solution as the test solution. Pipet 2 mL of this solution and add acetone to make exactly 20 mL. Pipet 1 mL of this solution, add acetone to make exactly 25 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of 1,2-dichloroethane, ether and ammonia water(28) (200 : 100 : 3) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the number of spots other than the principal spot from the test solution is NMT 2 and they are not more intense than the spot from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 °C, 4 hours).

Residue on ignition NMT 0.1% (1 g, platinum crucible).

Assay Weigh accurately about 0.5 g of Flunitrazepam, previously dried, dissolve in 20 mL of acetic acid(100), add 50 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 31.33 mg of $C_{16}H_{12}FN_3O_3$

Packaging and storage Preserve in light-resistant, tight containers.

Flunitrazepam Tablets
플루니트라제팜 정

Flunitrazepam Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of flunitrazepam ($C_{16}H_{12}FN_3O_3$: 313.28).

Method of preparation Prepare as directed under Tablets, with Flunitrazepam.

Identification Weigh an amount of Flunitrazepam Tablets, equivalent to 10 mg of flunitrazepam according to the labeled amount, add 5 mL of chloroform, shake to mix, centrifuge, and use the clear supernatant as the test solution. Separately, dissolve 20 mg of flunitrazepam RS in 10 mL of chloroform, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of ether, nitromethane, heptane and ammonia water(28) (60 : 30 : 15 : 2) (as the developing solvent) to a distance of about 15 cm, and air-dry the plate. Spray evenly 2 mol/L sodium hydroxide TS on the plate; the spots obtained from the standard solution exhibits R_f values corresponding to that of the test solution.

Disintegration Meets the requirements.

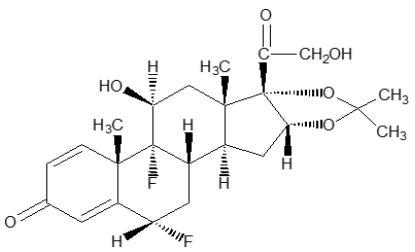
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Flunitrazepam Tablets, and powder. Weigh accurately an amount of the powder equivalent to about 5 mg of flunitrazepam ($C_{16}H_{12}FN_3O_3$), add 2 mL of water, and allow to stand for 2 minutes. Then, add 95% ethanol to make 100 mL. Centrifuge this solution, pipet 10 mL of the clear supernatant, add ethanol(95) to make exactly 50 mL, and use this solution as the test solution. Weigh accurately about 50 mg of flunitrazepam RS, add 2 mL of water, allow to stand for 2 minutes, and add ethanol(95) to make exactly 100 mL. Pipet 1 mL of this solution, add ethanol(95) to make exactly 50 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S of the test solution and the standard solution, at the wavelength of 309 nm as directed under the Ultraviolet-visible Spectroscopy, using ethanol(95) as a control solution.

Amount (mg) flunitrazepam ($C_{16}H_{12}FN_3O_3$)
= Amount (mg) of flunitrazepam RS × (A_T / A_S)× 0.1

Packaging and storage Preserve in tight containers.

Fluocinolone Acetonide
플루오시놀론아세토니드



Fluocinolone Acetonide $C_{24}H_{30}F_2O_6$: 452.49
2-{(6*S*,8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*R*,17*S*)-6,9-difluoro-11-ihydroxy-16,17-[(2-propylidene) *bis*(oxy)]-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a] phenanthren-17-yl)}-2-

oxoethanol [*67-73-2*]

Fluocinolone Acetonide, when dried, contains NLT 97.0% and NMT 102.0% of fluocinolone acetonide ($C_{24}H_{30}F_2O_6$).

Description Fluocinolone Acetonide occurs as white crystals or a crystalline powder. It is odorless.
It is freely soluble in acetic acid(100) and acetone, soluble in ethanol(99.5), sparingly soluble in methanol or chloroform, slightly soluble in acetonitrile, very slightly soluble in ether and practically insoluble in water.

Melting point—266 to 274 °C (with decomposition).

Identification (1) To 2 mg of Fluocinolone Acetonide, and add 2 mL of dilute nitric acid; the solution turns yellow.

(2) Dissolve 0.01 g of Fluocinolone Acetonide in 1 mL of methanol, add 1 mL of Fehling's TS, and heat; a red precipitate is produced.

(3) Weigh 10 mg of Fluocinolone Acetonide, and prepare the test solution as directed under the Oxygen Flask Combustion with a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as an absorbent; the test solution responds to the Qualitative Analysis for fluoride.

(4) Determine the infrared spectra of Fluocinolone Acetonide and fluocinolone acetonide RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the spectra, dissolve Fluocinolone Acetonide and fluocinolone acetonide RS in acetone, respectively, then evaporate the acetone to dryness, and repeat the test with the residues.

Optical rotation $[\alpha]_D^{20}$ Between +98° and +108° (after drying, 0.1 g, methanol, 10 mL, 100 mm).

Purity ***Related substance***—Dissolve 15 mg of Fluocinolone Acetonide in 25 mL of the mobile phase, and use this solution as the test solution. Pipet 2 mL of this solution, add the mobile phase to it make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas in each solution as directed in the automatic integration method; the total area of peaks other than the major peak from the test solution is not greater than the major peak area from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 to 25 cm in length, packed with silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of water-saturated chloroform, methanol and acetic acid(100) (200 : 3 : 2).

Flow rate: Adjust the flow rate so that the retention time of fluocinolone acetonide is about 12 minutes.

System suitability

Test for required detectability: Take exactly 5 mL of the standard solution, and add the mobile phase to make exactly 100 mL. Confirm that the major peak area of obtained from 20 mL of this solution is equivalent to 4% to 6% of that obtained from 20 μL of the standard solution.

System performance: Dissolve 15 mg each of Fluocinolone Acetonide and triamcinolone acetonide in 25 mL of the mobile phase. To 5 mL of this solution, add the mobile phase to make 20 mL. Proceed with 20 μL of this solution according to the above operating conditions; triamcinolone acetonide and fluocinolone acetonide are eluted in this order with the resolution being NLT 1.9.

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area ratios of fluocinolone acetonide is NMT 1.0%.

Time span of measurement: A range of about 2 times the retention time of fluocinolone acetonide after the solvent peak.

Loss on drying NMT 1.0% (0.2 g, in vacuum, 105 °C, 3 hours).

Residue on ignition NMT 0.1% (0.2 g, platinum crucible).

Assay Weigh accurately about 20 mg each of Fluocinolone Acetonide and fluocinolone acetonide RS, previously dried, dissolve in 40 mL of the mobile phase, add exactly 10 mL of the internal standard solution each, and add the mobile phase to make 100 mL. Use these solutions as the test solution and standard solution, respectively. Perform the test with 20 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios of the peak area, Q_T and Q_S, of fluocinolone acetonide to that of internal standard, respectively.

$$\text{Amount (mg) of fluocinolone acetonide } (C_{24}H_{30}F_2O_6) = \text{amount (mg) of fluocinolone acetonide RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of ethylparaben in methanol (1 in 2500).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octa-

decylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of water and acetonitrile (7 : 3).

Flow rate: Adjust the flow rate so that the retention time of fluocinolone acetonide is about 20 minutes.

System suitability

System performance: Dissolve 5 mg each of isopropyl p-hydroxybenzoate and propyl p-hydroxybenzoate in 50 mL of acetonitrile, and add water to make 100 mL. Proceed with 20 μL of this solution according to the above operating conditions; isopropyl p-hydroxybenzoate and propyl p-hydroxybenzoate are eluted in this order with the resolution being NLT 1.9.

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area ratios of fluocinolone acetonide is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Fluocinolone Acetonide Cream
플루오시놀론아세토니드 크림

Fluocinolone Acetonide Cream contains NLT 90.0% and NMT 110.0% of the labeled amount of fluocinolone acetonide ($C_{24}H_{30}F_2O_6$: 452.49).

Method of preparation Prepare as directed under Creams, with Fluocinolone Acetonide.

Identification Weigh an amount of Fluocinolone Acetonide Cream, equivalent to about 0.5 mg of fluocinolone acetonide, according to the labeled amount, put in a centrifuge tube, disperse in 5 mL of water, and add 10 mL of chloroform. Shake to mix, and then centrifuge. Discard the water layer, add 10 mL of water, shake, and then centrifuge. Dehydrate 2 mL of the chloroform extract by adding about 0.2 g of anhydrous sodium sulfate, and use this solution as the test solution. Separately, dissolve 5 mg of fluocinolone acetonide RS in 100 mL of chloroform, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 50 μL each of the test solution and the standard solution onto a thin-layer chromatographic plate made of silica gel with fluorescence indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform and diethylamine (2 : 1) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the color and R_f values of the principal spots from the test solution and standard solution are the same.

Assay Weigh accurately an amount of Fluocinolone Acetonide Cream, equivalent to about 0.75 mg of fluocinolone acetonide ($C_{24}H_{30}F_2O_6$), according to the labeled amount, add about 10 mL of acetonitrile, and dissolve by warming on a steam bath. Transfer to a 25-mL volumetric flask, using 2 mL each of acetonitrile 3 times. Add 3.0 mL of the internal standard solution and 5.0 mL of water to mix, then add acetonitrile to the gauge line, cool in iced water, and centrifuge. Use the clear supernatant as the test solution. Separately, weigh accurately an appropriate amount of fluocinolone acetonide RS, previously dried at 105 ℃ for 3 hours, and dissolve in acetonitrile to prepare a solution containing 300 μg per mL. Pipet 5 mL each of this solutions, add 6.0 mL of the internal standard solution and 15.0 mL of water, and then add acetonitrile to make exactly 50 mL. Use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, of fluocinolone acetonide to that of the internal standard, respectively.

$$\text{Amount (mg) of fluocinolone acetonide } (C_{24}H_{30}F_2O_6) = \text{Amount (mg) of fluocinolone acetonide RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of norethindrone in acetonitrile (2 in 10000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of water and acetonitrile (5 : 3).

Flow rate: 2 mL/min

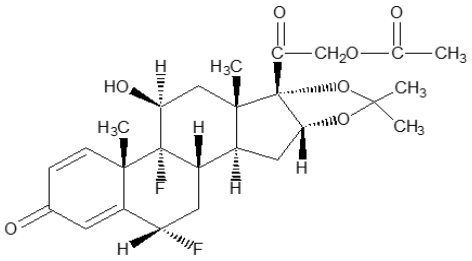
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the resolution between the peak of the internal standard and the peak of fluocinolone acetonide is NLT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio of fluocinolone acetonide to the peak area of the internal standard is NMT 1.5%.

Packaging and storage Preserve in tight containers.

Fluocinonide
플루오시노니드



Fluocinonide $C_{26}H_{32}F_2O_7$: 494.53
2-{(6*S*,8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*R*,17*S*)-6,9-difluoro-11-hydroxy-16,17-[(2-propylidene)*bis*(oxy)]-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-yl)}-2-oxoethyl acetate [*356-12-7*]

Fluocinonide, when dried, contains NLT 97.0% and NMT 103.0% of fluocinonide ($C_{26}H_{32}F_2O_7$).

Description Fluocinonide occurs as white crystals or a crystalline powder.
It is sparingly soluble in chloroform, slightly soluble in acetonitrile, methanol, ethanol(95) or ethyl acetate, very slightly soluble in ether, and practically insoluble in water.

Identification (1) To 10 mg of Fluocinonide, add 4 mL of water and 1 mL of Fehling's TS, and heat; a red precipitate is produced.

(2) Weigh 10 mg of Fluocinonide, and prepare the test solution as directed under the Oxygen Flask Combustion with a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as an absorbent; the test solution responds to the Qualitative Analysis for fluoride.

(3) Determine the absorption spectra of solutions of Fluocinonide and fluocinonide RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared spectra of Fluocinonide and fluocinonide RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the absorption spectra, dissolve Fluocinonide and fluocinonide RS in ethyl acetate, respectively, evaporate ethyl acetate to dryness, and perform the test with the residue in the same manner.

Optical rotation $[\alpha]_D^{20}$: Between -81° and +89° (0.2 g after drying, chloroform, 20 mL, 100 mm).

Purity ***Related substance***—Dissolve 10 mg of Fluocinonide in 2 mL of chloroform, and use this solution as the test solution. Pipet 1.0 mL of this solution, add chloroform to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of chloroform and methanol (97 : 3) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Spray evenly alkaline blue tetrazolium TS on the plate; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 1.0% (5 g, 105 °C, 3 hours).

Residue on ignition NMT 0.1% (0.5 g, platinum crucible).

Assay Weigh accurately about 20 mg each of Fluocinonide and fluocinonide RS, previously dried, dissolve each in 50 mL of acetonitrile, add 8.0 mL of the internal standard solution, respectively, and add the water to make exactly 100 mL. Use these solutions as the test solution and standard solution, respectively. Perform the test with 20 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios of the peak area, Q_T and Q_S, of fluocinonide to that of internal standard, respectively.

$$\text{Amount (mg) of fluocinonide } (C_{26}H_{32}F_2O_7) = \text{amount (mg) of fluocinonide RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of propyl benzoate in acetonitrile (1 in 100).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of acetonitrile and water (1: 1).

Flow rate: Adjust the flow rate so that the retention time of fluocinonide is about 8 minutes.

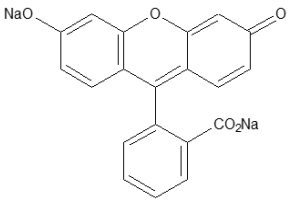
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above operating conditions; fluocinonide and the internal standard are eluted in this order with the resolution being NLT 6.

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above conditions; the relative standard deviation of the ratios of the peak area of fluocinonide to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Fluorescein Sodium
플루오레세인나트륨



Fluorescein Sodium $C_{20}H_{10}Na_2O_5$: 376.27
2-(6-Hydroxy-3-oxo-3*H*-xanthen-9-yl)benzoic acid [*518-47-8*]

Fluorescein Sodium contains NLT 98.5% and NMT 101.0% of fluorescein sodium ($C_{20}H_{10}Na_2O_5$), calculated on the dried basis.

Description Fluorescein Sodium is an orange powder, and is odorless and tasteless.
It is freely soluble in water, methanol or ethanol(95), and practically insoluble in ether.
It is hygroscopic.

Identification (1) An aqueous solution of Fluorescein Sodium (1 in 100) has a strong green fluorescence. Add a large quantity of water but the fluorescence remains. Acidify the solution with hydrochloric acid, and the fluorescence disappears. Then render the solution alkaline with sodium hydroxide TS; the fluorescence reappears.

(2) Place an aqueous solution of Fluorescein Sodium (1 in 2000) dropwise on a piece of filter paper; a yellow spot develops. Expose the filter paper, while moist, to the bromine gas for 1 minute and then to ammonia gas; the spot exhibits a red color.

(3) Ignite 0.5 g of Fluorescein Sodium to carbonize. After cooling, add 20 mL of water to the residue, shake to mix, and filter; the filtrate responds to the Qualitative Analysis for sodium salt.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Fluorescein Sodium in 10 mL of water; the resulting solution is clear and exhibits a red color.

(2) ***Chloride***—Dissolve 0.15 g of Fluorescein Sodium in 20 mL of water, add 6 mL of dilute nitric acid and water to make 30 mL, and filter. To 20 mL of the filtrate, add 2 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 1.0 mL of 0.01 mol/L hydrochloric acid (NMT 0.355%).

(3) ***Sulfate***—Dissolve 0.20 g of Fluorescein Sodium in 30 mL of water, add 2.5 mL of dilute nitric acid and water to make 40 mL, and filter. Add water to 20 mL of the filtrate to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.480%).

(4) ***Zinc***—Dissolve 0.1 g of Fluorescein Sodium in 10 mL of water, add 2 mL of hydrochloric acid, and filter. To the filtrate, add 0.1 mL of potassium hexacyanoferrate(II) TS; no turbidity is produced immediately.

(5) ***Related substances***—Weigh 0.20 g of Fluorescein Sodium, dissolve in exactly 10 mL of methanol and use this solution as the test solution. With this solution, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL of the test solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of chloroform, methanol and ammonia water(28) (30 : 15 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate; any colored spot other than the principal spot does not appear.

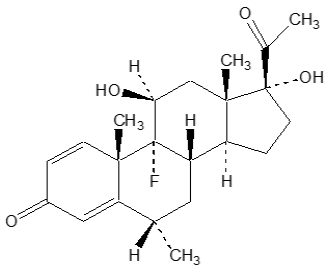
Loss on drying NMT 10.0% (1 g, 105 ℃, constant mass).

Assay Weigh accurately about 0.5 g of Fluorescein Sodium, transfer to a separatory funnel, dissolve in 20 mL of water, and add 5 mL of dilute hydrochloric acid. Extract 4 times with 20 mL of a mixture of 2-methyl-1-propanol and chloroform (1 : 1). Wash each extract successively with 10 mL of water. Evaporate the combined extracts on a steam bath with the aid of a current of air. Dissolve the residue in 10 mL of ethanol(99.5), evaporate the solution to dryness on a steam bath, dry the residue at 105 ℃ for 1 hour, and weigh as fluorescein ($C_{20}H_{12}O_5$: 332.31).

Amount (mg) of fluorescein sodium ($C_{20}H_{10}Na_2O_5$)
= Amount (mg) of fluorescein ($C_{20}H_{12}O_5$) × 1.1323

Packaging and storage Preserve in tight containers.

Fluorometholone
플루오로메톨론



Fluorometholone $C_{22}H_{29}FO_4$: 376.46
(6*S*,8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,17*R*)-17-Acetyl-9-fluoro-11,17-dihydroxy-6,10,13-trimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-3-one [*426-13-1*]

Fluorometholone, when dried, contains NLT 97.0% and NMT 103.0% of fluorometholone ($C_{22}H_{29}FO_4$).

Description Fluorometholone occurs as a white to pale yellowish white crystalline powder, and is odorless.
It is freely soluble in pyridine, slightly soluble in methanol, ethanol(95) or tetrahydrofuran, and practically insoluble in water or ether.

Identification (1) Proceed with 7 mg of Fluorometholone as directed under the Oxygen Flask Combustion, using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as the absorbent; the resulting test solution responds to the Qualitative Analysis (2) for fluoride.

(2) Determine the absorption spectra of solutions of Fluorometholone and fluorometholone RS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Fluorometholone and fluorometholone RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +52° and +60° (0.1 g after drying, pyridine, 10 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Fluorometholone according to Method 3 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 20 mg of Fluorometholone in 10 mL of tetrahydrofuran and use this solution as the test solution. Pipet 1 mL of this solution, add tetrahydrofuran to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 25 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of dichloromethane, acetone and methanol (45 : 5 : 1) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 1.0% (0.2 g, in vacuum, phosphorus pentoxide, 60 ℃, 3 hours).

Residue on ignition NMT 0.2% (0.2 g, platinum crucible).

Assay Weigh accurately about 0.10 g each of Fluorometholone and fluorometholone RS, previously dried, and dissolve each in methanol to make exactly 100 mL. Pipet 5 mL each of these solutions, and add diluted methanol (7 in 10) to make exactly 50 mL. Pipet 10 mL each of these solutions, add exactly 10 mL of the internal standard solution each, add again diluted methanol (7 in 10) to make 100 mL, and use these solutions as the test solution and the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of fluorometholone to that of the internal standard.

$$\text{Amount (mg) of fluorometholone } (C_{22}H_{29}FO_4) = \text{amount (mg) of fluorometholone RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of butyl p-hydroxybenzoate in methanol (1 in 10000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column, about 4 mm in internal diameter and 25 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 ℃.

Mobile phase: Diluted methanol (7 in 10).

Flow rate: Adjust the flow rate so that the retention time of fluorometholone is about 8 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; fluorometholone and the internal standard are eluted in this order with the resolution between their peaks being NLT 4.

Packaging and storage Preserve in light-resistant, well-closed containers.

Fluorometholone and Tetrahydrozoline Hydrochloride Ophthalmic Suspension
플루오로메톨론·테트라히드로졸린염산염 점안현탁액

Fluorometholone and Tetrahydrozoline Hydrochloride Ophthalmic Suspension contains NLT 90.0% and NMT 110.0% of the labeled amount of fluorometholone ($C_{22}H_{29}FO_4$: 376.47) and tetrahydrozoline hydrochloride ($C_{13}H_{16}N_2 \cdot HCl$: 236.75).

Method of preparation Prepare as directed under Ophthalmic Solutions, with Fluorometholone and Tetrahydrozoline Hydrochloride.

Identification (1) ***Fluorometholone***—Shake Fluorometholone and Tetrahydrozoline Hydrochloride Ophthalmic Suspension vigorously to mix, put 4 mL in a sep-

aratory funnel, add 1 g of sodium chloride, and shake vigorously until the sodium chloride is dissolved. Add 2 mL of 1 mol/L hydrochloric acid, extract 5 times with 20 mL of ethyl acetate, add the extract to a 250-mL round flask, and evaporate to dryness in an evaporator. Dissolve the residue in 4 mL of methanol, and use this solution as the test solution. Separately, weigh 20 mg of fluorometholone RS, dissolve in methanol to make 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 25 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescence indicator for thin-layer chromatography. Next, develop the plate with a mixture of toluene, methanol and ethyl acetate (4 : 1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm) or spray evenly a coloring agent onto the plate, and heat at 110 °C for 10 minutes; the R_f value and color of the spots obtained from the test solution and the standard solution are the same.

Coloring agent: While cooling with iced water, add carefully 10 mL of sulfuric acid into a beaker containing 10 mL of methanol. This test solution can be stored in a tight container for 1 week.

(2) ***Tetrahydrozoline hydrochloride***—Take 10 mL of Fluorometholone and Tetrahydrozoline Hydrochloride Ophthalmic Suspension, filter through a filter paper, and then take 8.0 mL of the filtrate to put in a separatory funnel. Add 2 mL of 2 mol/L sodium hydroxide solution and 2 g of sodium chloride, and shake vigorously until the sodium chloride is dissolved. Extract this 5 times with 10 mL of ethyl acetate, add the extracts to a 100-mL round flask, and evaporate to dryness in an evaporation concentrator. Dissolve the residue in 2 mL of ethanol, and use this solution as the test solution. Separately, weigh accurately about 50 mg of tetrahydrozoline hydrochloride RS, dissolve in ethanol to make exactly 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 25 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescence indicator for thin-layer chromatography. Next, develop the plate using a mixture of methanol, acetic acid and water (8 : 1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm) or spray evenly Dragendorff's TS onto the plate; the R_f values and color of the spots obtained from the test solution and the standard solution are the same.

pH Between 5.8 and 7.8.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

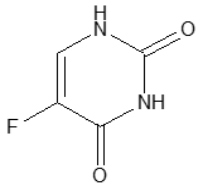
Particulate matter in Ophthalmic solutions Meets the requirements.

Assay (1) ***Fluorometholone***—Perform the test as directed under the section on Fluorometholone ophthalmic suspension in the US Pharmacopeia (USP).

(2) ***Tetrahydrozoline hydrochloride***—Perform the test as directed under the section on tetrahydrozoline hydrochloride ophthalmic solution in the US Pharmacopeia (USP).

Packaging and storage Preserve in tight containers.

Fluorouracil
플루오로우라실



Fluorouracil $C_4H_3FN_2O_2$: 130.08
5-Fluoropyrimidine-2,4(1*H*,3*H*)-dione [*51-21-8*]

Fluorouracil, when dried, contains NLT 98.5% and NMT 101.0% of fluorouracil ($C_4H_3FN_2O_2$). It also contains NLT 13.1% and NMT 16.1% of fluorine (F: 19.00).

Description Fluorouracil occurs as white crystals or a crystalline powder, which is odorless.
It is freely soluble in *N*,*N*-dimethylformamide, sparingly soluble in water, slightly soluble in ethanol(95) and practically insoluble in ether.

Melting point—About 282°C (with decomposition).

Identification (1) To 5 mL of an aqueous solution of Fluorouracil (1 in 500), add 0.2 mL of bromine TS; the color of the test solution disappears. Again, add 2 mL of barium hydroxide TS; a purple precipitate is formed.

(2) Weigh 10 mg of Fluorouracil, and prepare the test solution as directed under the Oxygen Flask Combustion with a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as an absorbent; the test solution responds to the Qualitative Analysis for fluoride.

(3) Determine the absorption spectra of solutions of solutions of Fluorouracil and fluorouracil RS in 0.1 mol/L hydrochloric acid TS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Purity (1) ***Clarity and color of solution***—Dissolve 0.20 g of Fluorouracil in 20 mL of water by warming; the so-

lution is clear and colorless.

(2) ***Fluoride***—Weigh 1.10 g of Fluorouracil and dissolve in 10.0 mL of 0.1 mol/L dilute sodium hydroxide (1 in 20). To 5.0 mL of this solution, add 10 mL of a mixture of alizarin complexone TS, acetic acid-potassium acetate buffer solution (pH 4.3) and cerium(III) nitrate TS (1 : 1 : 1), add water to make exactly 20 mL, allow to stand for 1 hour, and use this solution as the test solution. Separately, add 5.0 mL of 0.01 mol/L dilute sodium hydroxide TS (1 in 20) to 1.0 mL of standard fluorine solution, add 10 mL of a mixture of alizarin complexone TS, acetic acid-potassium acetate buffer solution (pH 4.3) and cerium(III) nitrate TS (1 : 1 : 1), and proceed in the same manner as the test solution. Use this solution as the standard solution. Determine the absorbance of these solutions as directed under the Ultraviolet-visible Spectroscopy using a solution obtained by proceeding with 5.0 mL of 0.01 mol/L dilute sodium hydroxide TS (1 in 20) in the same manner as the standard solution as a control; the absorbance of the test solution at 600 nm not greater than that of the standard solution (NMT 0.012%).

(3) ***Heavy metals***—Proceed with 1.0 g of Fluorouracil according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic***—Put 1.0 g of Fluorouracil into a crucible, add 10 mL of a solution of magnesium nitrate in ethanol(95) (1 in 10), ignite with ethanol(95) to combust, and then incinerate by heating at 750 to 850 °C. If a carbonized substance remains in this method, moisten with a small amount of nitric acid, and incinerate by ignition. Cool, add 10 mL of dilute hydrochloric acid to the residue, dissolve by warming on a steam bath, use this solution as the test solution, and perform the test (NMT 2 ppm).

(5) ***Related substances***—Weigh 0.10 g of Fluorouracil, dissolve in 10 mL of water, and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, acetone and water (7 : 4 : 1) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, 80 °C, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay (1) ***Fluorouracil***—Weigh accurately about 0.2 g of Fluorouracil, previously dried, dissolve in 20 mL of *N*,*N*-dimethylformamide, and titrate with 0.1 mol/L tetramethylammonium hydroxide VS (indicator: 3 drops of thymol blue-dimethylformamide TS). However, the endpoint of the titration is when this solution changes from yellow to bluish green and then finally to blue. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L tetramethylammonium hydroxide
= 13.008 mg of $C_4H_3FN_2O_2$

(2) ***Fluorine***—Weigh accurately about 4 mg of Fluorouracil, previously dried, and perform the test as directed under the Assay of fluorine under the Oxygen Flask Combustion, using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as an absorbent.

Packaging and storage Preserve in tight containers.

Fluorouracil Cream
플루오로우라실 크림

Fluorouracil Cream contains NLT 90.0% and NMT 110.0% of the labeled amount of fluorouracil ($C_4H_3FN_2O_2$: 130.08).

Method of preparation Prepare as directed under Creams, with Fluorouracil. Sodium hydroxide may be added to adjust the pH of Fluorouracil Cream.

Identification Weigh an amount of Fluorouracil Cream, equivalent to 5 mg of fluorouracil, according to the labeled amount, put in an Erlenmeyer flask with a stopper, add 50 mL of ethanol(95), and shake to mix. Use this solution as the test solution. Separately, weigh 5 mg of fluorouracil RS, dissolve in 50 mL of ethanol(95), and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Using 100 μL each of the test solution and the standard solution, spot 20 μL each of the solution 5 times at the line 3 cm from the bottom end of a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, methanol and ammonia water(28) (75 : 25 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f value and the color of the spots obtained from the test solution and the standard solution are the same.

Assay Weigh accurately an amount of Fluorouracil Cream, equivalent to about 10 mg of fluorouracil ($C_4H_3FN_2O_2$), add 20 mL of methanol, shake to mix, and add water to make 100 mL. Pipet 1 mL of this solution, add water to make 10 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 10 mg of

fluorouracil RS, previously dried, dissolve in water to make 100 mL, pipet 1 mL of this solution, and add water to make 10 mL. Use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the operating conditions under Fluorouracil injection, and determine the peak areas, A_T and A_S, of fluorouracil.

$$\text{Amount (mg) of fluorouracil } (C_4H_3FN_2O_2) = \text{Amount (mg) of fluorouracil RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers.

Fluorouracil Injection
플루오로우라실 주사액

Fluorouracil Injection is an aqueous solution for injection and contains NLT 90.0% and NMT 110.0% of the labeled amount of fluorouracil ($C_4H_3FN_2O_2$: 130.08).

Method of preparation Prepare as directed under Injections, with Fluorouracil by adding sodium hydroxide.

Description Fluorouracil Injection occurs as a clear, colorless liquid.

Identification (1) The retention times of the major peaks from the test solution and the standard solution obtained under the Assay are the same.

(2) Take an amount of Fluorouracil Injection equivalent to about 0.1 g of fluorouracil according to the labeled amount, carefully acidify with acetic acid(100), and shake the solution to precipitate fluorouracil. Collect the precipitate, wash with 1 mL of water, and dry at 80 ℃ for 4 hours in a desiccator (phosphorus pentoxide). Determine the infrared spectra of the precipitate and Fluorouracil RS, respectively, as directed in the paste method under Infrared Spectrophotometry: both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Proceed as directed under the Identification (1) under Fluorouracil.

pH Between 8.6 and 9.4.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.33 EU per mg of fluorouracil.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of fluorouracil injection equivalent to about 50 mg of fluorouracil ($C_4H_3FN_2O_2$) according to the labeled amount, and add water to make exactly 100 mL. Take 5 mL of this solution, add water to make 250 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of fluorouracil RS, previously dried, dissolve in water to make 100 mL, pipet 5 mL of this solution, add water to make 50 mL and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of fluorouracil for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of fluorouracil } (C_4H_3FN_2O_2) = \text{Amount (mg) of fluorouracil RS} \times \frac{A_T}{A_S} \times 5$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 to 10 μm in particle diameter).

Mobile phase: Water

Flow rate: 1.0 mL/min

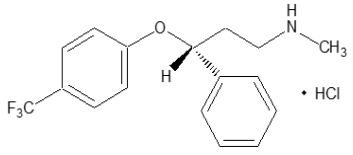
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the number of theoretical plates of the fluorouracil peak is NLT 2500.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of fluorouracil is NMT 2.0%.

Packaging and storage Preserve in light-resistant hermetic containers in a dark place, avoiding freezing.

Fluoxetine Hydrochloride
플루옥세틴염산염



and enantiomer

$C_{17}H_{18}F_3NO \cdot HCl$: 345.79

N-Methyl-3-phenyl-3-[4-

(trifluoromethyl)phenoxy]propan-1-aminehydrochloride [*56296-78-7*]

Fluoxetine Hydrochloride contains NLT 98.0% and NMT 102.0% of fluoxetine hydrochloride ($C_{17}H_{18}F_3NO \cdot HCl$), calculated on the anhydrous basis.

Description Fluoxetine Hydrochloride occurs as a white crystalline powder.
It is freely soluble in ethanol(95) or methanol, sparingly soluble in water or dichloromethane, and practically insoluble in ether.

Identification (1) Determine the infrared spectra of Fluoxetine Hydrochloride and fluoxetine hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Fluoxetine Hydrochloride (1 in 50) responds to the Qualitative Analysis for chloride.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Fluoxetine Hydrochloride as directed under Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(2) ***Related substances***—Weigh accurately about 56 mg of Fluoxetine Hydrochloride, dissolve in the mobile phase to make exactly 10 mL, and use this solution as the test solution (1). To 2.0 mL of the test solution (1), add the mobile phase to make exactly 10 mL, and use this solution as the test solution (2). Perform the test with exactly 10 μL each of the test solutions (1) and (2) as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak area of fluoxetine related substance I, i.e. [(α,α,α-(trifluoro-*m*-tolyl)oxy]propylamine hydrochloride}, A_T, and the peak area of fluoxetine, A_U, obtained from the test solution (2). Determine the peak area of individual related substance, A_i, and the total area of related substance peaks other than the major peak, A_S, obtained from the test solution (1). The amount of related substance I is NMT 0.15%, the amount of α-[2-(methylamino)ethyl]benzene methanol is NMT 0.25%, the amount of fluoxetine related substance II (*N*-methyl-3-phenylpropylamine) is NMT 0.25%, the amount of each related substance is NMT 0.1%, and the total amount of related substances is NMT 0.5%.

$$\text{Content (\%) of fluoxetine related substance I} = 100 \times \frac{A_T}{A_T + A_U}$$

$$\text{Content (\%) of individual related substances} = 100 \times \frac{A_T}{A_T + 5A_U}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with base-deactivated octylsilyl silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of triethylamine buffer solution, stabilizer-free tetrahydrofuran, and methanol (6 : 3 : 1).

Flow rate: 1 mL/min

System suitability

System performance: Dissolve about 22 mg of fluoxetine hydrochloride in 10 mL of 1 mol/L sulfuric acid TS, heat at 80 °C for 3 hours, cool it, put 0.4 mL of this solution into the 25 mL volumetric flask, weigh and add 28 mg of fluoxetine hydrochloride RS, 1 mg of fluoxetine related substance I RS and 1 mg of fluoxetine related substance II RS, then add the mobile phase to make exactly 25 mL. Proceed with 10 μL of this solution according to the above operation conditions; the relative retention times of peaks of α-[2-(methylamino)ethyl]benzene methanol, related substance II, related substance I, fluoxetine and 4-trifluoromethylphenyl are about 0.24, 0.27, 0.94, 1.0 and 2.17, respectively, while the peak height ratio of the related substance I to the valley depth between the fluoxetine peak and the related substance I peak, measured from the related substance I peak, is NMT 1.1.

Time span of measurement: At least 2 times the retention time of fluoxetine.

Triethylamine buffer solution—Add 980 mL of water to 10 mL of triethylamine, then add phosphoric acid to adjust the pH to 6.0.

Water NMT 0.5% (1 g, volumetric titration, direct titration).

Assay Weigh accurately about 10 mg each of Fluoxetine Hydrochloride and fluoxetine hydrochloride RS, dissolve in the mobile phase to make exactly 100 mL each, and use these solutions as the test solution and standard solution, respectively. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the major peak areas from each solution, A_T and A_S, respectively.

$$\text{Amount (mg) of fluoxetine hydrochloride } (C_{17}H_{17}F_3NO \cdot HCl) = \text{amount (mg) of fluoxetine hydrochloride RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with base-deactivated octylsilyl silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of triethylamine buffer solution, stabilizer-free tetrahydrofuran, and methanol (6 : 3 : 1).

Flow rate: 1 mL/min

System suitability

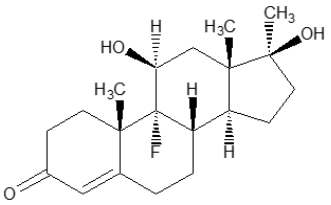
System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; the symmetry factor for fluoxetine peak is NMT 2.0.

System repeatability: Repeat the test 5 times with 10 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of fluoxetine is NMT 2.0%.

Triethylamine buffer solution—Add 980 mL of water to 10 mL of triethylamine, then add phosphoric acid to adjust the pH to 6.0.

Packaging and storage Preserve in tight containers.

Fluoxymesterone
플루옥시메스테론



Fluoxymesterone $C_{20}H_{29}FO_3$: 336.44
(8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,17*R*)-17-Acetyl-9-fluoro-11,17-dihydroxy-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[a]phenanthren-3-one [*76-43-7*]

Fluoxymesterone, when dried, contains NLT 97.0% and not more then 102.0% of fluoxymesterone ($C_{20}H_{29}FO_3$).

Description Fluoxymesterone occurs as white crystals or a crystalline powder. It is odorless.
It is sparingly soluble in methanol, slightly soluble in ethanol(95) or chloroform, very slightly soluble in ether, and practically insoluble in water.

Identification (1) Dissolve 5mL of Fluoxymesterone; the solution exhibits a yellow color.

(2) Prepare the test solution with 10 mg of Fluoxymesterone as directed under the Oxygen Flask Combustion, using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as an absorbent; the test solution responds to the Qualitative Analysis (2) for fluoride.

(3) Determine the absorption spectra of solution of Fluoxymesterone and fluoxymesterone RS in ethanol(95) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared spectra of Fluoxymesterone and fluoxymesterone RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit the similar intensity of absorption at the same wavenumbers. If there is any difference in these spectra, perform the test in the same manner with the residue prepared by dissolving each in ethanol(99.5) to evaporate.

Optical rotation $[\alpha]_D^{20}$: Between +104° and +112° (0.1 g after drying, ethanol(95), 10 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 0.5g of Fluoxymesterone as directed under Method 2 and perform the test. Prepare the control solution with 1.5 mL of lead standard solution (NMT 30 ppm).

(2) ***Related substances***—Dissolve 30 mg of Fluoxymesterone in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of toluene, ethanol(95) and acetate acid (3 : 1 : 1) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 366 nm); any spot other than the principal spot obtained from the test solution is not more intense than the spot from the standard solution.

Loss on drying NMT 1.0% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.2% (0.5 g, platinum crucible).

Assay Weigh accurately about 25 mg each of Fluoxymesterone and fluoxymesterone RS, previously dried, dissolve each in the internal standard solution to make exactly 100 mL and use these solutions as the test solution and the standard solution, respectively. With 10 μL each of the test solution and the standard solution, perform the test according to the Liquid Chromatograph under the following conditions to calculate the peak area ratios, Q_T and Q_S, of fluoxymesterone to the peak area of the internal standard.

$$\text{Amount (mg) of fluoxymesterone } (C_{20}H_{29}FO_3) = \text{Amount of fluoxymesterone RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of methylprednisolone in a mixture of chloroform and methanol (19 : 1) (1 in 5000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 30 cm in length, packed with silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of chloride *n*-butyl, water saturated *n*-butyl, tetrahydrofuran, methanol and acetic acid(100).

Flow rate: Adjust the flow rate so that the retention time of fluoxymesterone is about 9 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; fluoxymesterone and the internal standard are eluted in this order with the resolution being NLT 6.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the ratios of the peak area of fluoxymesterone to that of the internal standard is NMT 1.5%.

Packaging and storage Preserve in light-resistant, well-closed containers.

Fluoxymesterone Tablets
플루옥시메스테론 정

Fluoxymesterone Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of fluoxymesterone ($C_{20}H_{29}FO_3$: 336.44).

Method of preparation Prepare as directed under Tablets, with Fluoxymesterone.

Identification Weigh an amount of Fluoxymesterone Tablets, previously powdered, equivalent to 20 mg of fluoxymesterone, add 20 mL of warm chloroform, and shake to mix. Then filter the clear supernatant by tilting the flask to the side. Extract two more times with 20 mL of warm chloroform each, collect the extracts, and evaporate to dryness on a steam bath. Then dissolve the residue in 5 mL of acetone, and filter the clear supernatant by tilting the flask to the side. Add 20 mL of water and filter the resulting precipitate. Dissolve the precipitate in 5 mL of acetone, add 20 mL of water, and filter the resulting precipitate. Dry the precipitate at 105 °C for 3 hours and perform the test with this precipitate as directed under the Identification (4) of Fluoxymesterone.

Dissolution Perform the test with 1 tablet of Fluoxymesterone Tablets at 75 revolutions per minute according to Method 2, using 900 mL of 0.01 mol/L hydrochloric acid TS as the dissolution medium. Take the dissolved solution after 60 minutes from starting of the test, filter, take 20 mL of the filtrate, add 2.0 mL of the internal standard solution and 0.01 mol/L hydrochloric acid TS to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately about 28 mg of fluoxymesterone RS, and dissolve in ethanol(95) to make exactly 25 mL. Pipet 5 mL of this solution, and add 0.01 mol/L hydrochloric acid TS to make exactly 250 mL. Take exactly 5 mL of this solution and 2.0 mL of internal standard solution, add 0.01 mol/L hydrochloric acid TS to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of the peak areas of fluoxymesterone to that of internal standard, respectively.

Meets the requirements if the dissolution rate of Fluoxymesterone Tablets in 60 minutes is NLT 70%.

Internal standard solution—A solution of norethisterone in ethanol(95) (4.6 in 100000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of water and acetonitrile (58 : 42).

Flow rate: 3 mL/min

System suitability

System performance: Perform the test with 20 μL of the standard solution as directed under the above operating conditions; fluoxymesterone and norethindrone are eluted in this order with the resolution between their peaks being NLT 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratios of fluoxymesterone to the internal standard is NMT 2.0%.

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following method.

Take 1 tablet of Fluoxymesterone Tablets, place it in an appropriate container, add 2 mL of water, sonicate, and dissolve for about 30 minutes until completely disintegrated. Add the internal standard solution to obtain a solution containing about 250 μg of fluoxymesterone ($C_{20}H_{29}FO_3$) per mL. Shake to mix for 15 minutes, filter the chloroform layer, use the clear supernatant as the test solution, and perform the test as directed under the Assay of Fluoxymesterone.

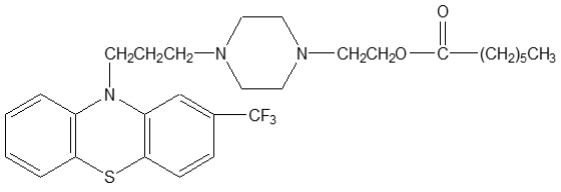
Assay Weigh accurately the mass of NLT 20 tablets of

Fluoxymesterone Tablets and powder them. Weigh accurately an amount of the powder equivalent to about 5 mg of fluoxymesterone ($C_{20}H_{29}FO_3$), add exactly 20 mL of internal standard solution, sonicate for 10 minutes, and shake for 15 minutes to mix. Filter this solution, use the clear supernatant as the test solution, and perform the test as directed under the Assay of Fluoxymesterone.

$$\text{Amount (mg) of fluoxymesterone } (C_{20}H_{29}FO_3) = \text{Amount (mg) of fluoxymesterone RS} \times \frac{Q_T}{Q_S}$$

Packaging and storage Preserve in light-resistant, well-closed containers.

Fluphenazine Enanthate
플루페나진에난테이트



$C_{29}H_{38}F_3N_3O_2S$: 549.69

2-[4-[3-[2-(Trifluoromethyl)phenothiazin-10-yl] propyl]piperazin-1-yl]ethylheptanoate [*2746-81-8*]

Fluphenazine Enanthate, when dried, contains NLT 98.5% and NMT 101.0% of fuphenazine eanthate ($C_{29}H_{38}F_3N_3O_2S$).

Description Fluphenazine Enanthate occurs as a pale yellow to yellowish orange viscous liquid. It is usually clear but becomes opaque by producing crystals.
It is freely soluble in methanol or ether, soluble in ethanol(95) or acetic acid(100), and practically insoluble in water.

Identification (1) Proceed with 10 mg of Fluphenazine Enanthate as directed under the Oxygen Flask Combustion, using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as the absorbent; the resulting test solution responds to the Qualitative Analysis for fluoride.

(2) Determine the absorption spectra of solutions of 2 mg each of Fluphenazine Enanthate and fluphenazine enanthate RS dissolved in 200 mL of a solution of 0.01 mol/L hydrochloric acid in methanol (17 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Fluphenazine Enanthate and fluphenazine enanthate RS as directed under the liquid film method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Acetylspiramycin according to Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(2) ***Related substances***—Dissolve 0.25 g of Fluphenazine Enanthate in 10 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 100 mL, and use it as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of acetone, hexane, and ammonia water(28) (16 : 6 : 1) as the developing solvent to a distance of about 15 cm and air-dry the plate. Expose the plate to ultraviolet light (main wavelength: 254 nm), and any spot other than the principal spot obtained from the test solution is not more intense than those from the standard solutions. Also, spray evenly diluted sulfuric acid (1 in 2) on the plate; the spots other than the principal spot from the test solution are not more intense than those from the standard solution.

Loss on drying NMT 1.0% (1 g, in vacuum, 60 ℃, 3 hours).

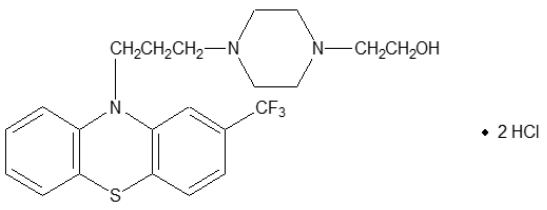
Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.5 g of Fluphenazine Enanthate, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid (indicator: 2 drop of methylrosanilinium chloride TS). Perform a blank test in the same manner and make any necessary correction.

$$\text{Each mL of 1 mol/L perchloric acid VS} = 27.485 \text{ mg of } C_{29}H_{38}F_3N_3O_2S$$

Packaging and storage Preserve in light-resistant, tight containers.

Fluphenazine Hydrochloride
플루페나진염산염



$C_{22}H_{26}F_3N_3Cl \cdot 2HCl$: 510.44

2-(4-{3-[2-(Trifluoromethyl)phenothiazin-10-yl]propy}piperazin-1-yl)ethanol dihydrochloride

[*146-56-5*]

Fluphenazine Hydrochloride contains NLT 97.0% and NMT 103.0% of fluphenazine hydrochloride ($C_{22}H_{26}F_3N_3Cl2HCl$), calculated on the dried basis.

Description Fluphenazine Hydrochloride occurs as a white crystalline powder and is odorless.
It is freely soluble in water, slightly soluble in ethanol or chloroform, and practically insoluble in benzene or ether.

Melting point—About 225 °C.

Identification (1) Determine the absorption spectra of solutions of Fluphenazine Hydrochloride and fluphenazine hydrochloride RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both exhibit an absorption maximum and minimum at the same wavelengths, and the difference in absorbances of the solutions, calculated on the dried basis, at the absorption maximum wavelength around 259 nm is NMT 2.5%.

(2) Determine the infrared spectra of Fluphenazine Hydrochloride and fluphenazine hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit maxima at the same wavenumbers.

(3) An aqueous solution of Fluphenazine Hydrochloride responds to the Qualitative Analysis for chloride.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Fluphenazine Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(2) ***Related substances*—**Weigh accurately 0.1 g of Fluphenazine Hydrochloride, dissolve in the sodium hydroxide-methanol TS to make 10 mL, and use this solution as the test solution. Separately, dissolve 10 mg of fluphenazine hydrochloride RS in sodium hydroxide-methanol TS to make exactly 10 mL. Pipet 0.1 mL, 0.5 mL, 1 mL and 2 mL each of the resulting solution, add sodium hydroxide-methanol TS to make exactly 10 mL, and use these solutions as the standard solutions (1), (2), (3) and (4), respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solutions (1), (2), (3) and (4) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of acetone, cyclohexane and diethylamine (40 : 15 : 1) as a developing solvent to a distance of about 15 cm, and air-dry the plate. Expose the plate to ultraviolet light (main wavelength: 254 nm), and total intensity of all spots other than the principal spot obtained from each of the test solutions are NMT 2.0% of that of the spots from each of the standard solutions.

Loss on drying NMT 1.0% (1 g, 65 ℃, 3 hours).

Residue on ignition NMT 0.5% (1 g).

Assay Weigh accurately about 0.12 g of Fluphenazine Hydrochloride, and dissolve in the mobile phase without triethylamine to make exactly 100 mL. Pipet accurately 5 mL of this solution, dilute with the mobile phase without triethylamine to make 100 mL, filter the resulting solution, and use the filtrate as the test solution. Separately, weigh accurately about 0.12 g of the fluphenazine hydrochloride RS and dissolve in the mobile phase without triethylamine to make exactly 100 mL. Pipet 5 mL of the solution, add the mobile phase without triethylamine to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of fluphenazine from the test solution and the standard solution, respectively.

$$\text{Amount (mg) of fluphenazine hydrochloride } (C_{22}H_{26}F_3N_3OS\cdot 2HCl) = \text{amount (mg) of fluphenazine hydrochloride RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 12.5 cm in length, packed with octylsilyl silica gel for chromatography (3 μm ~ 10 μm in particle diameter).

Mobile phase: Filter a mixture of 0.05 mol/L potassium dihydrogen phosphate (adjusted to pH 2.5 with phosphoric acid), acetonitrile and methanol. To the filtrate, add triethylamine to be its concentration of 0.2%.

Flow rate: 1 mL/min

System suitability

System performance: Proceed with 25 μL of the standard solution according to the above conditions; the symmetry factor is NMT 2.0.

System repeatability: Repeat the test 6 times with 25 μL of the standard solution according to the above conditions; the relative standard deviation is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Fluphenazine Hydrochloride Tablets
플루페나진염산염 정

Fluphenazine Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of fluphenazine hydrochloride ($C_{22}H_{26}F_3N_3OS\cdot 2HCl$: 510.44).

Method of preparation Prepare as directed under Tablets, with Fluphenazine Hydrochloride.

Identification Weigh an amount of Fluphenazine Hy-

drochloride Tablets, previously powdered, equivalent to 10 mg of fluphenazine hydrochloride according to the labeled amount and also weigh about 10 mg of fluphenazine hydrochloride RS. Place each in a separatory funnel, add 5 mL of water and 20 mL of diluted hydrochloric acid (1 in 120), shake to mix for 10 minutes, add 20 mL each of sodium carbonate solution (1 in 10) saturated with chloroform, and extract 5 times with 20 mL each of chloroform while shaking gently. Filter through an absorbent cotton, previously washed with chloroform, into a 150-mL beaker. Evaporate the extracts on a steam-bath to dryness and dissolve the residues separately in 0.5 mL of a mixture of methanol and water (4 : 1) and use the solutions as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of acetone, cyclohexane and diethylamine (40 : 15 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray sulfuric acid-methanol solution (2 in 5) evenly on the plate; the R_f values and the colors of the spots obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 tablet of Fluphenazine Hydrochloride Tablets at 100 revolutions per minute according to Method 1, using 900 mL of 0.01 mol/L hydrochloric acid as the dissolution medium. Take the dissolved solution after 45 minutes from the start of the test and perform the Assay with following differences. Dilute the amount of the dissolved solution to be withdrawn with an equal volume of mobile phase without triethylamine; inject a volume of 100 μL, in the preparation of the standard solution. The standard solution should have a similar concentration and composition compared to the test solution. The mobile phase should have a triethylamine concentration of 0.3%. in the chromatographic system, use a flow rate of about 2.0 mL per minute. It meets the requirements if the dissolution rate of Fluphenazine Hydrochloride Tablets in 45 minutes is NLT 75%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Fluphenazine Hydrochloride Tablets, and powder them. Weigh accurately an amount of the powder equivalent to about 6 mg of fluphenazine hydrochloride ($C_{22}H_{26}F_3N_3OS \cdot 2HCl$), add 80 mL of mobile phase without triethylamine, shake for 1 hour, and sonicate for 10 minutes to form a fine suspension. Add the mobile phase without triethylamine to make exactly 100 mL, and shake to mix. Filter this solution, and use the filtrate as the test solution. Separately, weigh accurately about 6 mg of Fluphenazine Hydrochloride RS, dissolve in the mobile phase without triethylamine to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas of fluphenazine, A_T and A_S, in each solution.

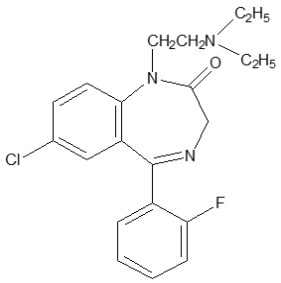
$$\text{Amount (mg) of fluphenazine hydrochloride } (C_{22}H_{26}F_3N_3OS \cdot 2HCl) = \text{Amount (mg) of fluphenazine hydrochloride RS} \times \frac{A_T}{A_S}$$

Operating conditions

For the detector, column, column temperature, mobile phase and system suitability, proceed as directed in the operating conditions under the Assay of Fluphenazine Hydrochloride.

Packaging and storage Preserve in tight containers.

Flurazepam
플루라제팜



Flurazepam $C_{21}H_{23}ClFN_3O$: 387.88
7-Chloro-1-[2-(diethylamino)ethyl]-5-(2-fluoro-phenyl)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one [*17617-23-1*]

Flurazepam, when dried, contains NLT 99.0% and NMT 101.0% of flurazepam ($C_{21}H_{23}ClFN_3O$).

Description Flurazepam occurs as white to pale yellow crystals or crystalline powder.
It is very soluble in chloroform, freely soluble in methanol, ethanol(95), acetic anhydride or ether, and practically insoluble in water.

Identification (1) Dissolve 10 mg of Flurazepam in 3 mL of sulfuric acid and examine the solution under ultraviolet light (main wavelength: 365 nm); the resulting solution exhibits a greenish yellow fluorescence.

(2) Dissolve 10 mg of Flurazepam in 3 mL of citric acid-acetic acid TS, and heat for 4 minutes on a steam bath; the resulting solution exhibits a dark red color.

(3) Proceed with 10 mg of Flurazepam as directed under the Oxygen Flask Combustion, using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as the absorbent; the resulting test solution responds to the Qualitative Analysis (2) for fluoride.

(4) Determine the absorption spectra of solutions of Flurazepam and flurazepam RS in methanol (1 in

100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths. Further, determine the absorption spectra of solutions of Flurazepam and flurazepam RS in methanol (1 in 10000); both spectra exhibit similar intensities of absorption at the same wavelengths.

(5) Perform the test with Flurazepam as directed under the Flame Coloration (2); it exhibits a green color.

Melting point Between 79 and 83 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Flurazepam in 10 mL of ethanol(95); the resulting solution is colorless to pale yellow and clear.

(2) ***Chloride***—Dissolve 1.0 g of Flurazepam in 50 mL of ether, add 46 mL of water and 4 mL of sodium carbonate TS, shake to mix, and collect the water layer. Wash the water layer twice each time with 20 mL of ether and filter the water layer. Pipet 20 mL of the filtrate, add dilute nitric acid to neutralize, then add another 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid (NMT 0.036%).

(3) ***Sulfate***—Take 20 mL of the filtrate in (2), add dilute hydrochloric acid to neutralize, then add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid VS (NMT 0.048%).

(4) ***Heavy metals***—Proceed with 2.0 g of Flurazepam according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Arsenic***—Proceed with 1.0 g of Flurazepam according to Method 3 and perform the test (NMT 2 ppm).

(6) ***Related substances***—Dissolve 0.20 g of Flurazepam in 20 mL of chloroform and use this solution as the test solution. Pipet 1 mL of this solution and add chloroform to make exactly 20 mL. Pipet 3 mL of this solution, add chloroform to make exactly 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of cyclohexane, acetone and ammonia water(28) (60 : 40 : 1) as the developing solvent to a distance of about 12 cm and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.2% (1 g, in vacuum, 60 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g, platinum crucible).

Assay Weigh accurately about 0.3 g of Flurazepam, previously dried, dissolve in 50 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS up to the second equivalence point (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid
= 19.394 mg of $C_{21}H_{23}ClFN_3O$

Packaging and storage Preserve in light-resistant, well-closed containers.

Flurazepam Capsules
플루라제팜 캡슐

Flurazepam Capsules contain NLT 93.0% and NMT 107.0% of the labeled amount of flurazepam ($C_{21}H_{23}ClFN_3O$: 387.88).

Method of preparation Prepare as directed under Capsules, with Flurazepam.

Identification (1) Take out the contents of Flurazepam Capsules and powder. Weigh an amount equivalent to 0.1 g of flurazepam according to the labeled amount. add 100 mL of 0.1 mol/L hydrochloric acid TS, shake to mix and filter. To 40 mL of the filtrate, add 80 mL of sodium hydroxide solution (1 in 250) and 100 mL of hexane, shake well to mix, and extract. Take the hexane layer and use this solution as the test solution. Take 25 mL of the test solution, and evaporate on a steam bath to dryness. Dissolve the residue in 3 mL of sulfuric acid and examine the solution under ultraviolet light; the solution exhibits a greenish yellow fluorescence.

(2) Take 25 mL of the test solution obtained from (1) and evaporate on a steam bath to dryness. Dissolve the residue in 3 mL of citric acid-acetic acid TS and heat on a steam bath for 4 minutes: the solution exhibits a dark red color.

(3) Determine the absorption spectrum of the test solution obtained in the Assay as directed under Ultraviolet-visible Spectroscopy: it exhibits a maximum between 315 nm and 319 nm and a minimum between 297 nm and 301 nm.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

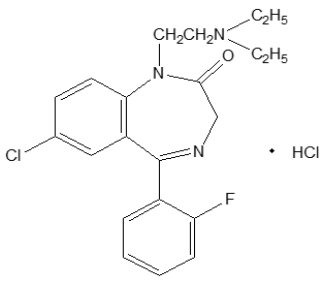
Assay Weigh accurately the mass of the contents of NLT 20 capsules of Flurazepam Capsules and powder. Weigh accurately an amount equivalent to about 50 mg of flurazepam ($C_{21}H_{23}ClFN_3O$), add about 30 mL of methanol, shake well to mix for about 30 minutes, and add metha-

nol to make exactly 50 mL. Filter this solution, discard the first 10 mL of the filtrate, take exactly 10 mL of the subsequent filtrate, add methanol to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of flurazepam RS, previously dried in vacuum at 60 ℃ for 2 hours, and dissolve in methanol to make exactly 50 mL. Pipet 6 mL of this solution, add methanol to make exactly 50 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 317 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of flurazepam } (C_{21}H_{23}ClFN_3O) = \text{Amount (mg) of flurazepam RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers.

Flurazepam Hydrochloride
플루라제팜염산염



$C_{21}H_{23}ClFN_3O \cdot HCl$: 424.34

7-Chloro-1-[2-(diethylamino)ethyl]-5-(2-fluorophenyl)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one hydrochloride [*36105-20-1*]

Flurazepam Hydrochloride, when dried, contains NLT 99.0% and NMT 101.0% of flurazepam hydrochloride ($C_{21}H_{23}ClFN_3O \cdot HCl$).

Description Flurazepam Hydrochloride occurs as white to yellowish-white crystals or crystalline powder.
It is freely soluble in water, ethanol(95), ethanol(99.5) or acetic acid(100).

Melting point—About 197 ℃ (with decomposition).

Identification (1) Determine the absorption spectra of solutions of Flurazepam Hydrochloride and flurazepam hydrochloride RS in sulfuric acid-ethanol TS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Flurazepam Hydrochloride and flurazepam hydrochloride RS, previously dried, as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Flurazepam Hydrochloride (1 in 20) responds to the Qualitative Analysis for chloride.

pH Dissolve 1.0 g of Flurazepam Hydrochloride in 20 mL of water; the pH of this solution is between 5.0 and 6.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Flurazepam Hydrochloride in 10 mL of water; the resulting solution is colorless to pale yellow and clear.

(2) ***Sulfate***—Perform the test with 1.5 g of Flurazepam Hydrochloride. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid VS (NMT 0.011%).

(3) ***Heavy metals***—Proceed with 1.0 g of Flurazepam Hydrochloride in a platinum crucible according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Related substances***—Dissolve 50 mg of Flurazepam Hydrochloride in 5 mL of ethanol(95) and use this solution as the test solution. Pipet 1 mL of this solution and add ethanol(95) to make exactly 50 mL. Pipet 1 mL of this solution, add ethanol(95) to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Place the plate in a chamber filled with ammonia vapor, allow to stand for about 15 minutes, and immediately develop the plate with a mixture of ether and diethylamine (39 : 1) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the number of spots other than the principal spot and the spot on the original point obtained from the test solution is NMT 3, and the spots are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Flurazepam Hydrochloride, previously dried, dissolve in 10 mL of acetic acid(100), add 40 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

$$\text{Each mL of 0.1 mol/L perchloric acid VS} = 21.22 \text{ mg of } C_{21}H_{23}ClFN_3O \cdot HCl$$

Packaging and storage Preserve in tight containers.

Flurazepam Hydrochloride Tablets
플루라제팜염산염 정

Flurazepam Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of flurazepam hydrochloride ($C_{21}H_{23}ClFN_3O \cdot HCl$: 424.34).

Method of preparation Prepare as directed under Tablets, with Flurazepam Hydrochloride.

Identification Weigh an amount of Flurazepam Hydrochloride Tablets, previously powdered, equivalent to 30 mg of flurazepam hydrochloride, dissolve in 2 mL of methanol, centrifuge, and use the clear supernatant as the test solution. Separately, dissolve 30 mg of flurazepam hydrochloride RS in 2 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of diethyl ether, dichloromethane, methanol and ammonia water(28) (90: 60 : 2 : 1) (as the developing solvent), and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots obtained from the standard solution exhibits R_f values and colors corresponding to that of the test solution.

Dissolution Perform the test with 1 tablet of Benproperine Phosphate Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of Solution 2 as the dissolution medium. Take the dissolved solution 45 minutes after starting the dissolution test, and filter. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add the dissolution medium to obtain exactly *V*' mL of a solution containing about 15 μg of flurazepam hydrochloride according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 15 mg of flurazepam hydrochloride RS, and add the dissolution medium to make exactly 100 mL. Pipet 10 mL of this solution, add the dissolution medium to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution according to the Assay, and determine the peak areas, A_T and A_S, of flurazepam hydrochloride ($C_{21}H_{23}ClFN_3O \cdot HCl$) in each solution. Meets the requirements if the dissolution rate of Flurazepam Hydrochloride Tablets in 45 minutes is NLT 80%.

Dissolution rate (%) of the labeled amount of flurazepam hydrochloride ($C_{21}H_{23}ClFN_3O \cdot HCl$)
$= W_S \times (V' / V) \times (A_T / A_S) \times (1 / C) \times 90$

W_S: Amount (mg) of flurazepam hydrochloride RS
C: Labeled amount (mg) of flurazepam hydrochloride ($C_{21}H_{23}ClFN_3O \cdot HCl$) per tablet

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Flurazepam Hydrochloride Tablets, and powder. Weigh accurately an amount of the powder, equivalent to about 15 mg of flurazepam hydrochloride ($C_{21}H_{23}ClFN_3O \cdot HCl$), and add the mobile phase to make exactly 100 mL. Filter this solution, pipet 10 mL of the filtrate, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 15 mg of the flurazepam hydrochloride RS, and dissolve in the mobile phase to make exactly 100 mL. Pipet 10 mL of this solution, add the mobile phase to it make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution according to the Liquid Chromatography under the following conditions, and determine the peak areas, A_T and A_S, of flurazepam hydrochloride ($C_{21}H_{23}ClFN_3O \cdot HCl$) in each solution.

Amount (mg) of flurazepam hydrochloride ($C_{21}H_{23}ClFN_3O \cdot HCl$)
= Amount (mg) of flurazepam hydrochloride RS × (A_T / A_S)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 239 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of methanol and 1% ammonium acetate solution (4 : 1).

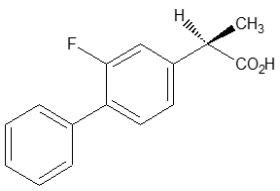
Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of flurazepam hydrochloride is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Flurbiprofen
플루르비프로펜



and enantiomer

Flurbiprofen $C_{15}H_{13}FO_2$: 244.26
(*RS*)-2-(2-fluorobiphenyl-4-yl)propanoic acid [*5104-49-4*]

Flurbiprofen, when dried, contains NLT 98.0% and NMT 101.0% of flurbiprofen ($C_{15}H_{13}FO_2$).

Description Flurbiprofen occurs as a white crystalline powder and has a slightly pungent odor.
It is freely soluble in methanol, ethanol(95), acetone or ether, soluble in acetonitrile, and practically insoluble in water.
A solution of Flurbiprofen in ethanol(95) (1 in 50) shows no optical rotation.

Identification (1) Determine the absorption spectra of solutions of Flurbiprofen and flurbiprofen RS in methanol (1 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Flurbiprofen and flurbiprofen RS, previously dried, as directed in the potassium bromide disk method under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 114 and 117 ℃.

Purity (1) ***Chloride***—Dissolve 0.6 g of Flurbiprofen in 40 mL of acetone and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 40 mL of acetone, 6 mL of dilute nitric acid and water to 0.25 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.015%).

(2) ***Heavy metals***—Dissolve 2.0 g of Flurbiprofen in 30 mL of acetone and add 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 30 mL of acetone, 2 mL of dilute acetic acid and water to 2.0 mL of lead standard solution to make 50 mL (NMT 10 ppm).

(3) ***Related substances***—Dissolve 20 mg of Flurbiprofen in 10 mL of a mixture of water and acetonitrile (11 : 9), and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of water and acetonitrile (11 : 9) to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area from each solution as directed in the automatic integration method; the area of each peak other than flurbiprofen from the test solution is not greater than the major peak area from the standard solution, and the total area of other peaks from the test solution is not greater than 2 times the major peak area from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column, about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 30 ℃.

Mobile phase: A mixture of water, acetonitrile and acetic acid(100) (12 : 7 : 1).

Flow rate: Adjust the flow rate so that the retention time of flurbiprofen is about 20 minutes.

System suitability

Test for required detectability: Pipet 5 mL of the standard solution, and add a mixture of water and acetonitrile (11 : 9) to make exactly 25 mL. Confirm that the peak area of flurbiprofen obtained from 20 μL of this solution is equivalent to 16% to 24% of the peak area of flurbiprofen obtained from the standard solution.

System performance: Dissolve 0.04 g of Flurbiprofen and 0.02 g of butyl p-hydroxybenzoate in 100 mL of a mixture of water and acetonitrile (11 : 9). To 5 mL of this solution, add a mixture of water and acetonitrile (11 : 9) to make 50 mL. Proceed with 20 μL of this solution according to the above conditions; butyl p-hydroxybenzoate and flurbiprofen are eluted in this order with the resolution being NLT 12.

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of flurbiprofen is NMT 2.0%.

Time span of measurement: About 2 times the retention time of flurbiprofen.

Loss on drying NMT 0.1% (1 g, NMT 0.67 kPa, silica gel, 4 hours).

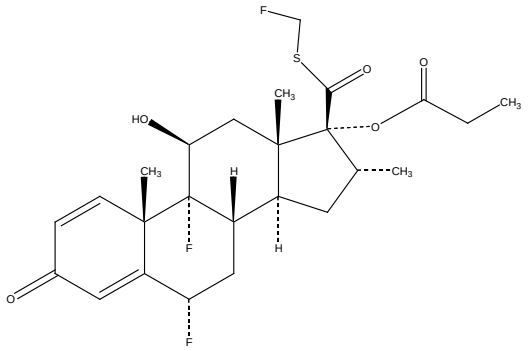
Residue on ignition NMT 0.1% (1 g, platinum crucible).

Assay Weigh accurately about 0.6 g of Flurbiprofen, previously dried, dissolve in 50 mL of ethanol(95), and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of phenolphthalein TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 24.43 mg of $C_{15}H_{13}FO_2$

Packaging and storage Preserve in well-closed containers.

Fluticasone Propionate
플루티카손프로피오네이트



$C_{25}H_{31}F_3O_5S$: 500.57

(6*S*,8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*R*,17*R*)-6,9-Difluoro-17-(((fluoromethyl)thio)carbonyl)-11-hydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-yl propanoate [*80474-14-2*]

Fluticasone Propionate contains NLT 98.0% and NMT 100.5% of fluticasone propionate, calculated on the anhydrous and solvent-free basis.

Description Fluticasone Propionate occurs as a white, fine powder.

It is sparingly soluble in dichloromethane, slightly soluble in ethanol(95) and practically insoluble in water.

Identification (1) Determine the infrared spectra of Fluticasone Propionate and fluticasone propionate RS as directed in the paste method under Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Optical rotation $[\alpha]_D^{20}$: Between +32° and +36° (on the anhydrous and solvent-free basis, 0.1 g, dichloromethane, 20 mL, 100 mm).

Purity (1) ***Related substances***—Weigh accurately about 20 mg of Fluticasone Propionate, dissolve in 5.0 mL of the mobile phase A by sonication, add 5.0 mL of the mobile phase C to mix, and use this solution as the test solution. Perform the test with 50 μL of the test solution by the percentage peak area method under the Liquid Chromatography according to the following conditions, and measure the area of each related substance and the total area of each peak, A_i and A_S; the amounts of each related substance are as shown in Table 1.

Table 1

Related substance	Relative retention time	Limit (%)
Fluticasone propionate related substance I	0.5	0.2
Fluticasone propionate related substance II	0.75	0.1
Fluticasone propionate related substance III	0.8	0.1
Fluticasone propionate related substance IV	0.95	0.3
Fluticasone propionate	1.0	-
Fluticasone propionate related substance V	1.3	0.3
Other related substances	-	0.1
Total related substances	-	1.0

If the total amount of the related substances is less than 0.05%, the amount is excluded.

$$\text{Content (\%) of each related substance} = 100 \times \frac{A_i}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 239 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: Mix 0.5 mL of phosphate with 1000 mL of acetonitrile.

Mobile phase B: Mix 0.5 mL of phosphor with 1000 mL of methanol.

Mobile phase C: Mix 0.5 mL of phosphor with 1000 mL of water.

Table 2

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)	Mobile phase C (vol%)
0	42	3	55
0 - 40	42 → 53	3	55 → 44
40 - 60	53 → 47	3	44 → 10
60 - 70	87	3	10
70 - 75	87 → 42	3	10 → 55

Flow rate: 1.5 mL/min

System suitability

System performance: Weigh about 2.0 mg of fluticason propionate RS, dissolve in 5.0 mL of the mobile phase A by sonication, add 5.0 mL of the mobile phase C to mix, and use this solution as the system suitability solution. Perform the test with 50 μL of this solution according to the above conditions; the resolution between peaks of fluticasone propionate related substance

II and fluticasone propionate related substance III is NLT 1.5 and the relative retention times are as shown in Table 1.

(2) ***Bromofluoromethan***—Dissolve 0.2 of Fluticasone Propionate in 1 mL of *N*,*N*-dimethylformamide, and use this solution as the test solution. Separately, take 20 uL of bromofluoromethane and add *N*,*N*-dimethylformamide to make 10 mL. To 10 μL of this solution, add *N*,*N*-dimethylformamide to make 1 mL. Put *N*,*N*-dimethylformamide in 10 μL of this solution to make 1 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions; the peak height of bromofluoromethane obtained from the test solution is less than the peak height of bromofluoromethane obtained from the standard solution.

Operating conditions

Detector: An electron capture detector

Column: A capillary column about 0.32 mm in internal diameter and about 25 m in length, coated with 5% phenyl-95% methylpolysiloxane with the thickness of 5 μm.

Column temperature: Maintain at 40 ℃ for the first 3.5 minutes, and increase by 30 ℃ each minute up to 200 ℃, and then keep the temperature for 10 minutes.

Carrier gas: Nitrogen

Flow rate: 2.8 mL/min

Sample injection port temperature: 85 ℃

Split ratio: About 70 : 1.

Detector temperature: 250 °C

(3) ***Acetone***—Weigh accurately 0.5 of Fluticasone Propionate, dissolve in the internal standard solution to make exactly 10 mL, and use this solution as the test solution. Take exactly 50 μL of acetone, add the inner standard solution to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 0.1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the peak height ratios, Q_T and Q_S, of acetone to the internal standard for each solution, respectively (NMT 1.0%).

$$\text{Content (\%) of acetone} = 0.05\times \frac{D}{C}\times \frac{Q_T}{Q_S}$$

D: Density of Acetone at 20 ℃

C: Concentration (g/mL) of Fluticasone Propionate in the test solution

Internal standard solution—Put *N*,*N*-dimethylformamide in 50 μL of tetrahydrofuran to make 100 mL.

Operating conditions

Detector: A flame ionization detector

Column: A capillary column about 0.53 mm in internal diameter and about 25 m in length, the inside coated with polyethylene glycol (mean molecular mass is between 3000 and 3700) with the thickness of 2 μm.

Column temperature: Maintain 60 ℃ for the first 3.5 minutes, and then increase by 30 ℃ each minute until 180 ℃, and then keep the temperature for three minutes.

Carrier gas: Nitrogen or helium

Flow rate: 5.5 mL/min

Sample injection port temperature: 150 ℃

Detector temperature: 250 ℃

System suitability

System repeatability: Repeat the test 6 times with 0.1 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak height ratios of acetone to the internal standard is NMT 5.0%.

Water NMT 0.2% (1 g, volumetric titration, direct titration).

Assay Weigh accurately about 40 mg each of Fluticasone Propionate and fluticasone propionate RS, and dissolve in the mobile phase to make exactly 100 mL. To 5.0 mL of this solution, add the mobile phase to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and measure the peak areas of fluticasone propionate, A_T and A_S, for each solutions.

$$\text{Amount (mg) of fluticasone propionate } (C_{25}H_{31}F_3O_5S) = \text{Amount (mg) of fluticasone propionate RS}\times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 239 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of methanol, 0.01 mol/L ammonium dihydrogen phosphate buffer solution and acetonitrile (50: 13: 15).

Flow rate: 1.5 mL/min

System suitability

System performance: Dissolve 2.0 mg of fluticasone propionate related substance IV RS in 50 mL of the mobile phase. Proceed with 20 μL each of this solution and the standard solution according to the above conditions; the relative retention times of peaks are about 1.1 for fluticasone propionate related substance IV and 1.0 for fluticasone propionate with the resolution being

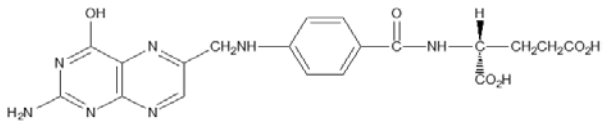
NLT 1.5.

System repeatability: Repeat the test 5 times with 20 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of fluticasone propionate is NMT 2.0%.

0.01 mol/L ammonium dihydrogen phosphate buffer solution—Dissolve 11.5g of ammonium dihydrogen phosphate in 1000 mL of water, add phosphoric acid to adjust the pH to 3.5 ± 0.05.

Packaging and storage Preserved in light-resistant, tight containers below 30 ℃.

Folic Acid
폴산



$C_{19}H_{19}N_7O_6$: 441.40

(2*S*)-2-[(4-{[(2-Amino-4-hydroxypteridin-6-yl)methyl]amino}phenyl)formamido]pentanedioic acid [*59-30-3*]

Folic Acid contains NLT 98.0% and NMT 102.0% of folic acid ($C_{19}H_{19}N_7O_6$), calculated on the anhydrous basis.

Description Folic Acid occurs as a yellow to orange crystalline powder, and is odorless.
It is practically insoluble in water, methanol, ethanol(95), pyridine or ether.
It dissolves in hydrochloric acid, sulfuric acid, dilute sodium hydroxide TS, or sodium carbonate TS (1 in 100), and the solution exhibits a yellow color.
It is gradually affected by light.

Identification (1) Dissolve 1.5 mg of Folic Acid and folic acid RS in dilute sodium hydroxide TS to make 100 mL. Determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Add 1 drop of potassium permanganate TS to 10 mL of the solution in (1), shake until the solution turns blue, and examine the solution immediately under ultraviolet light (main wavelength: 365 nm); it exhibits a blue fluorescence.

Purity (1) ***Clarity and color of solution*—**Dissolve 0.10 g of Folic Acid in 10 mL of dilute sodium hydroxide TS; the solution is yellow and clear.

(2) ***Free amine*—**Pipet 30 mL of the test solution from the Assay, add 20 mL of dilute hydrochloric acid and water to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of p-aminobenzoylglutamic acid RS, previously dried in a desiccator (in vacuum, silica gel) for 4 hours, and dissolve in diluted ethanol (2 in 5) to make exactly 100 mL. Pipet 3 mL of this solution again, add water to make exactly 1000 mL, and use this solution as the standard solution. Pipet 4 mL each of the test solution and the standard solution, perform in the same manner as the Assay below, and perform the test as directed under the Ultraviolet-visible Spectroscopy. Determine the absorbances, A_T and A_S, of each solution made from the test solution and standard solution at a wavelength of 550 nm; the amount of free amine is NMT 1.0%.

$$\text{Content (\%) of free amine} = \frac{A_T}{A_S} \times \frac{W'}{W}$$

W: Amount (mg) of Folic Acid calculated on the anhydrous basis

W′: Amount (mg) of p-aminobenzoylglutamic acid RS

Water NMT 8.5% (10 mg, coulometric titration).

Residue on ignition NMT 0.5% (1 g).

Assay Weigh accurately about 50 mg each of Folic Acid and folic acid RS, add 50 mL of dilute sodium hydroxide TS to each, shake well to dissolve, and then add dilute sodium hydroxide TS again to make exactly 100 mL. Use these solutions as the test solution and the standard solution, respectively. Pipet 30 mL of the test solution and standard solution, and add 20 mL of dilute hydrochloric acid and water to each to make exactly 100 mL. To 50 mL of these solutions, add 0.5 g of zinc powder, shake occasionally to mix, and allow to stand for 20 minutes. Next, filter this solution through a dried filter paper, discard the first 10 mL of the filtrate, take exactly 10 mL of the next filtrate, and add water to make exactly 100 mL. Pipet 4 mL each of these solutions, add 1 mL of water, 1 mL of dilute hydrochloric acid, and 1 mL of sodium nitrite solution (1 in 1000), mix, and allow to stand for 2 minutes. Then, add 1 mL of ammonium amidosulfate solution (1 in 200), shake to mix, and allow to stand for 2 minutes. Add 1 mL of oxalic acid *N*-(1-naphthyl)-*N*′-diethylethylenediamine solution (1 in 1000) to these solutions, shake to mix, allow to stand for 10 minutes, and add water to make exactly 20 mL. Separately, pipet 30 mL of the test solution, and add 20 mL of dilute hydrochloric acid and water to make exactly 100 mL. Pipet 10 mL of this solution, and add 18 mL of dilute hydrochloric acid and water to make exactly 100 mL. Proceed in the same manner as in the preparation of the test solution with exactly 4 mL of this solution, and use this solution as the blank test solution. Perform the test with these solutions using the solution prepared in the same manner with 4 mL of water as the control solution as directed

under the Ultraviolet-visible Spectroscopy, and determine the absorbances A_T, A_S and A_C of the test solution, standard solution, and blank test solution at a wavelength of 550 nm.

$$\text{Amount (mg) of folic acid } (C_{19}H_{19}N_7O_6) = \text{Amount (mg) of folic acid RS, as calculated on the anhydrous basis} \times \frac{A_T - A_C}{A_S}$$

Packaging and storage Preserve in light-resistant, tight containers.

Folic Acid Tablets
폴산 정

Folic Acid Tablets contain NLT 90.0% and NMT 115.0% of the labeled amount of folic acid ($C_{19}H_{19}N_7O_6$: 441.40).

Method of preparation Prepare as directed under Tablets, with Folic Acid.

Identification (1) Weigh an amount of Folic Acid Tablets, previously powdered, equivalent to 1.5 mg of folic acid according to the labeled amount, add 100 mL of dilute sodium hydroxide TS, shake to mix, and filter. Discard the first 10 mL of the filtrate, and perform the test with the subsequent filtrate as directed under the Identification (2) of Folic Acid.

(2) Determine the absorption spectrum of the filtrate from (1) as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 255 nm and 257 nm, between 281 nm and 285 nm, and between 361 nm and 369 nm. And when A1 is the absorbance at the absorption maximum between 255 nm and 257 nm, and A2 is the absorbance at the absorption maximum between 361 nm and 369 nm, the ratio, A2/A1, is between 2.80 and 3.00.

Dissolution Perform the test with 1 tablet of Folic Acid Tablets at 50 revolutions per minute according to Method 2, using 500 mL of water as the dissolution medium. Take the dissolved solution after 45 minutes from the start of the test and filter. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add diluent to make exactly *V′* mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of folic acid RS (previously determined water content), dissolve in the diluent to make a solution having the same concentration as the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of folic acid in each solution. The acceptable dissolution criterion of Folic Acid Tablets is NLT 75% (Q) dissolved in 45 minutes.

$$\text{Dissolution rate (\%) of the labeled amount of folic acid } (C_{19}H_{19}N_7O_6) = C_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 50000$$

C_S: Concentration (mg/mL) of the standard solution

C: Labeled amount (mg) of folic acid ($C_{19}H_{19}N_7O_6$) in 1 tablet

Diluent—Weigh 2 mL of ammonium hydroxide and 1 g of sodium perchlorate, and add water to make 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (1.5 to 10 μm in particle diameter).

Mobile phase: Weigh 35.1 g of sodium perchlorate and 1.40 g of potassium dihydrogen phosphate, add 7.0 mL of 1 mol/L potassium hydroxide and 40 mL of methanol, and add water to make 1000 mL. Adjust the pH to 7.2 with 1 mol/L potassium hydroxide or phosphoric acid.

Flow rate: 1 mL/min

System suitability

System repeatability: Repeat the test 5 times each with 25 μL of the standard solution according to the above conditions; the relative standard deviation of the peak areas of folic acid is NMT 2.0%.

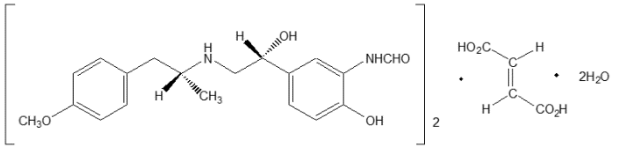
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Folic Acid Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 50 mg of folic acid ($C_{19}H_{19}N_7O_6$: 441.40). Add 50 mL of dilute sodium hydroxide TS, shake frequently, then filter into a volumetric flask and wash with dilute sodium hydroxide TS. Take the combined filtrate and washings, add dilute sodium hydroxide TS to make exactly 100 mL and use this solution as the test solution. Separately, weigh accurately about 50 mg of folic acid RS, dissolve in sodium hydroxide TS to make exactly 100 mL, and use this solution as the standard solution. Pipet 30 mL each of the test solution and standard solution, and perform the test as directed under the Assay of Folic Acid.

$$\text{Amount (mg) of folic acid } (C_{19}H_{19}N_7O_6) = \text{Amount (mg) of folic acid RS, calculated on the anhydrous basis} \times \frac{A_T - A_C}{A_S}$$

Packaging and storage Preserve in light-resistant, well-closed containers.

Formoterol Fumarate Hydrate
포르모테롤푸마르산염수화물



Formoterol Fumarate
$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$: 840.91
N-{2-Hydroxy-5-{(*RS*)-1-hydroxy-2-{[(*RS*)-1-(4-methoxyphenyl)propan-2-yl]amino}ethyl}phenyl}formamide (*E*)-but-2-enedioate [*43229-80-7*, anhydrous]

Formoterol Fumarate Hydrate contains NLT 98.5% and NMT 101.0% of formoterol fumarate [$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4$: 804.882], calculated on the anhydrous basis.

Description Formoterol Fumarate Hydrate occurs as a white to yellowish white crystalline powder.
It is freely soluble in acetic acid(100), soluble in methanol, very slightly soluble in water or ethanol(95), and practically insoluble in ether.
A solution of Formoterol Fumarate Hydrate in methanol (1 in 100) exhibits no optical rotation.

Melting point—About 138 ℃ (with decomposition).

Identification Determine the infrared spectra of Formoterol Fumarate Hydrate and formoterol fumarate hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Formoterol Fumarate Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 0.20 g of Formoterol Fumarate Hydrate in 10 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 200 mL, and use it as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of toluene, acetone, ethanol(99.5) ammonia water(28) (5 : 20 : 10 : 3) as a developing solvent to a distance of about 12 cm, and air-dry the plate. Allow the plate to stand for 5 minutes in iodine vapor; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Water Between 4.0% and 5.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.7 g of Formoterol Fumarate Hydrate, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 40.24 mg of $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4$

Packaging and storage Preserve in tight containers.

Formoterol Fumarate Tablets
포르모테롤푸마르산염 정

Formoterol Fumarate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of formoterol fumarate [$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4$: 804.88].

Method of preparation Prepare as directed under Tablets, with Formoterol Fumarate Hydrate.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Purity (1) Weigh an amount of Formoterol Fumarate Tablets, previously powdered, equivalent to 0.24 mg of formoterol fumarate, add 10 mL of anhydrous ethanol, shake well to mix, and then cool in cold water. Then, centrifuge. Take 5 mL of the clear supernatant, add 2 mL of water, then add 1 drop of sodium bicarbonate TS and 1 drop of 4-aminoantipyrine solution (1 in 100), and shake to mix. Then add 1 drop of potassium ferricyanide TS and shake to mix; the resulting solution exhibits a reddish orange color.

(2) Determine the absorption spectrum of the clear supernatant from (1) as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 242 nm and 248 nm and between 282 nm and 286 nm.

Disintegration Meets the requirements.

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following procedure. Take 1 tablet of Formoterol Fumarate Tablets, transfer into a glass stoppered centrifuge tube, add 5.0 mL of a mixture of ethanol and water (1 : 1), and dissolve by sonicating for 15 minutes. Then, filter through a Millipore filter paper, and use the filtrate as the test solution. Separately, weigh accurately about 50 mg of formoterol fumarate hydrate RS (with water content previously determined), and dissolve

to make 50 mL. Pipet 2.0 mL of this solution, add a mixture of ethanol and water (1 : 1) to make exactly 50 mL. To 2.0 mL of this solution, add a mixture of ethanol and water (1 : 1) to make 10 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of formoterol fumarate in each solution.

$$\text{Amount (mg) of formoterol fumarate } [(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4] = \text{Amount (mg) of formoterol fumarate hydrate RS} \times \frac{A_T}{A_S} \times \frac{804.88}{840.91} \times \frac{1}{1250}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile, water, triethanolamine, phosphoric acid and octanesulfonate (500 : 500 : 1 : 1 : 0.5).

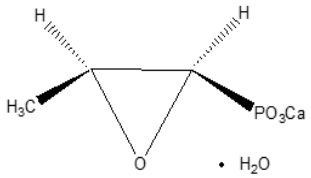
Flow rate: 0.7 mL/min

Assay Weigh accurately the mass of NLT 20 Formoterol Fumarate Tablets and powder. Weigh accurately an amount equivalent to about 0.08 mg of formoterol fumarate $[(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4]$, transfer into a centrifuge tube, dissolve in a mixture of ethanol and water (1 : 1) by sonicating for 15 minutes, and then add a mixture of ethanol and water (1 : 1) to make 10.0 mL. Then, filter through a Millipore filter paper, and use the filtrate as the test solution. Separately, weigh accurately about 50 mg of formoterol fumarate hydrate RS (with water content previously determined), and prepare as directed under the preparation of the standard solution under the Uniformity of dosage units. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the operating conditions of content uniformity test, and determine the peak areas, A_T and A_S, of formoterol fumarate in each solution.

$$\text{Amount (mg) of formoterol fumarate } [(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4] = \text{Amount (mg) of formoterol fumarate hydrate RS} \times \frac{A_T}{A_S} \times \frac{804.88}{840.91} \times \frac{1}{625}$$

Packaging and storage Preserve in tight containers.

Fosfomycin Calcium Hydrate
포스포마이신칼슘수화물



Fosfomycin Calcium Hydrate

$C_3H_5CaO_4P \cdot H_2O$: 194.14

Calcium [(2*R*,3*S*)-3-methyloxiran-2-yl] phosphonate [*26016-98-8*]

Fosfomycin Calcium Hydrate is the calcium salt of a compound having antibacterial activity obtained by *Streptomyces fradiae* culture or synthesis.

Fosfomycin Calcium Hydrate contains NLT 725 μg (potency) and NMT 805 μg (potency) of fosfomycin ($C_3H_7O_4P$: 138.06) per mg, calculated on the anhydrous basis.

Description Fosfomycin Calcium Hydrate occurs as a white crystalline powder.
It is slightly soluble in water and practically insoluble in methanol or ethanol(99.5).

Identification (1) Determine the infrared spectra of Fosfomycin Calcium Hydrate and fosfomycin calcium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Determine the ^1H spectrum of a solution of Fosfomycin Calcium Hydrate in deuterium oxide for nuclear magnetic resonance spectroscopy (1 in 300), using sodium 3-trimethylsilyl propane sulfate for nuclear magnetic resonance spectroscopy as the internal standard, as directed under the Nuclear Magnetic Resonance Spectroscopy; it exhibits a doublet signal at around δ 1.5 ppm, a double doublet signal at around δ 2.9 ppm, a multiplet signal at around δ 3.3 ppm, and no signal around δ 1.4 ppm.

(3) An aqueous solution of Fosfomycin Calcium Hydrate (1 in 500) responds to the Qualitative Analysis (3) for calcium salt.

Optical rotation $[\alpha]_D^{20}$: Between -2.5° and -5.4° (0.5 g calculated on the anhydrous basis, 0.4 mol/L disodium dihydrogen ethylenediaminetetraacetate TS, pH 8.5, 10 mL, 100 mm).

pH Suspend 40 mg of Fosfomycin Calcium Hydrate in 10 mL of water, dissolve by cooling to about 5 ℃, and make the solution back to room temperature; the pH of the solution is between 8.0 and 10.0.

Purity (1) ***Heavy metals***—To 1.0 g of Fosfomycin Cal-

cium Hydrate, add 40 mL of 0.25 mol/L acetic acid and water to make 50 mL. Use this solution as the test solution, proceed according to Method 1, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Fosfomycin Calcium Hydrate according to Method 3 and perform the test (NMT 2 ppm).

Water NMT 12.0% (0.1g, volumetric titration, direct titration). However, use a mixture of formamide for water determination and methanol for water determination (2 : 1) instead of methanol for water determination.

Phosphorus content Weigh accurately about 0.1 g of Fosfomycin Calcium Hydrate, add exactly 40 mL of sodium periodate solution (107 in 10000) and 2 mL of perchloric acid, and heat on a steam bath for 1 hour. After cooling, add water to make exactly 200 mL. Pipet 10 mL of this solution, and add exactly 1 mL of potassium iodide TS. Add sodium thiosulfate TS until this solution becomes colorless, add water to make exactly 100 mL, and use this solution as the test stock solution. Separately, weigh accurately about 70 mg of potassium dihydrogen phosphate, proceed in the same manner as the test solution, and use this solution as the standard stock solution. Proceed in the same manner as the test stock solution, and use this solution as the blank test stock solution. Pipet 5 mL each of the test stock solution, the standard stock solution and the blank test stock solution, transfer each into 25 mL volumetric flasks, and add 2.5 mL of ammonium molybdate-sulfuric acid TS and 1 mL of 1-amino-2-naphthol-4-sulfonic acid TS, respectively. Shake to mix, add water to make exactly 25 mL, and use these solutions as the test solution, the standard solution, and the blank test solution. Allow to stand these solutions at 20 ± 1 ℃ for 30 minutes, and determine the absorbances, A_T, A_S and A_B, as directed under the Ultraviolet-visible Spectrophotometry at the wavelength of 740 nm using water as a control solution (between 15.2% and 16.7%).

$$= \text{Amount (mg) of phosphorus}$$
$$= W \times \frac{A_T - A_B}{A_S - A_B} \times 0.22760$$

W: Amount (mg) of potassium dihydrogen phosphate taken

0.22760: Ratio of phosphorus in potassium dihydrogen phosphate

Calcium content Weigh accurately 0.2 g of Fosfomycin Calcium Hydrate, add exactly 4 mL of 1 mol/L hydrochloric acid TS, shake until completely dissolved, add exactly 100 mL of water, 9 mL of sodium hydroxide TS and 0.1 g of methylthymol blue sodium chloride indicator, and titrate with 0.05 mol/L disodium dihydrogen ethylenediaminetetraacetate VS. The endpoint of the titration is when the color of the solution changes from clear blue to gray or grayish purple. Perform a blank test in the same manner and make any necessary correction (between 19.6% and 21.7%).

Each mL of 0.05 mol/L disodium dihydrogen ethylenediaminetetraacetate VS
= 2.004 mg of Ca

Assay ***Cylinder plate method***—(1) Medium: Use the culture medium in the Assay (1) of Fosfomycin.

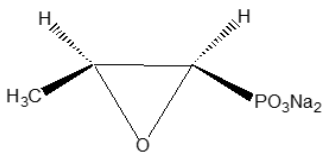
(2) Test organism: Use *Proteus sp* MB 838 as the test organism.

(3) Test microbial suspension: Proceed as directed under the Assay (3) of Fosfomycin Sodium.

(4) Weigh accurately an appropriate amount of Fosfomycin Calcium Hydrate, equivalent to about 20 mg (potency), and dissolve in 0.05 mol/L tris buffer solution, pH 7.0, to make exactly 50 mL. Pipet an appropriate amount of this solution, dilute with 0.05 mol/L tris buffer solution, pH 7.0, to make the solutions containing 10.0 μg (potency) and 5.0 μg (potency) per mL, and use these solutions as the high-concentration test solution and low-concentration test solution, respectively. Separately, weigh accurately about 20 mg (potency) of fosfomycin phenethylammonium RS, dissolve in 0.05 mol/L tris buffer solution, pH 7.0, to make exactly 50 mL, and use this solution as the standard stock solution. Store the standard stock solution at below 5 °C, and use within 7 days. Take exactly an appropriate amount of the standard stock solution, dilute with 0.05 mol/L tris buffer solution, pH 7.0, to make solutions containing 10.0 μg (potency) and 5.0 μg (potency) per mL, and use these solutions as the high-concentration standard solution and the low-concentration standard solution, respectively. Perform the test with these solutions as directed under the Microbial Assays for Antibiotics (A) (8).

Packaging and storage Preserve in tight containers.

Fosfomycin Sodium
포스포마이신나트륨



Fosfomycin Sodium $C_3H_5Na_2O_4P$: 182.02
Sodium [(2*R*,3*S*)-3-methyloxiran-2-yl] phosphonate [*26016-99-9*, anhydrous]

Fosfomycin Sodium is the sodium salt of a compound having antibacterial activity obtained by *Streptomyces fradiae* culture or synthesis.

Fosfomycin Sodium contains NLT 725 μg (potency) and NMT 770 μg (potency) of fosfomycin ($C_3H_7O_4P$: 138.06) per mg, calculated on the anhydrous basis.

Description Fosfomycin Sodium occurs as a white crystalline powder.
It is very freely soluble in water, sparingly soluble in methanol, and practically insoluble in ethanol(99.5).

Identification (1) Determine the infrared spectra of Fosfomycin Sodium and fosfomycin sodium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Determine the ^{1}H spectrum of a solution of Fosfomycin Sodium in deuterium oxide for nuclear magnetic resonance spectroscopy (1 in 300), using sodium 3-trimethylsilyl propane sulfonate for nuclear magnetic resonance spectroscopy as the internal standard, as directed under the Nuclear Magnetic Resonance Spectroscopy; it exhibits a doublet signal at around δ 1.5 ppm, a double doublet signal at around δ 2.8 ppm, a multiplet signals at around δ 3.3 ppm and no signal around δ 1.3 ppm.

(3) An aqueous solution of Fosfomycin Sodium (1 in 500) responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between -3.5° and -5.5° (0.5 g calculated on the anhydrous basis, water, 10 mL, 100 mm).

pH Dissolve 0.70 g of Fosfomycin Sodium in 10 mL of water; the pH of this solution is between 8.5 and 10.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Fosfomycin Sodium in 10 mL of water; the resulting solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Fosfomycin Sodium according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Fosfomycin Sodium according to Method 3 and perform the test (NMT 2 ppm).

Water NMT 3.0% (0.2g, volumetric titration, direct titration).

Sterility It meets the requirements when used in the manufacturing of a sterile preparation. However, it is excluded in cases where there is a final sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins Less than 0.125 EU per mg (potency) of fosfomycin when used in the manufacturing of sterile preparations.

Phosphorus content Weigh accurately about 0.1 g of Fosfomycin Sodium, add exactly 40 mL of sodium periodate solution (107 in 10000) and 2 mL of perchloric acid, and heat on a steam bath for 1 hour. After cooling, add water to make exactly 200 mL. Pipet 10 mL of this solution, and add exactly 1 mL of potassium iodide TS. Add sodium thiosulfate TS until this solution becomes colorless, add water to make exactly 100 mL, and use this solution as the test stock solution. Separately, weigh accurately about 70 mg of potassium dihydrogen phosphate, proceed in the same manner as the test solution, and use this solution as the standard stock solution. Without taking Fosfomycin Sodium, proceed in the same manner as the test stock solution, and use this solution as the blank test stock solution. Pipet 5 mL each of the test stock solution, the standard stock solution, and the blank test stock solution, transfer each into 25 mL volumetric flasks, and add 2.5 mL of ammonium molybdate-sulfuric acid TS and 1 mL of 1-amino-2-naphthol-4-sulfonic acid TS, respectively. Shake to mix, add water to make exactly 25 mL, and use these solutions as the test solution, the standard solution and the blank test solution. Allow to stand these solutions at 20 ± 1 ℃ for 30 minutes, and determine the absorbances, A_T, A_S, and A_B, as directed under the Ultraviolet-visible Spectroscopy at the wavelength of 740 nm using water as a control solution (between 16.2% and 17.9%).

$$\text{= Amount (mg) of phosphorus} = W \times \frac{A_T - A_B}{A_S - A_B} \times 0.22760$$

W: Amount (mg) of potassium dihydrogen phosphate taken

0.22760: Ratio of phosphorus in potassium dihydrogen phosphate

Assay ***Cylinder plate method***—(1) Medium: Agar medium for seed and base layer

Peptone	5.0 g	Yeast extract	2.0 g
Meat extract	3.0 g	Agar	15 g

Weigh the above ingredients, dissolve in purified water to make 1000mL, and make the pH between 6.5 and 6.6 after sterilization.

(2) Test organism: Use *Proteus sp* MB 838 as the test organism.

(3) Test microbial suspension: Inoculate the test organism in a slanted agar medium for transplantation of test organism, culture at 37 ℃ for 40 - 48 hours, and perform subculture at least 3 times. Inoculate this bacteria at the surface of 300 mL of the agar medium for transplantation of the test organism in a culture bottle, culture at 37 ℃ for 40 - 48 hours, and suspend this bacteria solution in about 30 mL of water. Dilute this solution 10-fold with water, and adjust the transmission rate to 17% as directed under the Ultraviolet-visible Spectroscopy at a wavelength of 560 nm. Store the microbial suspension at below 10 °C, and use it within 7 days. Dissolve 1 mL to 2 mL of this microbial suspension, mix with 100 mL of agar medium for see maintained at 48°C, and use this solution as the test microbial suspension.

(4) Weigh accurately an appropriate amount of Fosfomycin Sodium, equivalent to about 20 mg (poten-

cy), and add the 0.05 mol/L tris buffer solution, pH 7.0, to make exactly 50 mL. Pipet an appropriate amount of this solution, dilute with 0.05 mol/L tris buffer solution, pH 7.0, to make the solutions containing 10.0 μg (potency) and 5.0 μg (potency), and use these solutions as the high-concentration test solution and low-concentration test solution, respectively. Separately, weigh accurately about 20 mg (potency) of fosfomycin phenethylammonium RS, dissolve in 0.05 mol/L tris buffer solution, pH 7.0, to make exactly 50 mL, and use this solution as the standard stock solution. Store the standard stock solution at below 5 °C, and use within 7 days. Pipet an appropriate amount of this standard stock solution, dilute with 0.05 mol/L tris buffer solution, pH 7.0, to make the solutions containing each 10.0 μg and 5.0 μg (potency) per mL, and use these solutions as the high-concentration standard solution and the low-concentration standard solution, respectively. Perform the test with these solutions as directed under the Microbial Assays for Antibiotics (A) (8).

Packaging and storage Preserve in hermetic containers.

Fosfomycin Sodium for Injection
주사용 포스포마이신나트륨

Fosfomycin Sodium for Injection is an injection dissolved before use and contains NLT 90.0% and NMT 110.0% of the labeled amount of fosfomycin ($C_3H_7O_4P$: 138.06).

Method of preparation Prepare as directed under Injections, with Fosfomycin Sodium.

Description Fosfomycin Sodium for Injection occurs as a white crystalline powder.

Identification (1) Dissolve about 0.1 g of Fosfomycin Sodium for Injection in 3 mL of perchloric acid solution (1 in 4), add 1 mL of 0.1 mol/L sodium periodate solution, and warm for 30 minutes on a steam bath at 60 °C. After cooling, add 50 mL of water, and neutralize by adding a saturated solution of sodium bicarbonate. To this solution, add 1 mL of potassium iodide TS; the blank test sample exhibits a red color, but the test sample does not exhibit red.

(2) To 2 mL of aqueous solution of Fosfomycin Sodium for Injection (1 in 250), add 1 mL of perchloric acid and 2 mL of 0.1 mol/L sodium periodate solution, and warm for 10 minutes on a steam bath. After cooling, add 1 mL of ammonium molybdate-sulfuric acid TS and 1 mL of 1-amino-2-naphthol-4-5-sulfonic acid TS and allow to stand for 30 minutes; the solution exhibits a blue color.

(3) Dissolve an amount of Fosfomycin Sodium for Injection equivalent to 0.1 g (potency) of fosfomycin sodium according to the labeled amount in 50 mL of water; the resulting solution responds to Chemical identification reaction (1) for sodium salt.

pH Dissolve an amount of Fosfomycin Sodium for Injection, equivalent to 1.0 g (potency) of fosfomycin sodium, in 20 mL of water; the pH of this solution is between 6.5 and 8.5.

Purity ***Clarity and color of solution***—Dissolve an amount of Fosfomycin Sodium for Injection equivalent to 1.0 g (potency) of fosfomycin sodium according to the labeled amount in 10 mL of water; the solution is clear and colorless.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.025 EU per mg (potency) of fosfomycin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

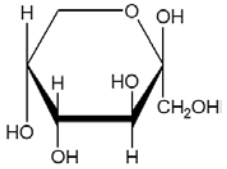
Uniformity of dosage units Meets the requirements.

Water NMT 4.0% (0.1 g, coulometric titration).

Assay Perform the test according to the Assay under Fosfomycin Sodium. Weigh accurately the mass of NLT 10 units of Fosfomycin Sodium for Injection. Weight accurately an amount equivalent to about 20 mg (potency) of fosfomycin sodium according to the labeled amount, and dissolve in 0.05 mol/L tris buffer solution (pH 7.0) to make exactly 50 mL. Pipet an appropriate amount of the resulting solution, add 0.05 mol/L tris buffer solution (pH 7.0), dilute to contain 10 μg (potency) and 5 μg (potency) per mL, and use these solutions as the high-concentration test solution and the low-concentration test solution, respectively.

Packaging and storage Preserve in hermetic containers. Plastic containers for aqueous injections may be used.

Fructose
과당



Fructose $C_6H_{12}O_6$: 180.16
(3*S*,4*R*,5*R*)-1,3,4,5,6-Pentahydroxyhexan-2-one [*57-48-7*]

Fructose, when dried, contains NLT 98.0% and

NMT 101.0% of fructose ($C_6H_{12}O_6$).

Description Fructose occurs as a colorless to white crystals or crystalline powder, is odorless and has a sweet taste.
It is very soluble in water, sparingly soluble in ethanol(95) and practically insoluble in ether.
It is hygroscopic.

Identification (1) Add 2 to 3 drops of an aqueous solution of Fructose (1 in 20) to 5 mL of boiling Fehling's TS; a red precipitate is produced.

(2) Determine the infrared spectra of Fructose and Fructose RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

pH Dissolve 4.0 g of Fructose in 20 mL of water; the pH of the solution is between 4.0 and 6.5.

Purity (1) ***Clarity and color of solution***—Dissolve 25.0 g of Fructose in 50 mL of water; the solution is clear and the color is not more intense than the following control solution.

Control Solution—Add water to a mixture of 3.0 mL of control stock solution of the color of iron(III) chloride hexahydrate, 1.0 mL of control stock solution of the color of cobalt(II) chloride hexahydrate, and 2.0 mL of control stock solution of the color of copper(II) sulfate pentahydrate, make 10.0 mL of solution, take 3.0 mL of the solution, and add water to make 50 mL.

(2) ***Acid***—Dissolve 5.0 g of Fructose in 50 mL of freshly boiled and cooled water, and add 3 drops of phenolphthalein TS and 0.60 mL of 0.01 mol/L sodium hydroxide TS; the color of the solution is red.

(3) ***Sulfite***—Dissolve 0.5 g of Fructose in 5 mL of water and add 0.25 mL of 0.01 mol/L iodine TS; the solution is yellow.

(4) ***Chloride***—Weigh 2.0 g of Fructose and perform the test. Prepare the control solution with 1.0 mL of 0.01 mol/L hydrochloric acid (NMT 0.018%).

(5) ***Sulfate***—Weigh 2.0 g of Fructose and perform the test. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.024%).

(6) ***Heavy metals***—Weigh 5.0 g of Fructose and perform the test according to Method 2. Prepare the control solution with 2.0 mL of lead standard solution (NMT 4 ppm).

(7) ***Calcium***—Dissolve 0.5 g of Fructose in 5 mL of water, add 2 to 3 drops of ammonia TS and 1 mL of ammonium oxalate TS, and allow to stand for 1 minute; the solution is clear.

(8) ***Arsenic***—Dissolve 1.5 g of Fructose in 5 mL of water, add 5 mL of dilute sulfuric acid and 1 mL of bromine TS, heat on a steam bath for 5 minutes, concentrate again to make 5 mL, cool, and perform the test using this solution as the test solution (NMT 1.3 ppm).

(9) ***5-Hydroxymethylfurfural***—Dissolve 5.0 g of Fructose in 100 mL of water. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at a wavelength of 284 nm is NMT 0.32.

Loss on drying NMT 0.5% (1 g, in vacuum, silica gel, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 4 g of Fructose, previously dried, dissolve in 0.2 mL of ammonia TS and 80 mL of water, allow to stand for 30 minutes, and add water to make exactly 100 mL. Measure the optical rotation α_D in 100 mm of layer length at 20 ± 1 ℃ as directed under the Optical Rotation.

Amount (mg) of fructose ($C_6H_{12}O_6$) = $|\alpha_D| \times 1087.0$

Packaging and storage Preserve in tight containers.

Fructose Injection
과당 주사액

Fructose Injection is an aqueous injection and contains NLT 95.0% and NMT 105.0% of the labeled amount of fructose ($C_6H_{12}O_6$: 180.16).

Method of preparation Prepare as directed under Injections, with Fructose.
No preservative is added.

Description Fructose Injection occurs as a clear, colorless liquid with a sweet taste.

Identification (1) Weigh an amount of Fructose Injection, equivalent to 1 g of fructose, according to the labeled amount, add water or concentrate on a steam bath, if necessary, to make 20 mL, and use it as the test solution. Add 2 - 3 drops of the test solution to 5 mL of boiling Fehling's TS; red precipitates are formed.

(2) Take 10 mL of the test solution obtained in (1), add 0.1 g of resorcinol and 1 mL of hydrochloric acid, and heat on a steam bath for 3 minutes; the resulting solution exhibits a red color.

pH Between 3.0 and 6.5. However, if the labeled concentration exceeds 5%, add water to prepare a 5% solution, and perform the test.

Purity (1) ***Heavy metals***—Weigh an amount of Fructose Injection, equivalent to 5.0 g of fructose, according to the labeled amount, and evaporate to dryness on a steam bath. Proceed with the residue according to Method 2 and perform the test. Prepare the control solution with 2.0 mL

of lead standard solution.

(2) ***Arsenic***—Weigh an amount of Fructose Injection, equivalent to 1.5 g of fructose, according to the labeled amount, and add water or concentrate on a steam bath, if necessary, to make 5 mL. Then, add 5 mL of dilute sulfuric acid and 1 mL of bromine TS, and perform the test as directed under the Purity (8) under Fructose.

(3) ***5-Hydroxymethylfurfurals***—Weigh an amount of Fructose Injection, equivalent to 5.0 g, and evaporate or add water to make 100 mL. Determine the absorbance of this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance is NMT 0.32 at a wavelength of 284 nm.

Residue on ignition Take exactly an amount of Fructose Injection, equivalent to 2.0 g of fructose, according to the labeled amount, evaporate to dryness on a steam bath, and perform the test; the residue is NMT 2.0 mg.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.5 EU/mL.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Weigh exactly an amount of Fructose Injection, equivalent to about 4 g of fructose ($C_6H_{12}O_6$), add 0.2 mL of ammonia TS and water to make exactly 100 mL, and shake well to mix, and allow to stand for 30 minutes. Measure the optical rotation α_D at 20 ± 1 °C with a layer length of 100 mm as directed under the Optical Rotation.

Amount (mg) of fructose ($C_6H_{12}O_6$) = $|\ \alpha_D\ | \times 1087.0$

Packaging and storage Preserve in hermetic containers. Plastic containers for aqueous injections may be used.

Fructose and Concentrated Glycerin Injection
과당·농글리세린 주사액

Fructose and Concentrated Glycerin Injection contains NLT 90.0% and NMT 110.0% of fructose (C6H12O6 : 180.16) and concentrated glycerin ($C_6H_{12}O_6$: 180.16).

Method of preparation Prepare as directed under Injections, with Fructose and Concentrated Glycerin

Injection (1) ***Fructose***—Weigh the amount equivalent to 0.5 g of fructose according to the labeled amount of Fructose and Concentrated Glycerin Injection, add 0.1 g of resorcin and 1 mL of hydrochloric acid, and warm it on a steam bath for 3 minutes; the solution exhibits a red color.

(2) ***Concentrated glycerin***—Perform the test with Fructose and Concentrated Glycerin Injection as directed under the assay of concentrated glycerin; the test solution shows the peak at the same retention time as the standard solution.

(3) According to the labeled amount of Fructose and Concentrated Glycerin Injection, pipet an amount equivalent to 0.1 g of concentrated glycerin, add ethanol to make 10 mL, and use it as the test solution. Separately, weigh 50 mg of fructose, dissolve it in 1 mL of water, add 0.1 g of concentrated glycerin and ethanol to make 10 mL, and use it as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of acetone, n-butanol and water (5:4:1) to a distance of about 10 cm, and air-dry the plate. Dissolve 1 g of potassium permanganate in water to make 50 mL and then dissolve 2 g of sodium carbonate in water to make 50 mL. When using, mix the two solutions in equal amounts and spray evenly. The R_f value and color of spots in the standard solution and test solution are the same.

pH Between 3.0 and 5.0.

Purity (1) ***Heavy Metals***—Take 10 mL of Fructose and Concentrated Glycerin Injection and perform the test according to Method 1. Prepare the control solution with 2.5 mL of lead standard solution (NMT 2.5 ppm).

(2) ***Arsenic***—Take 4 mL of Fructose and Concentrated Glycerin Injection and test it according to Method 1 under the Arsenic (NMT 0.5 ppm).

(3) ***5-Hydroxymethylfurfurals***—Determine the absorption spectrum directed under the Ultraviolet-visible Spectroscopy by taking 5 mL of Fructose and Concentrated Glycerin Injection and adding water to make 20 mL; it is NMT 0.8 at a wavelength of 284 nm (NMT 0.0024%).

(4) ***Acrolein***—Use Fructose and Concentrated Glycerin Injection directly as the test solution. Separately, weigh accurately about 0.1 g of acrolein RS and dissolve in water to make 100 mL. Take 5.0 mL of this solution and add water to make 100 mL. Again, take 4.0 mL of this solution, add water to make 100 mL, and use it as the standard solution. Perform the test according to the Gas Chromatography with 5.0 μL each of the test solution and standard solution under the following conditions; the peak height at the acrolein position in the chromatogram obtained from Fructose and Concentrated Glycerin Injection should be smaller than the peak height of acro-

lein obtained from the standard solution (NMT 2 ppm).

Operating conditions

Detector: Flame ionization detector

Column: A glass column, about 3 mm in internal diameter and about 1.5 m in length, is filled with 150 and 180 μm of porous ethylvinylbenzene-divinylbenzene copolymer for gas chromatography (average pore diameter of 0.0075 μm, 500 to 600 m^2/g).

Column temperature: A constant temperature of about 150 °C.

Sample injection port temperature: 180 °C

Carrier gas: Nitrogen

Flow rate: Between 35 and 45 mL/min.

Sterility Meets the requirements.

Bacterial endotoxins Fructose and Concentrated Glycerin Injection is NMT 0.6 EU per mL of fructose and concentrated glycerin.

Particulate contamination: Visible particles in injections and ophthalmic solutions Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay (1) ***Fructose*—**Pipet the amount equivalent to 1 g of fructose ($C_6H_{12}O_6$) according to the labeled amount, add 0.1 mL of ammonia TS and water to make 25 mL, and shake well to mix. Allow to stand for 30 minutes, and measure the optical rotation with a layer length of 100 mm.

$$\text{Amount (mg) of fructose } (C_6H_{12}O_6) = [\alpha]_D^{20} \times 271.74$$

(2) ***Concentrated glycerin*—**Pipet the amount equivalent to 0.2 g of concentrated glycerin ($C_3H_8O_3$) according to the labeled amount of Fructose and Concentrated Glycerin Injection, and add water to make 100 mL. Take 2.0 mL of this solution, add 2.0 mL of the internal standard solution, dry it under reduced pressure in a 35 °C water bath, and dry it again in a desiccator (reduced pressure, silica gel) for 1 hour. Dissolve in 6 drops of anhydrous pyridine, add 5 to 6 drops of 1,1,1,3,3,3-hexamethyldisilaic acid and 3 drops of trimethylchlorosilane, stopper, and warm it in a 60 °C water bath for 30 minutes while shaking occasionally to mix. After cooling it down, put 4.0 mL of hexane, add 1 mL of water, shake well, and allow it to stand. Use the clear solution above as the test solution.

Separately, weigh accurately about 0.2 g of concentrated glycerin RS, dissolve it by adding to make 100.0 mL. Take 2.0 mL of this solution and proceed in the same as the test solution to use it as the standard solution. Take 2 μL each of the test solution and the standard solution and perform the test according to the following conditions as directed under the Gas Chromatography to obtain the peak area ratio Q_T and Q of concentrated glycerin to the internal standard of each solution.

$$\text{Amount (mg) of concentrated glycerin } (C_3H_8O_3) = \text{Amount (mg) of concentrated glycerin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—0.1% mesoerythritol solution

Operating Conditions

Detector: Flame ionization detector

Column: A stainless steel column, about 3 mm in internal diameter and about 2 m in length, is filled with diatomaceous earth for gas chromatography (177 to 250 μm) coated with 3% polydimethylsiloxane.

Column temperature: Raise the temperature from 100 °C by 20 °C every minute.

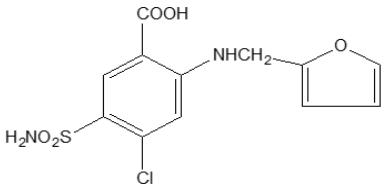
Sample injection port temperature: 220 °C

Carrier gas: Nitrogen

Flow rate: Between 20 to 30 mL/min.

Packaging and storage Preserve in tight containers.

Furosemide
푸로세미드



Furosemide $C_{12}H_{11}ClN_2O_5S$: 330.74

4-Chloro-2-(furan-2-ylmethylamino)-5-sulfamoylbenzoic acid [*54-31-9*]

Furosemide, when dried, contains NLT 98.0% and NMT 101.0% of furosemide ($C_{12}H_{11}ClN_2O_5S$).

Description Furosemide occurs as white crystals or a crystalline powder.

It is freely soluble in *N*,*N*-dimethylformamide, soluble in methanol, sparingly soluble in ethanol(95), slightly soluble in acetonitrile or acetic acid(100) and practically insoluble in water.

It is soluble in dilute sodium hydroxide TS.

It is gradually colored by light.

Melting point—About 205 °C (with decomposition).

Identification (1) Dissolve 25 mg of Furosemide in 10 mL of methanol. To 1 mL of this solution, add 10 mL of 2 mol/L hydrochloric acid TS, heat for 15 minutes on a steam bath with a reflux condenser. After cooling, make the solution weakly acidic with 18 mL of sodium hydrox-

ide TS; it responds to the Qualitative Analysis for primary aromatic amine. However, the solution exhibits a red to purple color.

(2) Determine the absorption spectra of the solutions of Furosemide and furosemide RS in dilute sodium hydroxide TS (1 in 125000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Determine the infrared spectra of Furosemide and furosemide RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Furosemide in 10 mL of sodium hydroxide solution (1 in 50); the solution is colorless and clear.

(2) ***Chloride***—Dissolve 2.6 g of Furosemide in 90 mL of dilute sodium hydroxide TS, add 2 mL of nitric acid, and filter. To 25 mL of the filtrate, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 6 mL of dilute nitric acid and water to 0.40 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.020%).

(3) ***Sulfate***—To 20 mL of the filtrate obtained from (2), add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 1 mL of dilute hydrochloric acid and water to 0.35 mL of 0.005 mol/L sulfuric acid to make 50 mL (NMT 0.030%).

(4) ***Heavy metal***—Proceed with 2.0 of Furosemide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Related substances***—Dissolve 25 mg of Furosemide in 25 mL of the solvent, and use this solution as the test solution. Weigh accurately 1 mL of this solution, add the solvent to make exactly 200 mL, and use this solution as the standard solution. Weigh accurately 20 μL each of the test solution and the standard solution, and perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the peak area of each peak that appears before the peak of furosemide obtained from the test solution is not greater than 2/5 times the peak area of furosemide from the standard solution; the peak area of each peak that appears after the peak of furosemide is not greater than 1/4 the peak area of furosemide from the standard solution. Also, the sum of each peak area is not greater than 2 times the peak area of furosemide from the standard solution.

Solvent—Add a mixture of water and acetonitrile (1:1) to 22 mL of solvent-acetic acid(100) to make 1000 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 272 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of water, tetrahydrofuran and acetic acid(100) (70 : 30 : 1).

Flow rate: Adjust the flow rate so that the retention time of furosemide is about 18 minutes.

System suitability

Test for required detectability: Weigh accurately 2 mL of the standard solution and add the solvent to make exactly 50 mL. Confirm that the peak area of furosemide obtained from 20 μL of this solution is 3.2% to 4.8% of that of furosemide obtained from the standard solution.

System performance: Proceed with 20 μL of the standard solution under the above operating conditions; the number of theoretical plates and symmetry factor of furosemide peak are NLT 7000 plates and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of furosemide is NMT 2.0%.

Time span of measurement: About 2.5 times the retention time of furosemide after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately 0.5 g of Furosemide, previously dried, dissolve in 50 mL of *N*,*N*-dimethylformamide, and titrate the solution with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of bromothymol blue TS). However, the endpoint of titration is when the color of the solution changes from yellow to blue. Separately, perform a blank test in the same manner with a solution prepared by adding 15 mL of water to 50 mL of *N*,*N*-dimethylformamide, and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 33.07 mg of $C_{12}H_{11}ClN_2O_5S$

Packaging and storage Preserve in light-resistant, tight containers.

Furosemide Tablets
푸로세미드 정

Furosemide Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of furosemide ($C_{12}H_{11}ClN_2O_5S$: 330.74).

Method of preparation Prepare as directed under Tablets, with Furosemide.

Identification (1) Weigh an amount of Furosemide Tablets, previously powdered, equivalent to 0.2 g of furosemide according to the labeled amount, add 40 mL of acetone, shake well to mix, and then filter. To 0.5 mL of the filtrate, add 10 mL of 2 mol/L hydrochloric acid TS, and heat on a steam bath for 15 minutes under a reflux condenser. After cooling, add 18 mL of sodium hydroxide TS to make weak acid; the resulting solution responds to the Qualitative Analysis for primary aromatic amine. However, the resulting solution exhibits a red to purple color.

(2) Determine the absorption spectrum of the test solution obtained in the Assay as directed under Ultraviolet-visible Spectrophotometry; it exhibits maxima between 227 nm and 231 nm, between 269 nm and 273 nm, and between 330 nm and 336 nm.

Purity Weigh an amount of Furosemide Tablets, previously powdered, equivalent to about 40 mg of furosemide according to the labeled amount, add 30 mL of acetone, shake well to mix, and then add acetone to make exactly 50 mL. Centrifuge this solution, add 3.0 mL of water to 1.0 mL of the clear supernatant, cool with ice, and then add 3.0 mL of dilute hydrochloric acid and 0.15 mL of sodium nitrite TS. Shake to mix, and allow to stand for 1 minute. To this solution, add 1.0 mL of ammonium amidosulfate TS, shake well to mix, allow to stand for 3 minutes, and then add 1.0 mL of *N*,*N*-diethyl-*N'*-1-naphthylethylenediamine oxalate TS. Allow to stand for 5 minutes. Perform the test with this solution as directed under Ultraviolet-visible Spectrophotometry, using a solution prepared in the same manner with 1.0 mL of acetone as the blank: the absorbance at 530 nm is NMT 0.10.

Dissolution Perform the test with 1 tablet of Definition of Zaltoprofen Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of the solution 2 for the dissolution test as the dissolution medium. Take 20 mL each of the dissolved solution 15 minutes after starting the test for 20 mg of tablet and 30 minutes after starting the test for 40 mg of tablet, and filter through a membrane filter with a pore size of NMT 0.45 μm. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add Solution 2 for dissolution test to make exactly *V'* mL of a solution containing about 10 μg of furosemide ($C_{12}H_{11}ClN_2O_5S$) per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 20 mg of furosemide RS, previously dried at 105 ℃ for 4 hours, dissolve in 5 mL of methanol, and add Solution 2 for dissolution test to make exactly 100 mL. Pipet 5 mL of this solution, add Solution 2 for dissolution test to make exactly 100 mL, and use this solution as the standard solution. With the test solution and the standard solution, perform the test as directed under the Ultraviolet-visible Spectroscopy using the dissolution medium as a control solution, and determine the absorbances, A_T and A_S, at the wavelength of 277 nm. The acceptable dissolution criterion is NLT 80% of Furosemide Tablets dissolved in 60 minutes.

Dissolution rate (%) of the labeled amount of furosemide ($C_{12}H_{11}ClN_2O_5S$)

$$= \text{Amount (mg) of furosemide RS} \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 45$$

C: Labeled amount (mg) of furosemide ($C_{12}H_{11}ClN_2O_5S$) in 1 tablet

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following method.

Take 1 tablet of Furosemide Tablets, add 0.05 mol/L sodium hydroxide TS, disintegrate by shaking well to mix, and add 0.05 mol/L sodium hydroxide TS to make exactly *V* mL of a solution containing about 0.4 mg of furosemide ($C_{12}H_{11}ClN_2O_5S$) per mL. Filter the solution, discard the first 10 mL of the filtrate, pipet the subsequent 2 mL of the filtrate, add 0.05 mol/L sodium hydroxide TS to make exactly 100 mL, and use this solution as the test solution. Perform the test as directed under the Assay.

Amount (mg) of furosemide ($C_{12}H_{11}ClN_2O_5S$)

$$= \text{Amount (mg) of furosemide RS} \times \frac{A_T}{A_S} \times \frac{V}{50}$$

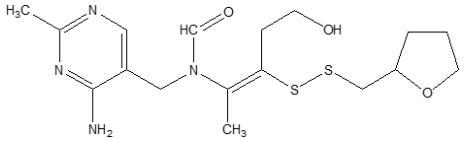
Assay Weigh accurately the mass of NLT 20 tablets of Furosemide Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 40 mg of furoscmide (C12H11ClN2O5S), add about 70 mL of 0.05 mol/L sodium hydroxide TS, shake well, and add 0.05 mol/L sodium hydroxide TS to make exactly 100 mL. Filter, discard the first 10 mL of the filtrate, pipet 2 mL of the subsequent filtrate, add 0.05 mol/L sodium hydroxide TS to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of furosemide RS, previously dried at 105 ℃ for 4 hours, and dissolve in 0.05 mol/L sodium hydroxide TS to make exactly 50 mL. Pipet 2 mL of this solution, add 0.05 mol/L sodium hydroxide TS to make exactly 100 mL, and use it as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 271 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of furosemide ($C_{12}H_{11}ClN_2O_5S$)

$$= \text{Amount (mg) of furosemide RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in light-resistant, well-closed containers.

Fursultiamine
푸르설티아민



Fursultiamine $C_{17}H_{26}N_4O_3S_2$: 398.54
N-[(4-Amino-2-methyl-5-pyrimi dinyl)methyl]-*N*-[4-hydroxy-1-methyl-2-[[(tetrahydro-2-furanyl)methyl]dithio]-1-butenyl]formamide, [*804-30-8*]

Fursultiamine, when dried, contains NLT 98.0% and NMT 102.0% of fursultiamine ($C_{17}H_{26}N_4O_3S_2$).

Description Fursultiamine occurs as white to yellowish white crystals or a crystalline powder, which is odorless or has a slight characteristic odor.
It is freely soluble in methanol, ethanol or chloroform, and sparingly soluble in water and soluble in dilute hydrochloric acid.

Melting point—About 130 °C (with decomposition).

Identification (1) Dissolve 5 mg of Fursultiamine in 6 mL of 0.1 mol/L hydrochloric acid, and add 0.1 g of zinc powder and allow to stand; it has a slight characteristic odor.

(2) To 3 mL of the solution obtained from (1), add 3 mL of sodium hydroxide TS and 0.5 mL of potassium ferricyanide TS, and shake vigorously to mix. Then, add 5 mL of isobutanol, shake vigorously to mix for 2 minutes, and examine the solution under ultraviolet light (main wavelength: 365 nm); the isobutanol layer exhibits a bluish violet fluorescence. This fluorescence disappears when the solution is acidified and reappears when it is alkalized.

Purity (1) ***Clarity and color of solution***—Dissolve 20 mL of 0.5 mol/L hydrochloric acid in 1.0 g of Fursultiamine; the resulting solution is clear and its color should not be more intense than that of the control solution.

Control solution—Take 1.5 mL of 1/60 mol/L potassium dichromate VS, and add water to make 1.0 L.

(2) ***Sulfate***—Dissolve 1.5 g of Fursultiamine with 3 mL of dilute hydrochloric acid, dissolve to 50 mL with water, and test according to the Sulfate. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid and 3 mL of dilute hydrochloric acid, and add water to make 50 mL (NMT 0.011%).

(3) ***Heavy metals***—Proceed with 1.0 g of Fursultiamine according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Related substances***—(i) Thiamine: Weigh accurately about 0.1 g of Fursultiamine, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of thiamine hydrochloride RS, dissolve in 0.1 mol/L hydrochloric acid TS, and make exactly 100 mL with 0.1 mol/L hydrochloric acid TS. Pipet 1 mL of this solution and add 0.1 mol/L hydrochloric acid TS to make exactly 50 mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of thiamine hydrochloride, A_T and A_S, in each solution. The amount of thiamine hydrochloride in the test solution is NMT 0.2%.

Operating conditions

For the detector, column, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; the number of theoretical plates for thiamine hydrochloride peak is NLT 2,000 and the symmetry factor is NMT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of thiamine hydrochloride is NMT 2.0%.

(ii) Total related substances: Weigh accurately about 0.1 g of Fursultiamine, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Pipet 1 mL of the test solution and add the mobile phase to make exactly 100 mL. Use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the total peak area other than the major peak of the test solution is smaller than the peak area of the standard solution.

Operating conditions

For the detector, column, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; the number of theoretical plates for fursultiamine peak is NLT 2,000 and the symmetry factor is NMT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of fursultiamine is NMT 2.0%.

Time span of measurement: A range of about 3 times the retention time of fursultiamine after the solvent peak

Loss on drying NMT 1.0% (1 g, in vacuum, phosphorus pentoxide, 5 hours).

Residue on ignition NMT 0.20% (1 g)

Assay Weigh accurately about 60 mg of Fursultiamine, previously dried, put it in a flask with a volume of 100 mL, and add the mobile phase to make exactly 100 mL. Pipet 10 mL of this solution, put it in a 100-mL volumetric flask, and add the mobile phase to make exactly 100 mL. Use this solution as the test solution. Separately, weigh accurately about 60 mg fursultiamine RS, proceed in the same manner as the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of fursultiamine in each solution.

Amount (mg) of fursultiamine ($C_{17}H_{26}N_4O_3S_2$)
= Amount (mg) of fursultiamine RS × (A_T / A_S)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 50 ℃.

Mobile phase: Dissolve 1.01 g of sodium 1-heptanesulfonate in 1000 mL of dilute acetic acid(100) (1 in 100). To 675 mL of this solution, add 325 ml of a mixture of methanol and acetonitrile (3 : 2).

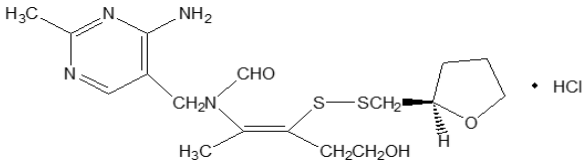
Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of fursultiamine is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Fursultiamine Hydrochloride
푸르설티아민염산염



and enantiomer

$C_{17}H_{26}N_4O_3S_2$·HCl: 435.00

N-[(4-Amino-2-methylpyrimidin-5-yl)methyl]-*N*-{(1*E*)-4-hydroxy-1-methyl-2-[((2*R*)-tetrahydrofuran-2-ylmethyl)disulfanyl]but-1-en-1-yl}formamide hydrochloride [*2105-43-3*]

Fursultiamine Hydrochloride contains NLT 98.5% and NMT 101.0% of fursultiamine hydrochloride ($C_{17}H_{26}N_4O_3S_2$·HCl), calculated on the anhydrous basis.

Description Fursultiamine Hydrochloride occurs as white crystals or a crystalline powder. It is odorless or has a slight characteristic odor and a bitter taste.
It is freely soluble in water, methanol or ethanol(95) and practically insoluble in ether.

Identification (1) Dissolve about 5 mg of Fursultiamine Hydrochloride in 6 mL of 0.1 mol/L hydrochloric acid TS, add 0.1 g of zinc powder, allow to stand for several minutes, and then filter. To 3 mL of the filtrate, add 3 mL of sodium hydroxide TS and 0.5 mL of potassium hexacyanoferrate(III) TS. Then, add 5 mL of 2-methyl-1-propanol, shake vigorously for 2 minutes to mix, allow to stand, and examine the solution under ultraviolet light (main wavelength: 365 nm); the 2-methyl-1-propanol layer exhibits a bluish violet fluorescence. This fluorescence disappears when it is acidified and reappears when alkalized.

(2) Determine the infrared spectra of Fursultiamine Hydrochloride and fursultiamine hydrochloride RS, previously dried in a desiccator (in vacuum, phosphorus pentoxide) for 24 hours, as directed the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibits similar intensities of absorption at the same wavenumbers. If there is a difference between the two spectra, dissolve Fursultiamine Hydrochloride in water, evaporate the water, and dry the residue in a desiccator (in vacuum, phosphorus pentoxide) for 24 hours, and perform the test with the residue in the same manner.

(3) Perform the test with an aqueous solution (1 in 50) of Fursultiamine Hydrochloride according to the Qualitative Analysis (2) for chloride.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Fursultiamine Hydrochloride in 20 mL of water; the solution is colorless and clear.

(2) ***Sulfate***—Perform the test with 1.5 g of Fursultiamine Hydrochloride. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid (NMT 0.011%).

(3) ***Heavy metal***—Weigh 1.0 g of Fursultiamine Hydrochloride according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Related substances***—Dissolve 0.10 g of Fursultiamine Hydrochloride in the mobile phase to make 100 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to it make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of each solution by the automatic integration method; the total area of peaks other than fursultiamine from the test solution is smaller than the peak area of fursultiamine from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase, flow rate and system suitability, proceed as directed in the operating conditions under the Assay.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of fursultiamine obtained from 10 μL of the standard solution is 20 mm to 30 mm.

Time span of measurement: A range of about 3 times the retention time of fursultiamine.

Water NMT 5.0% (0.3 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 55 mg each of Fursultiamine Hydrochloride and fursultiamine hydrochloride RS (Separately, determine the water before use, in the same manner as for Fursultiamine Hydrochloride), dissolve each in 50 mL of water, add exactly 10 mL each of internal standard solution, and add water to make exactly 100 mL. Pipet 8 mL each of this solution, add water to make exactly 50 mL, and use these solutions as the test solutions and the standard solutions, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of the peak area of fursultiamine to that of internal standard substance of each solution, respectively.

Amount (mg) of fursultiamine hydrochloride ($C_{17}H_{26}N_4O_3S_2$.HCl)
= Amount (mg) of fursultiamine hydrochloride RS, calculated on the anhydrous basis × (Q_T / Q_S)

Internal standard solution—4 A solution of isopropyl 4-aminobenzoate in ethanol(95) (3 in 400).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 50 °C.

Mobile phase: Dissolve 1.01 g of sodium 1-heptanesulfonate in 1000 mL of diluted acetic acid(100) (1 in 100). To 675 mL of this solution, add 325 ml of a mixture of methanol and acetonitrile (3 : 2).

Flow rate: Adjust the flow rate so that the retention time of fursultiamine is about 9 minutes.

System suitability

Selection of column: Proceed with 10 μL of the standard solution under the above conditions; fursultiamine and the internal standard substance are eluted in this order with the resolution being NLT 10.

Packaging and storage Preserve in tight containers.

Fursultiamin Hydrochloride Injection
푸르설티아민염산염 주사액

Fursultiamin Hydrochloride Injection contains NLT 90.0% and NMT 130.0% of the labeled amount of fursultiamine hydrochloride ($C_{17}H_{26}N_4O_3S_2$·HCl : 435.00).

Method of preparation Prepare as directed under Injections, with Fursultiamine Hydrochloride.

Identification Perform the test with Fursultiamin Hydrochloride Injection as directed under the Analysis for Vitamins.

pH Between 2.8 and 4.0.

Bacterial endotoxins Less than 3 EU per mg of fursultiamine.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

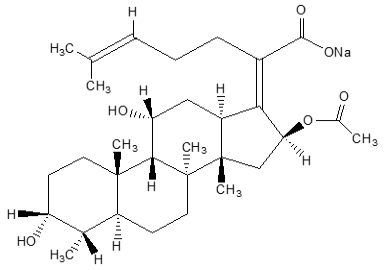
Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Perform the test with Fursultiamin Hydrochloride Injection as directed under the Analysis for Vitamins.

Packaging and storage Preserve in hermetic containers.

Fusidate Sodium
퓨시드산나트륨



Fusidate Sodium $C_{31}H_{47}NaO_6$: 538.69
Sodium(2*Z*)-2-[(3*R*,4*S*,5*S*,8*S*,9*S*,10*S*,11*R*,13*R*,14*S*,16*S*)-16-acetyloxy-3,11-dihydroxy-4,8,10,14-tetra-methyl-2,3,4,5,6,7,9,11,12,13,15,16-dodecahydro-1*H*-cyclopenta[a]phenanthren-17-ylidene]-6-methylhept-5-enoate [*751-94-0*]

Fusidate Sodium is a sodium salt compound having antibacterial activity produced by the growth of *Fusidium coccineum*.
Fusidate Sodium contains NLT 935 μg and NMT 969 μg (potency) of fusidic acid ($C_{31}H_{48}NO_6$: 516.71) per mg, calculated on the anhydrous basis.

Description Fusidate Sodium occurs as white crystals or a crystalline powder.
It is freely soluble in water, methanol or ethanol(99.5).

Identification (1) Weigh accurately about 0.10 g of Fusidate Sodium, dissolve in methanol to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately 0.25 g each of diethanolamine fusidate RS, dissolve in methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Thin Layer Chromatography. Take appropriate amounts of the test solution and the standard solution, and drop each solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Then, develop the plate with a mixture of chloroform, cyclohexane, acetic acid(100), and methanol (80 : 10 : 10 : 2.5) as a developing solvent. After air-drying the plate, spray saturated antimony(III) chloride TS, dry at 105 ℃ for 20 minutes, cool to room temperature, and examine the plate under ultraviolet light. The R_f values of the spots obtained from the test and standard solutions are the same.

(2) Perform the test as directed under the Assay; the retention time of the major peak in the chromatogram of the test solution corresponds to that in the chromatogram of the standard solution.

(3) Fusidate Sodium responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[a]_D^{20}$: Between -5° and +8° (3% aqueous solution with a few drops of ammonia TS, 100 mm).

pH Dissolve 125 mg (potency) of Fusidate Sodium in 10 mL of water; the pH of this solution is between 7.5 and 9.0.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Fusidate Sodium according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Perform the test as directed under the Purity of Fusidic Acid Hydrate (total related substances: NMT 2.0%).

Water NMT 2.0% (1 g, volumetric titration, direct titration).

Assay Perform the test as directed under the Assay of Fusidic Acid Hydrate.

Packaging and storage Preserve in light-resistant, tight containers (at 2 to 8 ℃).

Fusidate Sodium Ointment
퓨시드산나트륨 연고

Fusidate Sodium Ointment contains NLT 90.0% and NMT 120.0% of the labeled amount of fusidic acid ($C_{31}H_{48}O_6$: 516.71).

Method of preparation Prepare as directed under Ointments, with Fusidate Sodium.

Identification (1) Perform the test as directed under the Identification (1) under Fusidate Sodium. Take about 2 g of Fusidate Sodium Ointment, place it in a separatory funnel, add 25 mL of petroleum ether, and shake to mix. Add 5 mL of 70% ethanol solution, shake vigorously to extract, and take the ethanol layer. Use the ethanol layer as the test solution.

(2) The retention times of the major peaks obtained from the test solution and the standard solution in the Assay are the same.

Purity ***Related substances***—Perform the test as directed in Purity under Fusidic Acid Hydrate (total related substances NMT 4.0%). Weigh accurately about 50 mg (potency) of Fusidate Sodium Ointment according to the labeled potency, add 25 mL of *n*-heptane and 10 mL of the mobile phase, place in a separatory funnel, and mix until it is equalized. Take the lower layer, filter, and use this solution as the test solution. Exclude the areas of peaks identified to be derived from a diluent.

Assay Perform the test as directed in the Assay under Fusidic Acid Hydrate. Weigh accurately about 30 mg (potency) of Fusidate Sodium Ointment according to the labeled potency, place in a separatory funnel, add 10 mL

of *n*-heptane, and shake to mix until it is equalized. Extract with 25 mL of the mobile phase, add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 30 mg (potency) of diethanolamine fusidate RS and dissolve in the mobile phase to make exactly 50 mL. Use this solution as the standard solution.

Packaging and storage Preserve in tight containers.

Fusidate Sodium Tablets
퓨시드산나트륨 정

Fusidate Sodium Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of fusidic acid ($C_{31}H_{48}O_6$: 516.71).

Method of preparation Prepare as directed under Tablets, with Fusidate Sodium.

Identification Weigh an amount of Fusidate Sodium Tablets, equivalent to about 0.1 g (potency), if necessary, and previously remove the sugar coating of Fusidate Sodium Tablets, and powder. Add 10 mL of methanol, shake well to dissolve, filter, and use the filtrate as the test solution. Separately, prepare a solution of fusidic acid RS in 2.5% methanol as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot an appropriate amount each of the test solution and the standard solution on a thin-layer chromatographic plate made using silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform, cyclohexane, acetic acid(100) and methanol (80 : 10 : 10 : 2.5) as the developing solvent, and air-dry the plate. Spray a saturated chloroform solution of antimony(V) chloride on the plate, dry at 105 ℃ for 20 minutes, cool to room temperature, and examine the plate under the ultraviolet light; the Rf values obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the contents of NLT 20 tablets of Fusidate Sodium Tablets. If necessary, and previously remove the sugar coating of Fusidate Sodium Tablets, and powder. Weigh accurately an amount, equivalent to about 250 mg (potency) according to the labeled potency, dissolve in the mobile phase to make exactly 250 mL. Take 4 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg (potency) of fusidic acid RS, and add the mobile phase to make exactly 50 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of fusidic acid in each solution.

$$\text{Potency (μg) of fusidic acid } (C_{31}H_{48}O_6) = \text{Potency (μg) of fusidic acid RS} \times \frac{A_T}{A_S} \times 12.5$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 235 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile, 0.05 mol/L phosphoric acid solution and methanol (5 : 4 : 1).

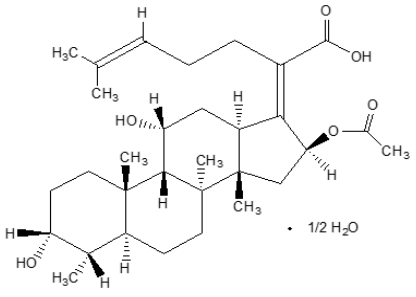
Flow rate: 1.2 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of fusidic acid is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Fusidic Acid Hydrate
퓨시드산수화물



$C_{31}H_{48}O_6 \cdot 1/2H_2O$: 525.72

(2*Z*)-2-[(3*R*,4*S*,5*S*,8*S*,9*S*,10*S*,11*R*,13*R*,14*S*,16*S*)-16-Acetyloxy-3,11-dihydroxy-4,8,10,14-tetramethyl-2,3,4,5,6,7,9,11,12,13,15,16-dodeca-hydro-1*H*-cyclopenta[a]phenanthren-17-ylidene]-6-methylhept-5-enoic acid [*6990-06-3*]

Fusidic Acid Hydrate contains NLT 975 μg (potency) as fusidic acid ($C_{31}H_{48}O_6$: 516.71) per mg, calculated on the anhydrous basis.

Description Fusidic Acid Hydrate occurs as a white crystalline powder.
It is freely soluble in ethanol(95) or chloroform, sparingly soluble in ether and practically insoluble in water.

Identification (1) Weigh 50 mg (potency) of Fusidic

Acid Hydrate and fusidic acid hydrate RS, and dissolve in 1 mL of chloroform, respectively. Determine the infrared spectra of these solutions as directed under the liquid film method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve 20 mg (potency) of Fusidic Acid Hydrate in 10 mL of ethanol(99.5), and use this solution as the test solution. Separately, dissolve 20 mg (potency) of diethanolamine fusidate RS in 10 mL of ethanol(99.5) and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot an appropriate amount each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Develop the plate with a mixture of chloroform, cyclohexane, acetic acid(100) and methanol (80 : 10 : 10 : 2.5) as the developing solvent, and air-dry the plate. Spray 10% sulfuric acid-ethanol solution on the plate, and dry at 110 ℃ for 10 minutes. Examine under ultraviolet light (main wavelength: 366 nm); the R_f values of the spots obtained from the test solution and the standard solution are the same.

(3) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Purity ***Related substances*—**Perform the test as directed as directed under the Assay, determine the area of each peak from the test solution according to the automatic integration method and calculate the content (%) of related substances; the total amount of the related substances is NMT 2.0%. However, weigh accurately about 50 mg (potency) of Fusidic Acid Hydrate, dissolve in the mobile phase to make 10 mL, and use this solution as the test solution.

$$\text{Content (\%) of each related substance} = 100 \times \frac{A_i}{A_S}$$

A_i: Peak area of each related substance with relative retention time between 0.3 and 3.5, other than the major peak

A_S: Total area of all peaks

Exclude peak areas NMT 0.01% of the fusidic acid peak area.

Detection sensitivity: Pipet 1 mL of the standard solution as directed under the Assay and add the mobile phase to make 100 mL. Proceed with 10 μL of this solution according to the above conditions; adjust the detection sensitivity so that the peak height of fusidic acid is about 5 mm.

Water Between 1.4% and 2.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.2% (1.0 g).

Assay Weigh accurately about 50 mg (potency) each of Fusidic Acid Hydrate and diethanolamine fusidate RS, dissolve in the mobile phase to make exactly 50 mL, respectively, and use these solutions as the test solution and the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of fusidic acid of each solution.

$$\text{Potency (μg) of fusidic acid } (C_{31}H_{43}O_6) = \text{Potency (μg) of fusidic acid RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 235 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 125 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile, 0.05 mol/L phosphoric acid solution and methanol (5 : 4 : 1).

Flow rate: 1.2 mL/min

Packaging and storage Preserve in light-resistant, tight containers (2 to 8 ℃).

Fusidic Acid Cream
퓨시드산 크림

Fusidic Acid Cream contains NLT 90.0% and NMT 120.0% of the labeled amount of fusidic acid ($C_{31}H_{48}O_6$: 516.71).

Method of preparation Prepare as directed under Creams, with Fusidic Acid Hydrate.

Identification (1) Perform the test according to Identification (2) under Fusidic acid hydrate. Weigh 10 mg (potency) each of Fusidic Acid Cream and fusidic acid diethanolamine RS, dissolve in 10 mL of water, and use these solutions as the test solution and the standard solution, respectively.

(2) The retention times of the major peaks obtained from the test solution and the standard solution in the Assay are the same.

pH Dissolve an amount of Fusidic Acid Cream, equivalent to 1.0 g (potency) of fusidic acid, in 10 mL of water; the pH of this solution is 4.5 to 6.0.

Purity ***Related substances***—Perform the test as directed under the Purity under Fusidic acid hydrate (total related

substances are NMT 5.0%). Weigh accurately an amount, equivalent to about 15 mg (potency) of Fusidic Acid Cream, add 25 mL of the mobile phase, warm on a steam bath until the cream dissolves, and shake vigorously for 15 minutes. Cool to below 10 ℃, filter, discard the first 4 to 5 mL of filtrate, bring the subsequent filtrate to room temperature, and use this solution as the test solution.

Assay Proceed as directed under the Assay under Fusidic acid hydrate. Weigh an amount, equivalent to about 15 mg (potency) of the labeled potency of Fusidic Acid Cream, add 50 mL of the mobile phase, warm on a steam bath until the cream dissolves, and shake vigorously. Cool to below 10 ℃, filter, discard the first 4 to 5 mL of filtrate, bring the subsequent filtrate to room temperature, and use this solution as the test solution. Separately, weigh accurately about 15 mg (potency) of fusidic acid diethanolamine RS, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the standard solution.

Packaging and storage Preserve in tight containers.

Fusidic Acid Gel
퓨시드산 겔

Fusidic Acid Gel contains NLT 90.0% and NMT 120.0% of the labeled amount of fusidic acid ($C_{31}H_{48}O_6$: 516.71).

Method of preparation Prepare as directed under Gels, with Fusidic Acid.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

pH Between 4.5 and 6.0.

Purity ***Related substances***—Perform the test according to the Assay, and determine each peak area to calculate the amount of related substances; the sum of the related substances is NMT 2.0%. However, weigh accurately about 30 mg (potency) according to the labeled potency of Fusidic Acid Gel, add 20 mL of the mobile phase, and shake vigorously for 5 minutes. Then add 0.5 g of potassium nitrate, and shake vigorously again for 1 minute. Use a syringe to pass this solution through a solid-phase extraction cartridge, followed by eluting it with 15 mL of diluent. Discard 10 mL of the first filtrate, use the subsequent 10 mL of the filtrate. Add 1% acetic acid(100) to 8.0 mL of the above filtrate to make 10 mL, and use this solution as the test solution.

$$\text{Content (\%) of related substances} = \frac{A_i}{A_S} \times 100$$

A_i: The sum of peak areas with 0.3 to 3.5 of the relative retention time for fusidic acid other than the major peak

A_S: The sum of peak areas

However, exclude peak areas NMT 0.01% of the fusidic acid area.

Detection sensitivity Weigh accurately about 50 mg (potency) of fusidic acid RS, dissolve in the mobile phase to make 50 mL, take 1 mL of this solution, and add the mobile phase to make 100 mL. Perform the test with 10 μL of this solution according to the operating conditions under the Assay; adjust so that the peak height of fusidic acid is about 5 mm.

Assay Weigh accurately an amount of Fusidic Acid Gel, equivalent to about 20 mg (potency), according to the labeled potency, and add 50 mL of the mobile phase. Warm on a steam bath until the gel dissolves, and shake vigorously. Cool to below 10 °C, and filter. Discard 4 to 5 mL of the first filtrate, bring the next filtrate to room temperature, and use this solution as the test solution. Separately, weigh accurately about 20 mg (potency) of fusidic acid RS, add the mobile phase make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of fusidic acid, A_T and A_S, in each solution.

$$\text{Potency (μg) of fusidic acid } (C_{31}H_{48}O_6) = \text{Potency (μg) of fusidic acid RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 235 nm).

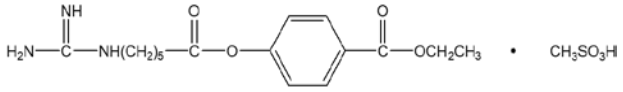
Column: A stainless steel column about 4 mm in internal diameter and 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile, 0.05 mol/L phosphoric acid solution and methanol (50 : 50 : 40).

Flow rate: 1.2 mL/min

Packaging and storage Preserve in tight containers.

Gabexate Mesilate
가벡세이트메실산염



$C_{16}H_{23}N_3O_4 \cdot CH_4O_3S$: 417.48

Ethyl 4-[6-(diaminomethylideneamino)hexanoyloxy] benzoate;methanesulfonic acid [*56974-61-9*]

Gabexate Mesilate, when dried, contains NLT 98.5% and NMT 101.0% of gabexate mesilate ($C_{16}H_{23}N_3O_4 \cdot CH_4O_3S$).

Method of preparation If there is any possibility of alkyl methanesulfonate esters (methyl, ethyl, isopropyl, etc.) to be contained as the potential impurities by the manufacturing process of Gabexate Mesilate, take caution with starting material, manufacturing process, and intermediate material control to minimize the residue of impurities in consideration of risk assessment results. If needed, the manufacturing process can be justified by the test data proving that there is no quality risk in final drug substances.

Description Gabexate Mesilate occurs as white crystals or a crystalline powder. It is very soluble in water, freely soluble in ethanol(95) and practically insoluble in ether.

Identification (1) Take 4 mL of a solution of Gabexate Mesilate (1 in 2000), add 2 mL of 1-naphthol TS and 1 mL of diacetyl TS, and allow to stand for 10 minutes; the resulting solution exhibits a red color.

(2) Dissolve 1 g of Gabexate Mesilate in 5 mL of water, add 2 mL of sodium hydroxide TS, and heat in the water bath for 5 minutes. After cooling, add 2 mL of dilute nitric acid and 5 mL of ethanol(95), shake, put 5 drops of iron(III) chloride TS, and shake to mix; the resulting solution exhibits a violet color.

(3) Determine the absorption spectra of solutions of Gabexate Mesilate and gabexate mesilate RS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Gabexate Mesilate responds to the Qualitative Analysis for mesylate.

Melting point Between 90 and 93 °C.

pH Dissolve 1.0 g of Gabexate Mesilate in 10 mL of water; the pH of this solution is between 4.5 and 5.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Gabexate Mesilate in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 2.0 g of Gabexate Mesilate as directed under the Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Weigh 2.0 g of Gabexate Mesilate, dissolve in 20 mL of 1 mol/L hydrochloric acid TS by heating in the water bath, and continue to heat for 20 minutes. After cooling it down, centrifuge and take 10 mL of the clear supernatant. Use this solution as the test solution and perform the test (NMT 2 ppm).

(4) ***Ethyl p-hydroxybenzoate***—Weigh 50 mg of Gabexate Mesilate, previously dried, and dissolve in dilute ethanol to make exactly 100 mL. Pipet 5.0 mL of this solution, add exactly 5 mL of the internal standard solution, and use this solution as the test solution. Separately, weigh 5.0 mg of ethyl p-hydroxybenzoate and dilute in dilute ethanol to make exactly 100 mL. Pipet 1.0 mL of this solution and add dilute ethanol to make exactly 20 mL. Pipet 5 mL of this solution, add exactly 5 mL of the internal standard solution, and use this solution as the standard solution. Perform the test with 3 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the operating conditions in the Assay and calculate the peak area ratios, Q_T and Q_S, of ethyl p-hydroxybenzoate to internal standard, respectively; Q_T is not larger than Q_S.

Internal standard solution—A solution of butyl parahydroxybenzoate in diluted ethanol (1 in 5000).

(5) ***Related substances***—Dissolve 0.20 g of Gabexate Mesilate in 5 mL of ethanol(95) and use this solution as the test solution. Pipet 1 mL of the test solution, add ethanol(95) to make exactly 100 mL, and use this solution as the standard solution. With the solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, water and acetic acid(100) (3 : 1 : 1) to a distance of about 10 cm and air-dry the plate until it has no acetic odor. Spray evenly a solution of 8-quinolinol in acetone (1 in 1000) on the plate and after air-drying, spray evenly bromine-sodium hydroxide TS; the spots other than the principal spot from the test solution are not darker than the spots from the standard solution.

Loss on drying NMT 0.3% (1 g, in vacuum, silica gel, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg of Gabexate Mesilate and gabexate mesilate RS, previously dried, and dissolve each in dilute ethanol to make exactly 100 mL. Pipet 5.0 mL each of these solutions, add exactly 5 mL each of the internal standard solution and use these solutions as the test solution and the standard solution, respectively. Perform the test with 3 μL each of these solutions as directed under Liquid Chromatography according to the following conditions and calculate the peak area

ratios, Q_T and Q_S, of gabexate to internal standard, respectively.

$$\text{Amount of Gabexate Mesilate } (C_{16}H_{23}N_3O_4\cdot CH_4O_3S)\text{ (mg)} = \text{Amount of gabexate mesilate RS} \times \frac{Q_T}{Q_S}\text{ (mg)}$$

Internal standard solution—A solution of butyl parahydroxybenzoate in diluted ethanol (1 in 5000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 245 nm).

Column: A stainless steel column about 5 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of methanol, sodium lauryl sulfate (1 in 1000), sodium 1-heptanesulfonate (1 in 200) and acetic acid(100) (540 : 200 : 20 : 1).

Flow rate: Adjust the flow rate so that the retention time of gabexate is about 13 minutes.

System suitability

System performance: Proceed with 3 μL of the standard solution according to the above conditions; the internal standard and gabexate are eluted in this order with the resolution being NLT 5.

System repeatability: Repeat the test 6 times with 3 μL each of the standard solution according to the above conditions; the relative standard deviation of the ratios of the peak area of gabexate to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Gabexate Mesilate for Injection
주사용 가벡세이트메실산염

Gabexate Mesilate for Injection is a preparation for injection which is dissolved before use, and contains NLT 95.0% and NMT 105.0% of labeled amount of gabexate mesilate ($C_{16}H_{23}N_3O_4\cdot CH_3SO_3H$: 417.48).

Method of preparation Prepare as directed under Injections, with Gabexate Mesilate.

Description Gabexate Mesilate for Injection occurs as a white mass or a powder.

Identification (1) Weigh about 1 g of Gabexate Mesilate for Injection, add 20 mL of acetone, dissolve, and filter. Evaporate the filtrate in the water bath, pipet about 10 mg of the residue, and dissolve in 10 mL of water. Add 1 mL of 1 mol/L Sodium hydroxide TS, heat for 5 minutes in the water bath, cool it down, and add 1 mL of dilute nitric acid. Put 5 drops of Iron(III) chloride TS in it, and heat for 2 minutes in the water bath; the resulting solution exhibits a violet color.

(2) Dissolve 0.1 g of the residue from (1) to make 20 mL, put 2 mL of 1-naphthol TS, 1 mL of diacetyl TS and 15 mL of water in 4 mL of the solution, and allow to stand for 30 minutes; the resulting solution exhibits a red color.

(3) Add 0.2 g of powdered sodium hydroxide to 0.1 g of the residue from (1), shake, melt by heating, and continue to heat for 20 to 30 seconds. After adding 0.5 mL of water, put a slight excessive amount of dilute hydrochloric acid and heat; the resulting gas changes the color of potassium Iodide starch paper to blue.

(4) Gabexate Mesilate for Injection responds to the Qualitative Analysis for mesylate.

pH Between 4.0 and 5.0 (10% solution).

Sterility Meets the requirements.

Bacterial endotoxins Less than 1 EU/mg of gabexate mesilate. Weigh accurately 10 mg of Gabexate Mesilate for Injection, dissolve in water for endotoxin assay, add 5 mL of 0.1 mol/L sodium hydroxide TS for endotoxin assay, and add water for endotoxin assay again to make exactly 50 mL of solution. Pipet a certain amount of this solution, add water for endotoxin assay to reach an appropriate concentration, and use it as the test solution.

Particulate contamination: Visible particles in injections and ophthalmic solutions Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Purity (1) ***Guanidino chromic acid***—Weigh a volume of Gabexate Mesilate for Injection, equivalent to 40 mg of gabexate mesilate according to the labeled amount, add 10 mL of ethanol, and dissolve by shaking for 10 minutes Transfer to a centrifuge tube, centrifuge, and use the supernatant as the test solution. Spot 5 μL of the test solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, water and acetic acid(100) (3 : 1 : 1) to a distance of about 10 cm, and air-dry the plate. Spray evenly a solution of 8-quinolinol in acetone (1 in 1000) on the plate, and spray sodium hypobromate TS; a single spot appears at an Rf value of 0.7.

(2) ***Ethyl p-hydroxybenzoate***—Weigh a volume of Gabexate Mesilate for Injection, equivalent to 0.2 g of gabexate mesilate according to the labeled amount, add 30 mL of water, dissolve, and extract 3 times by 50 mL of ether. Combine the ether extracts, wash twice with 30 mL of water, filter through the absorbent cotton, and

wash the absorbent cotton with a small amount of ether. Collect the ether layers, and evaporate ether in the water bath. Add ethanol to the residue to make 250 mL, and use this solution as the test solution. Separately, weigh 10 mg of ethyl p-hydroxybenzoate RS, and add ethanol to make 250 mL. Pipet 10 mL of the resulting solution, add ethanol to make 100 mL, and use this solution as the standard solution. With the test and standard solutions, and ethanol as the control solution, determine the absorbances A_T and A_S at 258 mm of wavelength as directed under the Ultraviolet-visible Spectroscopy; A_T is not greater than A_S.

Loss on drying NMT 0.3% (1 g, in vacuum, silica gel, 4 hours).

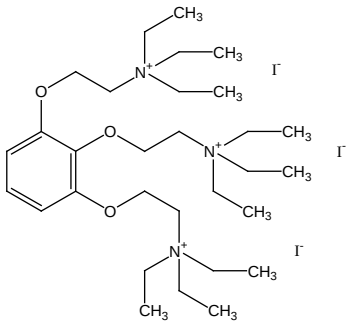
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately the mass of NLT 20 samples of Gabexate Mesilate for Injection. Weigh accurately about 0.1 g of gabexate mesilate ($C_{16}H_{23}N_3O_4 \cdot CH_3SO_3H$), and add water to make 100 mL. Pipet 2.0 mL of the resulting solution, add water to make 200 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of gabexate mesilate RS, proceed the same manner used in the test solution with Phytonadione RS, and use this solution as the standard solution. With the test solution and standard solutions, determine the absorbances AT and AS at 236 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of Gabexate Mesilate } (C_{16}H_{23}N_3O_4 \cdot CH_3SO_3H) = \text{Amount (mg) of gabexate mesilate RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserved in hermetic containers.

Gallamine Triethiodide
갈라민트리에티오디드



Gallamine Triethiodide $C_{30}H_{60}I_3N_3O_3$: 891.53
2-[2,3-*bis*[2-(Triethylazaniumyl)ethoxy]phenoxy]ethyltriethylazanium triiodide [*65-29-2*]

Gallamine Triethiodide contains NLT 98.0% and NMT 101.0% of gallamine triethiodide ($C_{30}H_{60}I_3N_3O_3$), calculated on the dried basis.

Description Gallamine Triethiodide occurs as a white, amorphous power and is odorless.
It is very soluble in water, sparingly soluble in ethanol(95) and very slightly soluble in chloroform.
It is hygroscopic.

Identification (1) Determine the infrared spectra of Gallamine Triethiodide and gallamine triethiodide RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) A solution of Gallamine Triethiodide (1 in 100) responds to the Qualitative Analysis for iodide.

pH Dissolve 1 g of Gallamine Triethiodide in 50 mL of water; the pH of this solution is between 5.3 and 7.0.

Purity (1) ***Clarity and color of solution***—A solution of Gallamine Triethiodide (1 in 100) is colorless and clear.

(2) ***Heavy metals***—Perform the test with 1.0 g of Gallamine Triethiodide as directed under the Method 1. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Loss on drying NMT 1.5% (1 g, 100 °C, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 25 mg each of Gallamine Triethiodide and gallamine triethiodide RS, dissolve in the mobile phase to make exactly 25 mL each, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas A_T and A_S of gallamine triethiodide for the test solution and the standard solution, respectively.

$$\text{Amount of gallamine triethiodide } (C_{30}H_{60}I_3N_3O_3) \text{ (mg)} = 25 \times C \times (A_T / A_S)$$

C: Concentration of gallamine triethiodide in the standard solution (mg/mL)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 200 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 - 10 μm in particle diameter).

Mobile phase: A mixture of sodium perchlorate buffer and acetonitrile (69 : 31).

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the number of theoretical plates is NLT 5000 with the symmetry factor being NMT 1.4.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solution under the above conditions; the relative standard deviation of peak areas of gallamine triethiodide is NMT 2.0%.

Sodium perchlorate buffer—Dissolve sodium perchlorate in water to reach the concentration of 0.14 mol/L and add 10 mol/L sodium hydroxide TS or 0.05 mol phosphoric acid to adjust pH to 3.0.

Packaging and storage Preserve in light-resistant, tight containers.

Garlic Oil and Tocopherol Capsules
마늘유·토코페롤 캡슐

Garlic Oil and Tocopherol Capsules contain NLT 90.0% of the labeled amount of allicin ($C_6H_{10}OS_2$: 162.27) and NLT 90.0% and NMT 150.0% of the labeled amount of tocopherol ($C_{29}H_{50}O_2$: 430.71).

Method of preparation Prepare as directed under Capsules, with Garlic Oil and Tocopherol.

Identification (1) ***Garlic oil*—**(i) Weigh an amount of Garlic Oil and Tocopherol Capsules equivalent to 0.1 g of garlic oil, dissolve in 10 mL of methanol, and use this solution as the test solution. Separately, dissolve 0.1 g of Garlic Oil in 10 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethanol(95) and 6 mol/L ammonia water (160 : 20) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly 0.5% p-anisaldehyde TS on the plate and heat at 105 ℃; the R_f values and colors of the spots from the test solution and the standard solution are the same.

(ii) Perform the test as directed under the Assay; diallyl disulfide, 144-I (3-vinyl-1,2-dithi-5-ene) and 144-II (3-vinyl-1,2-dithi-4-ene) are confirmed.

(2) ***Tocopherol*—**Take an amount of Garlic Oil and Tocopherol Capsules equivalent to 0.1 g of tocopherol ($C_{29}H_{50}O_2$: 430.71), add 3 mL of a solution of ethanol(95) and potassium hydroxide (1 : 2), attach the reflux condenser and saponify at 90 ℃ for 30 minutes, and cool it down. Transfer to a separatory funnel, add 50 mL of water, and extract NLT 3 times of 30 mL of ether each. Collect the previous extract, transfer to a separatory funnel, and wash with 30 mL of water. Wash until the washing neutralizes, dehydrate with anhydrous sodium sulfate, evaporate to dryness in the nitrogen atmosphere, and dissolve the residue in 50 mL of ethanol. Use this solution as the test solution. Separately, make in the same procedure as the test solution with 0.1 g of tocopherol RS and use this solution as the standard solution. With the test solution and the standard solution, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of cyclohexane and ether (4 : 1) as the developing solvent to a distance of about 10 cm and air-dry the plate. Spray evenly sulfuric acid or perchloric acid TS on the plate, heat at 100 ℃ for 10 minutes; the R_f values and colors of the spots from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Allicin from Garlic oil***—Weigh accurately the mass of NLT 20 capsules of Garlic Oil and Tocopherol Capsules. Weigh accurately the amount equivalent to about 2.0 mg of allicin ($C_6H_{10}OS_2$: 162.27), transfer to a centrifuge tube, add 5 mL of the internal standard solution, and sonicate on a steam bath for 3 minutes. Centrifuge, take the clear supernatant, and use this solution as the test solution. Separately, weigh accurately about 5 mg of diallyl disulfide, dissolve in acetonitrile to make 100 mL, and use this solution as the standard solution. Separately, weigh accurately about 10 mg of dipropyl disulfide and dissolve in acetonitrile to make 100 mL, and use this solution as the internal standard solution. Pipet 10 mL of this solution, add acetonitrile to make exactly 100 mL, and use the solution as the internal standard solution. Perform the test with the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, check the peaks of 144-I and 144-II of the following relative retention time, determine the peak areas, Q_T and Q_S, of the test solution and the standard solution, and calculate the content of diallyl disulfide, 144-I and 144-II. Add them and use as the content of allicin.

Relative retention time
1. Dipyridyl disulfide: 1.00
2. 144-I: 1.47
3. 144-II: 1.62

(1) Content (%) of 144-I and 144-II $= \frac{Q_T \times C_S \times 5}{Q_S \times S_a} \times 100$

Q_T: Sum of peak areas of 144-I and 144-II from the test solution

Q_S: Peak area of the internal standard solution (dipropyl disulfide)

C_S: Concentration (mg/mL) of the internal standard solution

S_a: Amount (mg) of sample taken

(2) Content (%) of diallyl disulfide $= \frac{Q_T \times C_S \times 5}{Q_S \times S_a} \times 100$

Q_T: Peak area of diallyl disulfide from the test solution

Q_S: Peak area of diallyl disulfide from the standard solution

C_S: Concentration (mg/mL) of the internal standard solution

S_a: Amount (mg) of sample taken

144-I: 3-Vinyl-1,2-dithi-5-ene
144-II: 3-Vinyl-1,2-dithi-4-ene

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A capillary steel column about 0.32 mm in internal diameter and about 30 m in length, packed with diatomaceous earth for gas chromatography, covered with polyethylene glycol for gas chromatography (0.25 μm in particle diameter).

Column temperature: A constant temperature of about 120 °C.

Sample injection port temperature: A constant temperature of about 200 °C.

Detector temperature: A constant temperature of about 300 °C.

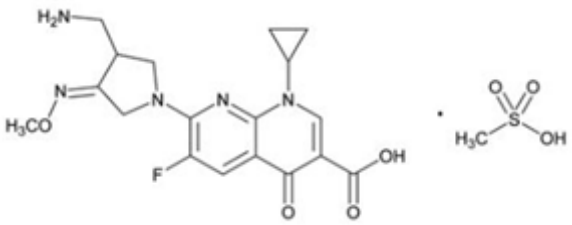
Carrier gas: Helium

Flow rate: 25 mL/min

(2) ***Tocopherol***—Weigh accurately the mass of NLT 20 capsules of Garlic Oil and Tocopherol Capsules and perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in tight containers.

Gemifloxacin Mesilate
제미플록사신메실산염



Gemifloxacin Mesilate

$C_{18}H_{20}FN_5O_4 \cdot CH_4O_3S$: 485.49

(*Z*)-7-[3-(Aminomethyl)-4-(methoxyimino)-1-pyrrolidinyl]-1-cyclopropyl-6-fluor o-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid monomethanesulfonate;
(±)-7-[3-(Aminomethyl)-4-oxo-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, 74-(*Z*)-(O-methyloxime),monomethanesulfonate; (*Z*)-7-[3-(Aminomethyl)-4-(methoxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate
[*210353-53-0*]

Gemifloxacin Mesilate contains NLT 98.0% and NMT 102.0% of gemifloxacin mesilate ($C_{18}H_{20}FN_5O_4 \cdot CH_4O_3S$), calculated on the anhydrous and solvent-free basis.

Method of preparation If there is a possibility that alkyl (e.g., methyl, ethyl and isopropyl) methanesulfonate esters may be introduced during the manufacturing process of Gemifloxacin Mesilate as potential impurities, pay attention to the control of starting materials, manufacturing processes, and intermediates to minimize the amount of residual impurities by considering the results of the risk assessment. If necessary, the manufacturing process may be verified by the test data that proves there is no quality risk in the final drug substance.

Description Gemifloxacin Mesilate occurs as a white or light brown powder.
It is freely soluble in water, very slightly soluble in methanol or ethanol(99.5), and practically insoluble in acetone and chloroform.
It is hygroscopic.

Melting point—Between 200 and 205 °C (with decomposition).

Identification (1) Determine the infrared spectra of Gemifloxacin Mesilate and gemifloxacin mesilate RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of major peak of the test solution and the standard solution for Assay is the same.

(3) Gemifloxacin Mesilate responds to the Qualitative Analysis (1) for mesylate.

Purity ***Related substances***—Perform the test without exposure to light, using a light-resistant container. To Gemifloxacin Mesilate, add the diluent to make 0.5 mg/mL, and use this solution as the test solution Separately, add the diluent to gemifloxacin mesilate RS to make 0.0005 mg/mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution according to the automatic integration method to calculate the amount of related substances; the amount of each related substance is NMT the acceptance criteria (%).

Content (%) of related substances
$$= \frac{C_S}{C_T} \times \frac{A_i}{A_S} \times \frac{1}{F} \times 100$$

C_S: Concentration (mg/mL) of gemifloxacin mesilate RS in the standard solution

C_T: Concentration (mg/mL) of Gemifloxacin mesilate in the test solution

A_I: Peak area of each related substance obtained from the test solution

A_S: Peak area of gemifloxacin obtained from the standard solution

F: Relative response factor

Compound	Relative retention time	Wavelengths (nm)	Relative response factor	Acceptance criteria (%)
Gemifloxacin related substance A*	0.16	207	0.43	0.15
Gemifloxacin related substance B	0.33	272	1.0	0.2
Gemifloxacin related substance C	0.37	272	1.0	0.1
Gemifloxacin *E*-isomer	0.77	272	1.0	0.7
Gemifloxacin	1.0	272	-	-
Naphthyridine carboxylic acid analog	1.79	272	0.45	0.15
Gemifloxacin dimers	1.97	272	0.90	0.15
Individual related substances	-	272	1.0	0.1
Total related substances	-	-	-	1.5

* Applicable when there is a possibility of producing the related substance depending on the manufacturing process.

Diluent—A mixture of water and acetonitrile (80 : 20).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 0 min to 5 min 207 nm, 5.1 min to 37 min 272 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Use mobile phases A and B to control stepwise or based on the gradient elution as follows.

Mobile phase A: A mixture of water, acetonitrile and trifluoroacetic acid (80 : 20 : 0.1).

Mobile phase B: A mixture of acetonitrile, water and trifluoroacetic acid (80 : 20 : 0.1).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 15	100	0
15 - 35	100 → 0	0 → 100
35 - 37	0 → 100	100 → 0

Flow rate: 1.0 mL/min

System suitability

System performance: Add diluent to gemifloxacin mesilate RS to make 0.5 mg/mL, and use this solution as the system suitability solution. Proceed with 5 μL of this solution according to the above operating conditions; the resolution between the peaks of gemifloxacin E-isomer and gemifloxacin is NLT 5.0. Add diluent to gemifloxacin mesilate RS to make 0.25 μg/mL, and use this solution as the sensibility test solution. Proceed with 5 μL of this solution according to the above operating conditions; the signal-to-noise ratio is NLT 10.

System repeatability: Repeat the test 6 times with 5 μL each of standard solution according to the above operating conditions; the relative standard deviation of the peak areas of gemifloxacin is NMT 10%.

Water Between 4.0% and 7.0% (0.1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Proceed with light-resistant containers, away from the light. Dissolve Gemifloxacin Mesilate in water to make 0.5 mg/mL, and use this solution as the test solution. Separately, dissolve gemifloxacin mesilate RS in water to make 0.5 mg/mL, and use this solution as the standard solution. Perform the test with 5 mL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions; determine the peak areas of gemifloxacin in each solution, r_U and r_S.

Content (%) of gemifloxacin mesilate

$$(C_{18}H_{20}FN_5O_4 \cdot CH_4O_3S) = \left(\frac{r_U}{r_S}\right) \times \left(\frac{C_S}{C_U}\right) \times 100(\%)$$

r_U: Peak area of gemifloxacin in the test solution

r_S: Peak area of gemifloxacin in the standard solution

C_S: Concentration (mg/mL) of gemifloxacin mesilate RS in the standard solution
C_U: Concentration (mg/mL) of gemifloxacin mesilate in the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 272 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of water, acetonitrile, and trifluoroacetic acid (80 : 20 : 0.1).

Flow rate: 1 mL/min

Time span of measurement: NLT 1.2 times the retention time of gemifloxacin.

System suitability

System performance: Proceed with 5 μL of the standard solution according to the above operating conditions; the resolution between the peaks of gemifloxacin E-isomer and gemifloxacin is NLT 5.0, and the symmetry factor of the gemifloxacin peak is NMT 1.5.

System repeatability: Repeat the test 6 times with 5 μL each of standard solution according to the above operating conditions; the relative standard deviation of the peak areas of gemifloxacin is NMT 1.0%.

Packaging and storage Preserve in light-resistant, well-closed containers.

Note

Gemifloxacin related substance A: (Z)-4-(Aminomethyl)pyrrolidin-3-one O-methyl oxime Dimethanesulfonate

Gemifloxacin related substance B: (*R,S*)-7-[3-(Aminomethyl)-4-hydroxy-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid monomethanesulfonate

Gemifloxacin related substance C: 7-[3-(Aminomethyl)-4-oxo-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid monomethanesulfonate

Gemifloxacin *E*-isomer: (E)-7-[3-(Aminomethyl)-4-(methoxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid monomethanesulfonate

Naphthyridine carboxylic acid analog: 7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid

Gemifloxacin dimer: (Z)-7-({[1-(6-Carboxy-8-cyclopropyl-3-fluoro-5-oxo-5,8-dihydro-1,8-naphthyridin-2-yl)-4-(methoxyimino)pyrrolidin-3-yl]methyl}amino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid

Gemifloxacin Mesilate Tablets
제미플록사신메실산염 정

Gemifloxacin Mesilate Tablets contains NLT 90.0% and NMT 110.0% of labeled amount of gemifloxacin ($C_{18}H_{20}FN_5O_4$: 389.38).

Method of preparation Prepare as directed under Tablets, with Gemifloxacin Mesilate.

Identification (1) Determine the infrared spectra of Gemifloxacin Mesilate Tablets and gemifloxacin mesilate RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of major peak of the test solution and the standard solution for Assay is the same.

Purity ***Related substances***—Perform the test without exposure to light using light-resistant vessels.
Perform the test with 20 μL each of the test solution and the standard solution obtained from Assay as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the amount of each related substance is NMT acceptance criteria (%).

$$\text{Amounts (\%) of related substances} = (C_S / C_T) \times (A_i / A_S) \times 0.802 \times 100$$

C_S: Concentration (mg/mL) of gemifloxacin mesilate in the standard solution

C_T: Concentration (mg/mL) according to labeled amount of gemifloxacin ($C_{18}H_{20}FN_5O_4$) in the test solution

A_i: Peak area of each related substance obtained from the test solution

A_S: peak area of gemifloxacin obtained from the standard solution

0.802: Conversion factor from gemifloxacin mesilate ($C_{18}H_{20}FN_5O_4 \cdot CH_4O_3S$) to gemifloxacin ($C_{18}H_{20}FN_5O_4$)

Compound	Relative retention time	Acceptance criteria(%)
Gemifloxacin *E*-isomer	0.78	1.0
Gemifloxacin	1.0	-
Each related substance	-	0.2
Total related substances	-	1.5

Operating conditions

For diluent, detector, column, column temperature, mobile phase and flow rate, proceed as directed under the operating conditions under Assay.

Time span of measurement: About 1.3 times the retention time of gemifloxacin.

System suitability

Test for required detectability: Add diluent to gemifloxacin mesilate RS to make 0.06 μg/mL, and use this solution as a sensitivity confirmation solution. Proceed with 20 μL of this solution according to the above operating conditions; the signal-to-noise ratio is NLT 10.

System performance: Add diluent to gemifloxacin mesilate RS to make 0.5 mg/mL, and use this solution as a system suitability solution. Proceed with 20 μL of this solution as directed under the above operating conditions; the resolution between gemifloxacin *E*-isomer peak and gemifloxacin peak is NLT 5.0. Proceed with 20 μL of the system suitability solution according to the above conditions; the symmetry factor for the gemifloxacin peak is NMT 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of gemifloxacin is NMT 1.0%.

Dissolution Perform the test with 1 tablet of Gemifloxacin Mesilate Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of 0.01 mol/L hydrochloric acid TS as the dissolution medium. Take the medium30 minutes after starting the test and filter through a membrane filter with a pore size not exceeding 0.45 μm. Pipet V mL of the filtrate, add the medium to make exactly V' mL, and use this solution as the test solution. Separately, dissolve gemifloxacin mesilate RS in the medium to make 0.01 mg/mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 343 nm as directed under the Ultraviolet-visible Spectroscopy. The dissolution rate in 30 minutes is NLT 70% (Q).

Dissolution rate (%) of the labeled amount of gemifloxacin ($C_{18}H_{20}$ FN $_5O_4$)

$$= C_S \times (A_T / A_S) \times (V'/ V) \times (1 / C) \times 0.802 \times 90000$$

C_S: Concentration (mg/mL) of gemifloxacin mesilate in the standard solution

A_T: Absorbance of the test solution

A_S: Absorbance of the standard solution

C: The labeled amount (mg) of gemifloxacin ($C_{18}H_{20}FN_5O_4$) in 1 tablet

0.802: Conversion factor from gemifloxacin mesilate ($C_{18}H_{20}FN_5O_4 \cdot CH_4O_3S$) to gemifloxacin ($C_{18}H_{20}FN_5O_4$)

Uniformity of dosage units Meets the requirements.

Assay Perform the test without exposure to light using light-resistant vessels.

Weigh accurately the mass of NLT 20 tablets of Gemifloxacin Mesilate Tablets, and power. Weigh accurately a portion of the powder, equivalent to about 320 mg of gemifloxacin ($C_{18}H_{20}FN_5O_4$), add about 350 mL of diluent, shake to mix for about 15 minutes, and sonicate for about 30 minutes. Add diluent to the resulting solution to make exactly 500 mL. Take this solution, add diluent to make 0.13 mg/mL gemifloxacin ($C_{18}H_{20}FN_5O_4$), and use this solution as the test solution. Separately, dissolve gemifloxacin mesilate RS in diluent to make 0.17 mg/mL, and use this solution as the standard solution.

Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area, A_T and A_S, of gemifloxacin in each solution.

Amount (mg) of gemifloxacin ($C_{18}H_{20}FN_5O_4$)

$$= \text{Amount (mg) of gemifloxacin mesylate RS} \times (A_T / A_S) \times 0.802$$

A_T: Peak area of gemifloxacin obtained from the test solution

A_S: Peak area of gemifloxacin obtained from the standard solution

0.802: Conversion factor from gemifloxacin mesilate ($C_{18}H_{20}FN_5O_4 \cdot CH_4O_3S$) to gemifloxacin ($C_{18}H_{20}FN_5O_4$)

diluent—A mixture of water, acetonitrile and 1 mol/L phosphate buffer solution (18 : 5 : 2).

1 mol/L phosphate buffer solution—Dissolve 138 g of sodium dihydrogen phosphate monohydrate in water to make 1000 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 272 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of water, acetonitrile and trifluoroacetic acid (80 : 20 : 0.1).

Flow rate: 1.0 mL/min

Time span of measurement: About 1.3 times the retention time of gemifloxacin.

System suitability

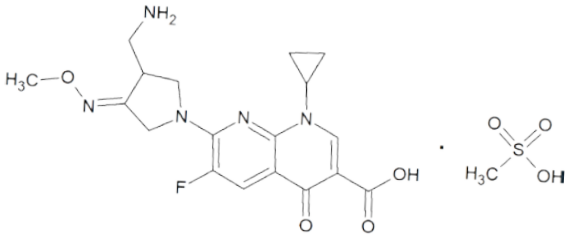
System performance: Proceed with 20 μL of the standard solution according to the above conditions; the symmetry factor of the gemifloxacin peak is NMT 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution; the relative standard deviation of the peak areas of gemifloxacin is NMT 1.0%.

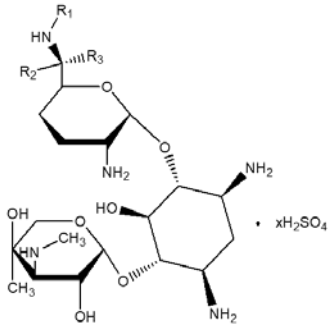
Packaging and storage Preserve in light-resistant, tight containers.

Note

gemifloxacin *E*-isomer: (E)-7-[3-(aminomethyll)-4-(methoxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-di Hydro-1,8-naphthyridine-3-carboxylic acid monomethanesulfonate



Gentamicin Sulfate
겐타마이신황산염



Gentamicin C_1: $R_1 = CH_3$ $R_2 = CH_3$ $R_3 = H$
Gentamicin C_{1a}: $R_1 = H$ $R_2 = H$ $R_3 = H$
Gentamicin C_2: $R_1 = H$ $R_2 = CH_3$ $R_3 = H$
Gentamicin C_{2a}: $R_1 = H$ $R_2 = H$ $R_3 = CH_3$
Gentamicin C_{2b}: $R_1 = CH_3$ $R_2 = H$ $R_3 = H$
Gentamicin Sulfate
(3*R*,4*R*,5*R*)-2-{[(1*S*,2*S*,3*R*,4*S*,6*R*)-4,6-Diamino-3-{[(2*R*,3*R*,6*S*)-3-amino-6-[(1*R*)-1-(methylamino)ethyl]oxan-2-yl]oxy}-2-hydroxycyclohexyl]oxy}-5-methyl-4-(methylamino)oxane-3,5-diol; sulfuric acid [*1405-41-0*]

Gentamicin Sulfate is the sulfate of a mixture of aminoglycoside compounds having antibacterial activity produced by the growth of *Micromonospora purpurea* or *Micromonospora echinospora*.

Gentamicin Sulfate contains NLT 590 μg and NMT 775 μg (potency) per mg of gentamicin C1 ($C_{21}H_{43}N_5O_7$: 477.60), calculated on the dried basis.

Description Gentamicin Sulfate occurs as a white to pale yellow powder.
It is very soluble in water and practically insoluble in ethanol(99.5).
It is hygroscopic.

Identification (1) Dissolve 50 mg of Gentamicin Sulfate in 1 mL of water and add 2 drops of the solution of 1-naphthol in ethanol(95) (1 in 500). Inject slowly this solution into 1 mL of sulfuric acid along the inner wall; a bluish purple color develops at the boundary layer.

(2) Pipet 50 mg each of Gentamicin Sulfate and gentamicin sulfate RS, dissolve in 10 mL of water, and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solutions and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, put a mixture of chloroform, ammonia water(28) and methanol (2 : 1 : 1) into a separatory funnel, shake to mix, and allow to stand for over 1 hour at room temperature. Take 20 mL from the bottom layer of this solution, add 0.5 mL of methanol, develop the plate to a distance of about 17 cm with the developing chamber cover open about 20 mm^2 and without placing filter paper inside the container, and air-dry the plate. Expose the plate to iodine steam, cover the plate with the glass sheet, and compare the spots; the R_f value and the color of the three spots obtained from the test solution are identical to that of each spot from the standard solution.

(3) Put 50 mg of Gentamicin Sulfate in 5 mL of water, dissolve, and add 5 mL of barium chloride TS; a white precipitate develops.

Optical rotation $[\alpha]_D^{20}$: Between +107° and +121° (0.25 g calculated on the dried basis, water, 25 mL, 100 mm).

pH Dissolve 0.20 g of Gentamicin Sulfate in 5 mL of water; the pH of this solution is between 3.5 and 5.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Gentamicin Sulfate in 10 mL of water; the solution is clear and colorless to pale yellow color.

(2) ***Heavy metals***—Proceed with 2.0 g of Gentamicin Sulfate as directed under Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 50 mg of Gentamicin Sulfate in 10 mL of water and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solutions and the standard solution on a plate made of silica gel for thin-layer chromatography. Separately, put a mixture of chloroform, ammonia water(28) and methanol (2 : 1 : 1) into a separatory funnel, shake to mix, and allow to stand for over 1 hour at room temperature. Take 20 mL from the bottom layer of this solution, add 0.5 mL of methanol, develop the plate to a distance of about 17 cm with the developing chamber cover open about 20 mm^2 and without placing filter paper inside the container, and air-dry the plate. Expose the plate to iodine steam, cover the plate with the glass sheet, and compare the spots; the spots, other than that of Gentamicin C_1 (R_f = about 0.3), Gentamicin C_2 (R_f = about

0.2) and Gentamicin C_{1a} (R_f = about 0.1) from the test solution, are not darker than the spots of Gentamicin C_2 from the standard solution.

Sterility It meets the requirements when Gentamicin Sulfate is used in aseptic preparations. However, the manufacturing process of aseptic preparations, which include the final sterile process, is exceptional.

Bacterial endotoxins Less than 0.50 EU/mg per mg (potency) of gentamicin when used in the manufacturing of aseptic preparations.

Loss on drying NMT 18.0% (0.15 g, in vacuum, NMT·0.67 kPa, 110 ℃, 3 hours). Avoid moisture absorption upon sampling.

Content ratio of Gentamicin Weigh accurately an appropriate amount of Gentamicin Sulfate and gentamicin sulfate RS, dissolve in water, and make a solution so that each mL contains 0.65 mg (potency). Pipet 10 mL each of these solutions, add 5 mL of 2-propanol and 4 mL of *o*-phthaldehyde, shake to mix, and add 2-propanol to make exactly 25 mL. Heat for 15 minutes in the water bath at 60℃, cool down, and use these solutions as the test solution and the standard solution, respectively. Perform the test with these solutions as directed under the Liquid Chromatography according to the following conditions, and determine each peak area of the test solution and the standard solution, respectively (Gentamicin C_1: 25 to 50%, Gentamicin C_{1a}: 10 to 35%, and Gentamicin C_2 and C_{2a}: 25 to 55%).

$$\text{Each content of Gentamicin } C_1\text{, Gentamicin } C_{1a}\text{, and Gentamicin } C_2 \text{ and } C_{2a\,(\%)} = \frac{A_F}{A_S} \times 100$$

A_F: Each peak area of gentamicin
A_S: Sum of peak areas of gentamicin

Operating Conditions

Detector: An ultraviolet absorption photometer (wavelength: 330 nm).

Column: A stainless steel column about 5 mm in internal diameter and about 100 mm in length, packed with octadecylsilanized silica gel for liquid chromatography or fine ceramic particles (5 to 10 μm in particle diameter).

Mobile phase: Add 250 mL of water and 50 mL of acetic acid(100) to 700 mL of methanol, shake to mix, and dissolve 5 g of sodium 1-heptanesulfonate in this solution.

Flow rate: About 1.5 mL/min.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the distribution factor k for the Gentamicin C_1 peak is 2 to 7, the number of theoretical plates for the Gentamicin C_2 peak is NLT 1200, and the resolution R between any two peaks is NLT 1.25. The elution order is Gentanicin C_1, Gentanicin C_{1a}, Gentamicin C_{2a} and Gentamicin C_2.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions under the above operating conditions; the relative standard deviation of any peak is NMT 2.0%.

o-phthaldehyde—Dissolve 1.0 g of o-phthaldehyde in 5 mL of methanol, add 95 mL of 0.4 mol/L boric acid previously adjusted by a solution of 8 mol/L potassium hydroxide to pH 10.4, add 2 mL of thioglycolic acid, and add a solution of 8 mol/L potassium hydroxide again to adjust pH to 10.4.

Assay ***Cylinder-plate method*** (1) Medium: (i) Agar medium for strata and base layers

Peptone	6.0 g	Glucose	1.0 g
Yeast extract	3.0 g	Sodium chloride	10.0 g
Meat extract	1.5 g	Agar	15.0 g

Weigh the above amount of substances, add purified water to make 1000 mL, sterilize, and adjust pH to between 7.8 and 8.0.

(ii) Agar medium for transferring test organisms: Use the medium in (i) (2) (ii) ②b under the Microbial Assays for Antibiotics.

(2) Test organism: *Staphylococcus epidermidis* ATCC 12228.

(3) Weigh accurately about 25 mg (potency) of Gentamicin Sulfate, dissolve in 0.1 mol/L phosphate buffer solution, pH 8.0 to make the solution containing 1 mg per mL (potency), and use this solution as the test stock solution. Take exactly an appropriate amount of the test stock solution, add 0.1 mol/L phosphate buffer solution, pH 8.0 to make solutions that contain 4 μg (potency) and 1 μg (potency) per mL, and use these solutions as the high concentration test solution and low concentration test solution, respectively. Separately, weigh accurately about 25 mg (potency) of gentamicin sulfate RS, previously dried, add 0.1 mol/L phosphate buffer solution, pH 8.0, and dissolve to make the standard stock solution containing 1 mg per mL (potency). Keep the standard stock solution below 15 °C, and use it within 30 days. Take exactly an appropriate amount of the standard stock solution, add 0.1 mol/L phosphate buffer solution, pH 8.0 to make solutions that contain 4.0 μg and 1.0 μg (potency) per mL, and use these solutions as the high concentration standard solution and low concentration standard solution, respectively. Perform the test with these solutions as directed in (A) (8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in tight containers.

Gentamicin Sulfate Cream
겐타마이신황산염 크림

Gentamicin Sulfate Cream contains NLT 90.0% and NMT 120.0% of the labeled amount of gentamicin.

Method of preparation Prepare as directed under Creams, with Gentamicin Sulfate.

Identification Weigh an appropriate amount of Gentamicin Sulfate Cream, put it in a blender, add an appropriate amount of 0.1 mol/L phosphate buffer solution, pH 8.0, previously warmed at 70 - 85 ℃, and mix at a high speed for 3 - 5 minutes. Perform the test as directed under the Identification (2) under Gentamicin Sulfate.

Assay Perform the test as directed under the Assay under Gentamicin Sulfate.

Packaging and storage Preserve in tight containers.

Gentamicin Sulfate Injection
겐타마이신황산염 주사액

Gentamicin Sulfate Injection contains NLT 90.0% and NMT 120.0% of the labeled amount of gentamicin.

Method of preparation Prepare as directed under Injections, with Gentamicin Sulfate.

Description Gentamicin Sulfate Injection occurs as a clear and colorless to pale yellow liquid.

Identification Weigh an amount equivalent to 0.1 g (potency) of gentamicin sulfate and 0.1 g (potency) of gentamicin sulfate RS according to the labeled amount of Gentamicin Sulfate Injection, and perform the test as directed under the Identification (2) of Gentamicin Sulfate.

pH Between 3.0 and 5.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.50 EU per mg (potency) of gentamicin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay ***Cylindrical plate method***—Perform the test according to the Assay of Gentamicin Sulfate. However, take accurately an appropriate amount according to the labeled potency of Gentamicin Sulfate Injection, and add 0.1 mol/L phosphate buffer (pH 8.0) to make a solution with a suitable concentration. Then, take an appropriate amount of this solution, dilute it with 0.1 mol/L phosphate buffer (pH 8.0), make the same concentration as in (3), and use this solution as the test solution.

Packaging and storage Preserve in hermetic containers.

Gentamicin Sulfate Ophthalmic Ointment
겐타마이신황산염 안연고

Gentamicin Sulfate Ophthalmic Ointment contains NLT 90.0% and NMT 120.0% of the labeled amount of gentamicin.

Method of preparation Prepared as directed under ophthalmic ointments, with Gentamicin Sulfate.

Identification Weigh an appropriate amount of Gentamicin Sulfate Ophthalmic Ointment, add an appropriate amount of 0.1 mol/L phosphate buffer (pH 8.0), previously warmed to 70 - 85 ℃, disperse well, and centrifuge it. Decant the supernatant and perform the test according to the Identification (2) under Gentamicin Sulfate.

Sterility Meets the requirements.

Foreign metallic matter in ophthalmic ointments Meets the requirements.

Assay ***Cylinder plate method***—Perform the test according to the Assay of Gentamicin Sulfate. However, weigh accurately this drug equivalent to about 1.0 mg (potency) according to the labeled potency, put it into a separatory funnel, add 50 mL of ether, and mix by shaking until it becomes uniform. Extract three times with 25 mL of 0.1 mol/L phosphate buffer (pH 8.0), combine the extracted solution, and add 0.1 mol/L phosphate buffer (pH 8.0) to make 100 mL. Take exactly an appropriate amount of this solution and dilute it with 0.1 mol/L phosphate buffer (pH 8.0) to make the concentration of (3) and use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Gentamicin Sulfate Ophthalmic Solution
겐타마이신황산염 점안액

Gentamicin Sulfate Ophthalmic Solution is an aqueous ophthalmic solution and contains NLT 90.0% and NMT 110.0% of the labeled amount of gentamicin.

Method of preparation Prepare as directed under Ophthalmic Solutions, with Gentamicin Sulfate.

Identification Weigh an amount of Gentamicin Sulfate

Ophthalmic Solution, equivalent to 10 mg (potency) of Gentamicin Sulfate, according to the labeled amount, add water to make 5 mL, and use this solution as the test solution. Separately, weigh about 10 mg (potency) of gentamicin sulfate RS, dissolve it in 5 mL of water, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, Develop the plate with a mixture of chloroform, ammonia water(28) and methanol (2 : 1 : 1) to a distance of about 15 cm, and air-dry the plate. Spray evenly 0.2% ninhydrin-water saturated 1-butanol TS on the plate and heat the plate at 100 ℃ for 5 minutes; the three spots from the test solution have the same color and R_f value as each spot from the standard solution.

pH Between 5.5 and 7.5.

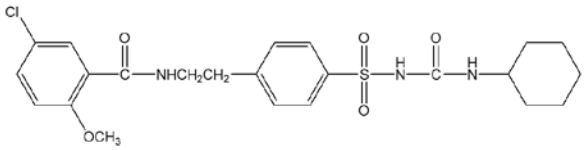
Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Assay Perform the test as directed under the Assay under Gentamicin Sulfate. Take exactly an amount of Gentamicin Sulfate Ophthalmic Solution, equivalent to about 12 mg (potency) of gentamicin, and dissolve it in 0.1 mol/L phosphate buffer solution, pH 8.0 to prepare a solution containing about 1 mg (potency) of gentamicin in 1 mL. Take exactly a suitable amount of this solution, and dilute it with 0.1 mol/L phosphate buffer solution, pH 8.0 to prepare two solutions containing each 4.0 and 1.0 μg (potency) of gentamicin in 1 mL, and use them as the high-concentration test solution and the low-concentration test solution, respectively.

Packaging and storage Preserve in tight containers.

Glibenclamide
글리벤클라미드



Glibenclamide $C_{23}H_{28}ClN_3O_5S$: 494.00
5-Chloro-*N*-[2-[4-(cyclohexylcarbamoylsulfamoyl)phenyl]ethyl]-2-methoxybenzamide [*10238-21-8*]

Glibenclamide, when dried, contains NLT 98.5% and NMT 101.0% of glibenclamide ($C_{23}H_{28}ClN_3O_5S$).

Description Glibenclamide occurs as a pale yellow (white to almost yellow) crystalline powder.
It is freely soluble in *N*,*N*-dimethylformamide, sparingly soluble in chloroform, slightly soluble in methanol or ethanol(95), and practically insoluble in water or ether.

Identification (1) Determine the absorption spectra as directed under the Ultraviolet-visible Spectroscopy with methanol VS of Glibenclamide and Glibenclamide RS (1 in 10000); both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Glibenclamide and Glibenclamide RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Perform the Flame Coloration 2) with Glibenclamide; it exhibits a green color.

Melting point Between 169 and 174 ℃.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Glibenclamide and perform the test according to Method 2. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 0.20 g of Glibenclamide in 20 mL of chloroform and use this solution as the test solution. Pipet 1 mL of this solution and add the chloroform to make exactly 20 mL. Pipet 1.0 mL of this solution, add chloroform to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test according to the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of 1-propanol, chloroform and diluted ammonia TS (4 in 5) (11 : 7 : 2) to a distance of about 12 cm, and air-dry the plate. Observe the plate under ultraviolet light (main wavelength: 366 nm); any spot other than the principal spot obtained from the test solution is not darker than the spot from the standard solutions.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 h.).

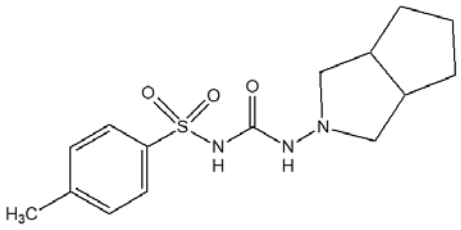
Residue on ignition NMT 0.5% (1 g).

Assay Weigh accurately about 0.9 g of Glibenclamide, previously dried, dissolve in 50 mL of *N*,*N*-dimethylformamide, and titrate the solution with 0.1 mol/L sodium hydroxide solution (Indicator: 3 drops of phenolphthalein TS). Perform a blank test with a solution prepared by adding 18 mL of water to 50 mL of *N*,*N*-dimethylformamide and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 49.40 mg of $C_{23}H_{28}ClN_3O_5S$

Packaging and storage Preserve in tight containers.

Gliclazide
글리클라지드



Gliclazide $C_{15}H_{21}N_3O_3S$: 323.41
N-((Hexahydrocyclopenta[c]pyrrol-2(1*H*)-yl)carbamoyl)-4-methylbenzenesulfonamide [*21187-98-4*]

Gliclazide, when dried, contains NLT 99.0% and NMT 101.0% of gliclazide ($C_{15}H_{21}N_3O_3S$).

Description Gliclazide occurs as a white crystalline powder.
It is freely soluble in dichloromethane, sparingly soluble in acetone, slightly soluble in ethanol(95) and practically insoluble in water.

Identification Determine the infrared spectra of Gliclazide and gliclazide RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 165 and 169 ℃.

Purity (1) ***Heavy metals***—Weigh 1.5 g of Gliclazide according to Method 2 and perform the test. Prepare the control solution with 1.5 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances I—***Weigh accurately 0.4 g of Gliclazide, dissolve in 2.5 mL of dimethylsulfoxide, and add water to make exactly 10mL. Shake the mixture for 10 minutes to mix and allow to stand for 30 minutes at 4 ℃, and then filter it to use this solution as the test solution. Weigh 20.0 mg of gliclazide related substance I RS [2-nitroso-octahydrocyclopenta[c]pyrrole] and add dimethylsulfoxide to make exactly 100 mL. To 1.0 mL of this solution, add 12 mL of dimethylsulfoxide and water to make exactly 50 mL, and use this solution as the standard solution (1). To 1.0 mL of the standard solution (1), add 12 mL of dimethylsulfoxide and water to make exactly 50 mL, and use this solution as the standard solution (2). Perform the test with 50 μL each of the test solution and the standard solution (2) as directed under the Liquid Chromatography according to the operating conditions of the related substances test; the area of the related substance I peak, obtained from the test solution, is not greater than that from the standard solution (2) (2 ppm).

(3) ***Related substances—***Weigh accurately 50 g of Gliclazide, dissolve in 23 mL of acetonitrile, and then add water to make exactly 50 mL. Use this solution as the test solution. To 1.0 mL of the test solution, add a mixture of water and acetonitrile (55 : 45) to make exactly 100 mL. Next, add a mixture of water andacetonitrile (55 : 45) to 10.0 mL of this solution to make exactly 100 mL, and use this solution as the standard solution (1). Dissolve 5 mg of Gliclazide and 15 mg of gliclazide related substance II RS [1-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-3-[(2-methylphenyl) sulfonyl]urea] in 23 mL of acetonitrile, add water to make exactly 50 mL, and then add a mixture of water and acetonitrile (55 : 45) to 1.0 mL of this solution to make exactly 20 mL. Use this solution as the standard solution (2). Dissolve 10.0 mg of gliclazide related substance II RS in 45 mL of acetonitrile and add water to make exactly 100 mL, add a mixture of water and acetonitrile (55 : 45) to 1.0 mL of this solution to make exactly 100 mL, and then use this solution as the standard solution (3). Perform the test with 20 μL each of the test solution, the standard solutions (1) and (3) as directed under the Liquid Chromatography according to the following operating conditions. The peak area corresponding to the related substance II obtained from the test solution is not greater than the area of the major peak obtained from the standard solution (3) (0.1%), the area of any peak other than the major peak or the related substance II peak is not greater than the area of the major peak from the standard solution (1) (0.1%), and the total area of these other peaks is not more than twice the area of the major peak from the standard solution (1) (0.2%). Disregard any peak having an area smaller than 0.2 times the area of the major peak from the standard solution (1).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 235 nm).

Column: A stainless-steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of water, acetonitrile, trifluoroacetic acid and triethylamine (55 : 45 : 0.1 : 0.1).

Flow rate: 0.9 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution (2) under the above operating conditions to determine the performance; the heights of the two major peaks are adjusted to be NLT 50% of the full scale of the data collection device. The resolution between the two peaks is NLT 1.8.

Loss on drying NMT 0.25% (1 g, 105 ℃, 2 h.).

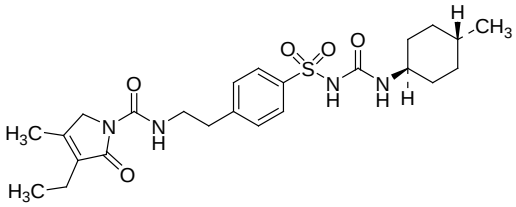
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Gliclazide, dissolve in 50 mL of acetic acid(100) and titrate with 1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Separately, perform a blank test, and make any necessary correction.

Each mL of perchloric acid VS
= 32.34 mg of $C_{15}H_{21}N_3O_3S$

Packaging and storage Preserve in well-closed containers.

Glimepiride
글리메피리드



Glimepiride $C_{24}H_{34}N_4O_5S$: 490.62
3-Ethyl-4-methyl-*N*-(4-(*N*-(((1r,4r)-4-methylcyclohexyl)carbamoyl)sulfamoyl)phenethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxamide [*93479-97-1*]

Glimepiride contains NLT 98.0% and NMT 102.0% of glimepiride ($C_{24}H_{34}N_4O_5S$), calculated on the anhydrous basis.

Description Glimepiride occurs as a white crystalline powder. It is slightly soluble in dichloromethane, very slightly soluble in methanol and ethanol(99.5), and practically insoluble in water.

Melting point—About 202 °C (with decomposition).

Identification (1) Determine the absorption spectra as directed under the Ultraviolet-visible Spectroscopy with methanol VS (1 in 125,000) of Glimepiride and glimepiride RS; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the absorption spectra of Glimepiride and glimepiride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Glimepiride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Glimepiride isomer***—Dissolve 10 mg of Glimepiride in 5 mL of dichloromethane, add the mobile phase to make 20.0 mL, and use this solution as the test solution. Pipet 1.0 mL of this solution, add the mobile phase to it make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area from each of the solutions according to the automatic integration method; the peak area of glimepiride isomer obtained from the test solution with the relative retention time to the Glimepiride of about 0.9 is not greater than 3/4 of the peak area of Glimepiride from the standard solution.

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 228 nm).

Column: A stainless steel column of about 3 mm in internal diameter and 15 cm in length, packed with dihydropropane silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of heptane, 2-propanol and acetic acid(100) (900 : 100 : 1).

Flow rate: Adjust the flow rate to ensure that the retention time of Glimepiride is about 14 minutes.

System suitability

Detection sensitivity: Weigh accurately 5 mL of the standard solution and add the mobile phase to make exactly 10 mL. Confirm that the peak area of Glimepiride obtained from 10 μL of this solution is equivalent to between 33% and 65% of the peak area of Glimepiride obtained from the standard solution.

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the number of theoretical plates for the peak of Glimepiride is NLT 3000 with the symmetry factor being NMT 1.5.

System repeatability: Repeated the test 6 times with 10 mL of the standard solution according to the above conditions; the relative standard deviation of the peak area of Glimepiride is NMT 2.0%.

(3) ***Related substances*—**Prepare the test solution and the standard solution and store them at NMT 4 ℃. Dissolve 20 mg of Glimepiride in 100 mL of a mixture of acetonitrile and water (4 : 1) and use this solution as the test solution. Pipet 1 mL of this solution, and add the mobile phase to make exactly 100 mL. Pipet 1 mL of this solution, add the mobile phase to it make exactly 10 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution according to the automatic integration method: the peak area for the test solution with the relative retention time to the Glimepiride of about 0.25 is NMT 4 times the peak area of Glimepiride for the standard solution; the peak area with the relative retention time of about 1.1 is not than twice the peak area of Glimepiride for the standard solution; the peak area with the relative retention time of about 0.32 is NMT 1.5 times the peak area of Glimepiride for the standard solution. Also, the sum of peak areas other than the peak of Glimepiride and peak with the relative retention time to Glimepiride of about 0.25 in the test solution is NMT 5 times the peak area of Glimepiride in the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, follow the operating conditions under the Assay.

System suitability

Detection sensitivity: Pipet 5 mL of the standard solution and add the mobile phase to make exactly 10 mL. Confirm that the peak area of Glimepiride obtained from 20 μL of this solution is equivalent to between 35% and 65% of the peak area of Glimepiride obtained from the standard solution.

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the number of theoretical plates for the Glimepiride peak is NLT 9,000 with the symmetry factor being NMT 1.5.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of Glimepiride is NMT 2.0%.

Water NMT 0.5% (0.25 g, coulometric titration).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately 20 mg each of Glimepiride and Glimepiride RS (water previously measured), dissolve each in a mixture containing acetonitrile and water (4 : 1) to make exactly 100 mL, and use each as the test solution and the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of Glimepiride, A_T, and A_S, in each solution.

$$\text{Amount (mg) of Glimepiride } (C_{24}H_{34}N_4O_5S) = \text{Amount (mg) of glimepiride RS as calculated on the anhydrous basis} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 228 nm).

Column: A stainless steel column of about 4 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (4 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 0.5 g of sodium dihydrogen phosphate dihydrate in 500 mL of water, adjust the pH to 2.5 by adding phosphoric acid, and add 500 mL of acetonitrile.

Flow rate: Adjust the flow rate to ensure that the retention time of Glimepiride is about 17 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the number of theoretical plates for the peak of Glimepiride is NLT 9,000 with the symmetry factor being NMT 1.5.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of Glimepiride is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Glimepiride Tablets
글리메피리드 정

Glimepiride Tablets contain NLT 93.0% and NMT 107.0% of glimepiride ($C_{24}H_{34}N_4O_5S$: 490.62) of the labeled amount.

Method of preparation Glimepiride Tablets are prepared as directed under Tablets, with Glimepiride.

Identification Weigh a portion of powdered Glimepiride Tablets, equivalent to 20 mg of glimepiride according to the labeled amount, add 40 mL of acetonitrile, shake to mix for 15 minutes, and then perform centrifugation. Allow to dry the clear supernatant in a vacuum on a steam bath, add 1 mL of water to the residue to suspend, and then filter it in a vacuum. Wash the residue with 1 mL of water, allow to dry at 105 °C for 1 hour, and determine the absorption as directed in the potassium bromide disk method of the Mid-infrared Spectroscopy; it exhibits absorption at the wavenumbers of about 3370 cm^{-1}, 3290 cm^{-1}, 2930 cm^{-1}, 1708 cm^{-1}, 1674 cm^{-1}, 1347 cm^{-1}, 1156 cm^{-1} and 618 cm^{-1}.

Purity ***Related substances***—After preparing the test solution and the standard solution, preserve them at below 4℃. Weigh a portion of powdered Glimepiride Tablets, equivalent to 9 mg of Glimepiride according to the labeled amount, put 0.5 mL of water, and add 80% acetonitrile to make 50 mL. After shaking to mix, perform centrifugation, and use the clear supernatant as the test solution. Take exactly 1 mL of this solution and add 80% acetonitrile to make 100 mL, and use this solution as the standard solution. Take exactly each 5 μL of the test solution and the standard solution and perform the test under the following conditions as directed under the Liquid Chromatography. Determine each peak area of each solution by the automatic integration method: the peak area in the test solution with the relative retention time to the Glimepiride of about 0.3 is NMT 2.6 times the peak area of Glimepiride in the standard solution; the peak area other than the peak in the test solution with the relative retention time of about 0.3 is NMT 3/10 than the peak area of Glimepiride in the standard solution; the sum of peak areas is not greater than the peak area of Glimepiride in the standard solution. Additionally, the sum of the peaks other than Glimepiride's in the test solution is not three times more than the peak area of Glimepiride in the standard solution.

Operating conditions

For the detector, column, column temperature and mobile phase, comply with the operating conditions as directed under the Assay.

Flow rate: Adjust the flow rate to achieve a retention time of about 12 minutes for Glimepiride.

System suitability

Test for required detectability: Take exactly 2 mL of the standard solution, and add the mobile phase to make exactly 20 mL. Confirm that the peak area of Glimepiride obtained from 5 μL of this solution is within the range between 7% and 13% of the peak area of Glimepiride in the standard solution.

System performance: Proceed with 5 μL of the standard solution under the above conditions; the number of theoretical plates of the Glimepiride's peak is NLT 6,000, and the symmetry factor is NMT 1.5.

System repeatability: Repeat the test six times with 5 μL each of the standard solution under the conditions specified above; the relative standard deviation of the peak area of Glimepiride is NMT 2.0%.

Time span of measurement: About 2 times the retention time of Glimepiride.

Dissolution Take one Glimepiride Tablet and perform the test at 50 revolutions per minute according to Method 2 under the Dissolution using 900 mL of phosphate-citrate buffer solution, pH 6.0 as the dissolution medium. Take NLT 20 mL of the dissolved solution after 15 minutes from the start of the Dissolution, and filter through a membrane filter with a pore size of NMT 0.45 μm. Discard the first 10 mL of the filtrate, take exactly the subsequent filtrate of *V* mL, add the dissolution medium to make exactly *V'* mL, containing about 1.1 μg of glimepiride ($C_{24}H_{34}N_4O_5S$) per mL, according to the labeled amount, and then use this solution as the test solution. Separately, weigh accurately about 20 mg of glimepiride RS (previously measure the water) and add acetonitrile to make exactly 100 mL. Weigh exactly 2 mL of this solution, add 8 mL of acetonitrile and then the dissolution medium to make exactly 200 mL. Take exactly 10 mL of this solution, add the dissolution medium to make exactly 20 mL, and use this as the standard solution. Pipet 50 μL each of the test solution and the standard solution, and perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S of Glimepiride of each solution. Meets the requirements if the dissolution rate of Glimepiride Tablets in 15 minutes is NLT 75%.

Dissolution rate (%) with respect to the labeled amount of glimepiride ($C_{24}H_{34}N_4O_5S$)
= Amount (mg) of glimepiride RS, calculated on the anhydrous basis
$$\times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times \frac{9}{2}$$

C: Labeled amount (mg) of glimepiride ($C_{24}H_{34}N_4O_5S$) in 1 tablet

Operating conditions

For the detector, column temperature, mobile phase and flow rate, comply with the operating conditions as directed under the Assay.

Column: A stainless-steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

System suitability

System performance: Proceed with 50 μL of the standard solution according to the above conditions; the number of theoretical plates of the glimepiride peak is NLT 3,000, and the symmetry factor is NMT 1.5.

System repeatability: Repeat the test six times with 50 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of glimepiride is NMT 1.5%.

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to following method.

With one Glimepiride Tablet, put *V* / 20 mL of water to disintegrate, add *V* / 2 mL of 80% acetonitrile, and shake to mix. To this solution, put exactly *V* / 10 mL of the internal standard solution, and add 80% acetonitrile to make *V* mL, containing about 50 μg of glimepiride ($C_{24}H_{34}N_4O_5S$) per mL. Centrifuge this solution, and use the clear supernatant as the test solution. Separately, weigh exactly about 20 mg of glimepiride RS (previously measure the water) and dissolve in a 80% acetonitrile to make exactly 100 mL. Weigh exactly 5 mL of this solution, put exactly 2 mL of the internal standard solution, and add a mixture of acetonitrile and water (4 : 1) to make 20 mL, and use this solution as the standard solution. Perform the test as directed under the Assay below.

Amount (mg) of glimepiride ($C_{24}H_{34}N_4O_5S$)
= Amount (mg) of glimepiride RS, calculated on the anhydrous basis
$$\times \frac{Q_T}{Q_S} \times \frac{V}{400}$$

Internal standard solution— A mixture of acetonitrile and water (4 : 1) of butyl p-hydroxybenzoate VS (1 in 1000).

Assay Weigh accurately the mass of NLT 20 Glimepiride Tablets, and powder. Weigh accurately an amount, equivalent to about 3 mg of glimepiride ($C_{24}H_{34}N_4O_5S$), put 3 mL of water, add 30 mL of 80% acetonitrile, and shake to mix. Add exactly 6 mL of the internal standard solution, put 80% acetonitrile to make 50 mL, perform centrifugation, and use the clear supernatant as the test solution. Separately, weigh accurately about 20 mg of glimepiride RS (previously measure the water), and dissolve in 80% acetonitrile to make exactly 100 mL. Weigh exactly 15 mL of this solution, put exactly 6 mL of the internal standard solution, add 80% ace-

tonitrile to make 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak area ratios, Q_T and Q_S of glimepiride to the internal standard.

Amount (mg) of glimepiride ($C_{24}H_{34}N_4O_5S$) = Amount (mg) of glimepiride RS, calculated on the anhydrous basis $\times \frac{Q_T}{Q_S} \times \frac{3}{20}$

Internal standard solution— A mixture of acetonitrile and water (4 : 1) of butyl p-hydroxybenzoate VS (1 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 228 nm).

Column: A stainless-steel column about 4 mm in internal diameter and about 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 0.5 g of sodium dihydrogen phosphate dihydrate in 500 mL of water, put 500 mL of acetonitrile, and add diluted phosphoric acid (1 in 5) to adjust the pH to 3.5.

Flow Rate: Adjust the flow rate to achieve a retention time of about 10 minutes for glimepiride.

System suitability

System performance: Proceed with 10 μL of the standard solution under the above conditions; the internal standard and glimepiride are eluted in this order with the resolution being NLT 6.

System repeatability: Repeat the test six times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of glimepiride is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Crystallized Glucosamine Sulfate
결정글루코사민황산염

Crystallized Glucosamine Sulfate, when stabilized by adsorbing sodium chloride to the crystal spacing of glucosamine sulfate, contains NLT 76.0% and NMT 84.0% of glucosamine sulfate ($C_{12}H_{26}N_2O_{14}S$).

Description Crystallized Glucosamine Sulfate occurs as a white to light brown crystalline powder that is odorless and has a strong salty taste.
It is soluble in water and slightly soluble in methanol.

Identification (1) ***Glucosamine aldehyde group***—Dissolve 0.5 g of Crystallized Glucosamine Sulfate in 10 mL of water, adjust the pH to neutral or slightly alkaline, add several mL of Fehling's TS, and warm slowly to form a red precipitate of cuprous oxide.

(2) ***Glucosamine***—To 1 mL of Crystallized Glucosamine Sulfate aqueous solution, add 1 mL of 2% acetylacetone·0.5 mol/L sodium bicarbonate solution, heat on a steam bath for 20 minutes, cool, and then add 4 mL of ethanol and 1 mL of p-dimethylaminobenzaldehyde TS in order. When heated at 65 to 70 °C for 10 minutes, it exhibits a violet color (absorbance maximum wavelength: 535 ± 5 nm).

(3) ***Sulfate***—(i) To Crystallized Glucosamine Sulfate aqueous solution acidified with hydrochloric acid, add barium chloride TS; a white precipitate is formed. This precipitate is insoluble in hydrochloric acid or nitric acid.

(ii) To Crystallized Glucosamine Sulfate aqueous solution, add lead acetate solution (9.5 in 100); a white precipitate is formed, which is soluble in ammonium acetate TS.

(4) ***Sodium***—To Crystallized Glucosamine Sulfate aqueous solution, add 5 mL of cobalt/uranyl acetate TS and shake to form a golden precipitate.

(5) ***Chlorine***—To Crystallized Glucosamine Sulfate aqueous solution acidified with dilute nitric acid, add silver nitrate solution; a white precipitate is formed, which is soluble in ammonia water.

(6) Weigh 20 mg of Crystallized Glucosamine Sulfate and dissolve it in 2 mL of water to use as the test solution. Separately weigh about 20 mg of silver nitrate TS and dissolve it in 2 mL of water to use as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made using silica gel with fluorescent indicator for thin-layer chromatography (fluorescent indicator added). Next, develop the plate by about 10 cm using a mixture of ethanol and ammonia (8:2) as a developing solvent, and air-dry the plate. After drying at 105 ℃ for 10 minutes, check according to the following method.

(i) Add 2 mol/L potassium permanganate solution and 4 mol/L hydrochloric acid mixture (1:1), put the thin-layer plate in a developing tank saturated with chlorine vapor, blow off excess chlorine, and spray solution (I). Glucosamine exhibits goldish blue spots at an R_f value of 0.4, and chlorine exhibits white spots at an R_f value of 0.74.

Solution (I)—A solution obtained by adding 3 mL of acetic acid(100) to 150 mL of water, dissolving 1 g of potassium iodide and 100 mg of *o*-tolidine, and filtering the solution.

(ii) Spray ninhydrin ethanol solution evenly on the thin-layer chromatographic plate and heat it at 110 ℃ for several minutes. Glucosamine shows violet spots on a pink background, and sulfate shows yellow spots, but

chlorine is not detected.

(7) When measured according to the potassium bromide purification method under the Mid-infrared Spectroscopy with Crystallized Glucosamine Sulfate and glucosamine sulfate RS, absorption of the same intensity is shown at the same wavenumber.

Optical rotation $[\alpha]_D^{20}$: Between +53 ± 1° and +65 ± 1° (3 hours) (10% aqueous solution, 200 mm, 25 °C).

pH Between 4.0 and 4.4 (5% aqueous solution, 25 °C).

Purity ***Heavy metals***—Weigh about 2.0 g of this solution and perform the test according to Method 1. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

Water NMT 0.5%.

Residue on ignition NMT 0.2% (1 g). Perform the test according to the residue on ignition test method and subtract 24.78% equivalent to sodium from the result.

Assay Weigh accurately about 0.3 g of Crystallized Glucosamine Sulfate aqueous solution and dissolve it in water to make 250 mL. Take 10.0 mL of this solution, add water to make 250 mL, and use it as the test solution. Separately, weigh accurately about 0.25 g of the glucosamine sulfate RS, put it into a 250-mL volumetric flask, bring it to the gauge line with water, take 10.0 mL of this solution, add water to make 250 mL, and use it as the standard solution. Take 5 mL each of the test solution, standard solution, and water in a test tube, add 2 mL of acetylacetone solution (prepared before use) in which 2% acetylacetone is dissolved in 0.5 mol/L sodium bicarbonate solution, mix well, and heat on a steam bath for exactly 20 minutes. Cool with cold water, sequentially add 2 mL of a dimethylaminobenzaldehyde solution in which 12 mL of anhydrous ethanol and 3.2 g of dimethylaminobenzaldehyde are dissolved in a mixture of 120 mL of hydrochloric acid and 120 mL of methanol, mix well, and warm on a steam bath at between 65 and 70 °C for exactly 10 minutes. Cool with cold water and when using the blank test solution as a control and testing according to the UV-visible spectrophotometry, measure the absorbance A_T and A_S at a wavelength of 530 nm.

Amount (mg) of glucosamine sulfate ($C_{12}H_{26}N_2O_{14}S$)
= Amount (mg) of glucosamine sulfate RS × $\frac{A_T}{A_S}$

Packaging and storage Preserve in tight containers.

Crystallized Glucosamine Sulfate Capsules
결정글루코사민황산염 캡슐

Crystallized Glucosamine Sulfate Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of glucosamine sulfate [$(C_6H_{13}NO_5)_2 \cdot H_2SO_4$: 456.42].

Method of preparation Prepare as directed under Capsules, with Crystallized Glucosamine Sulfate.

Identification Weigh an amount equivalent to 20 mg of glucosamine sulfate according to the labeled amount of Crystallized Glucosamine Sulfate Capsules, dissolve it in 2 mL of water, and use this solution as the test solution. Separately, weigh 20 mg of glucosamine sulfate RS, dissolve it in 2 mL of water, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography(fluorescent indicator added). Next, develop the plate with a mixture of ethanol and ammonia (8 : 2) to a distance of about 10 cm, and air-dry the plate. After drying at 105 °C for 10 minutes, (i) expose to chlorine vapor as Solution (I) and evaporate excess chlorine, and spray Solution (II); Glucosamine shows golden blue spots at R_f value of about 0.4, and chlorine shows white spots at an R_f value of about 0.74.

Solution (I)—A mixture of 2 mol/L potassium permanganate solution and 4 mol/L hydrochloric acid TS (1 : 1).

Solution (II)—A solution obtained by adding 3 mL of acetic acid(100) to 150 mL of water, dissolving 1 g of potassium iodide and 100 mg of *o*-tolidine, and filtering.

(ii) Spray 0.2% ninhydrin-ethanol solution evenly and heat it at 110 °C for several minutes; Glucosamine shows violet spots on a pink background, and sulfate shows yellow spots, but chlorine is not detected.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

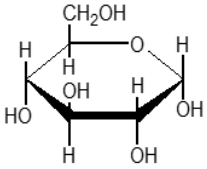
Assay Weigh accurately the mass of NLT 20 Crystallized Glucosamine Sulfate Capsules. Weigh accurately an amount equivalent to about 0.25 g of glucosamine sulfate ($(C_6H_{13}NO_5)_2 \cdot H_2SO_4$), put it into a 250-mL volumetric flask, and bring it to the gauge line with water. Take 10.0 mL of this solution, transfer it to a 250-mL volumetric flask, fill it up to the gauge line with water, and use this solution as the test solution. Separately, weigh accurately about 0.25 g of the glucosamine sulfate RS, put it in a 250-mL volumetric flask and bring it to the gauge line with water. Transfer 10.0 mL of this solution into a 250-mL volumetric flask, fill it up to the gauge line with water, and use this solution as the standard solution. Take 5 mL each of the test solution, the standard solution and water (blank test) in a blank test tube, add 2 mL of acetylacetone solution (prepared before use) in which 2%

acetylacetone is dissolved in 0.5 mol/L sodium bicarbonate solution, mix well and heat on a steam bath for exactly 20 minutes. Cool it with cold water, add 12 mL of anhydrous ethanol and 2 mL of 4-dimethylaminobenzaldehyde TS in order, mix well, warm it on a steam bath at 65 °C - 70 °C for exactly 10 minutes, and then cool. With the test and standard solutions using the blank test solution as a reference, measure the absorbance A_T and A_S at a wavelength of 530 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of glucosamine sulfate } ((C_6H_{13}NO_5)_2 \cdot H_2SO_4) = \text{Amount (mg) of glucosamine sulfate RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in well-closed containers.

Glucose
포도당



$C_6H_{12}O_6$: 180.16

(2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanal [*50-99-7*]

Glucose is *D*-glucopyranose obtained from starch.

Glucose contains NLT 97.5% and NMT 102.0% of glucose [*D*-glucopyranose ($C_6H_{12}O_6$)], calculated on the anhydrous basis.

Description Glucose occurs as white crystals or a crystalline powder. It is odorless and has a sweet taste.
It is freely soluble in water and slightly soluble in ethanol(95).

Identification (1) Determine the infrared spectra of Glucose and glucose RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Perform the test as directed under the Assay; the major peaks obtained from the test solution and the standard solution exhibit same peaks at the same retention time.

Purity (1) ***Clarity and color of solution***—To 10.0 g of Glucose, add 15 mL of water, dissolve by heating on a steam bath, and cool. Use this as the test solution and perform the test as directed under the Turbidity; the solution is clear. Transfer the test solution, the control solution and water into the colorless and transparent glass columns with a flat bottom and an internal diameter of 15 mm to 25 mm to make 40 mm of a liquid layer, and observe from the above using scattered light against a white background; the solutions are not more intense than the control solution.

Control solution—Mix 2.4 mL of iron(III) chloride hexahydrate colorimetric stock solution, 1.0 mL of cobalt(II) chloride hexahydrate colorimetric stock solution, 0.4 mL of copper(II) sulfate pentahydrate colorimetric stock solution and 6.2 mL of diluted hydrochloric acid (1 in 10). To 2.5 mL of this solution, add 97.5 mL of diluted dilute hydrochloric acid (1 in 10).

(2) ***Related substances***—Weigh accurately an amount of Glucose, equivalent to 0.300 g of glucose calculated on the dried basis, dissolve in water to make exactly 10 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 250 mL, and use this solution as the standard solution (1). Pipet 25 mL of this solution, add water to make exactly 200 mL, and use this solution as the standard solution (2). Pipet 20 μL each of the test solution, the standard solution (1) and the standard solution (2) and perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the each peak area as directed in the automatic integration method; the sum of the peak areas of maltose and isomaltose is not greater than the peak area of glucose from standard solution (1) (NMT 0.4%), the peak area of maltotriose is not greater than half of the peak area of glucose from standard solution (1) (NMT 0.2%), and the peak area of fructose is NMT 3 times the peak area of glucose from the standard solution (2) (NMT 0.15%). The peak area of glucose from the test solution and each peak area are NMT 2 times the peak area of glucose from standard solution (2) (NMT 0.1%). Also, the sum of peak areas other than glucose from the test solution is NMT 1.25 times the peak area of glucose from the standard solution (1) (NMT 0.5%). However, peaks having the area NMT the peak area of glucose from standard solution (2) are not included in the calculation (NMT 0.05%).

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed under the test conditions under the Assay.

Time span of measurement: About 1.5 times the retention time of glucose.

System suitability

For system suitability solution and the system performance, proceed as directed under the Assay.

(3) ***Dextrin***—To 1.0 g of Glucose, previously powdered, add 20 mL of ethanol(95), and boil under a reflux condenser; the resulting solution is clear.

(4) ***Soluble starch or sulfite***—Dissolve 6.7 g of Glucose in 15 mL of water by heating on a steam bath. After cooling, add 25 μL of 0.05 mol/L iodine; the resulting solution exhibits a yellow color (NMT 15 ppm as

SO_3)

Conductivity Dissolve 20.0 g of Glucose in freshly boiled and cooled water to make 100 mL, and use it as the test solution. Determine the conductivity of the test solution while gently stirring with the magnetic stirrer; it is NMT 20 $\mu S \cdot cm^{-1}$.

Water NMT 1.0% (0.5 g, volumetric titration, direct titration).

Assay Weigh accurately an amount of Glucose and glucose RS, equivalent to 0.300 g of glucose calculated on the anhydrous basis, dissolve each in water to make exactly 10 mL, and use these solutions as the test solution and the standard solution, respectively. Pipet 20 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of glucose from the test solution and the standard solution, respectively.

Amount (g) of glucose ($C_6H_{12}O_6$)
= Amount (mg) of glucose RS, calculated on the anhydrous basis × (A_T / A_S)

Operating conditions

Detector: A constant-temperature differential refractometer (e.g., at 40 ℃).

Column: A stainless steel column about 7.8 mm in internal diameter and about 30 cm in length, packed with strongly acidic ion exchange resin for liquid chromatography composed of a sulfonated styrene-divinylbenzene copolymer (cross-linking rate: 8%) (Ca form).

Column temperature: 85 ± 1 ℃

Mobile phase: Water

Flow rate: 0.3 mL/min (adjust the flow rate so that the retention time of glucose is about 21 minutes).

System suitability

System performance: Dissolve 5 mg of maltose, 5 mg of maltotriose and 5 mg of fructose in 50 mL of water, and use this solution as the system suitability solution. Perform the test with 20 mL each of the system suitability solution and the standard solution (2); the relative retention times of maltotriose, maltose, isomaltose and fructose to that of glucose is about 0.7, about 0.8, about 0.8 and about 1.3, respectively. Also, the resolution between maltotriose and maltose is NLT 1.3.

Packaging and storage Preserve in tight containers.

Glucose Injection
포도당 주사액

Glucose Injection is an aqueous solution for injection. Glucose Injection contains NLT 95.0% and NMT 105.0% of the labeled amount of glucose ($C_6H_{12}O_6$: 180.16).

Method of preparation Prepare as directed under Injections, with Glucose.
No preservative is added.

Description Glucose Injection occurs as a clear, colorless liquid and has a sweet taste. When the labeled concentration is NLT 40%, it is a clear, colorless to pale yellow liquid.

Identification Take an amount of Glucose Injection equivalent to 0.1 g of glucose according to the labeled amount, add water or concentrate on a steam bath as needed to make 2 mL, and add 2 to 3 drops of this solution to 5 mL of boiling Fehling's TS; a red precipitate is formed.

pH Between 3.5 and 6.5. In the case where the labeled concentration of the injection exceeds 5%, dilute to 5% with water before the test.

Purity ***5-Hydroxymethylfurural***—Take an amount of glucose injection equivalent to 2.5 g of glucose according to the labeled amount, and add water to make exactly 100 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at a wavelength of 284 nm is NMT 0.80.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.50 EU per mL of glucose injection.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

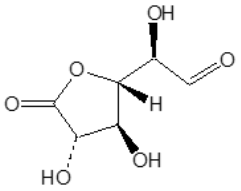
Extractable volume of injections Meets the requirements.

Assay Pipet an amount of glucose injection equivalent to about 4 g of glucose ($C_6H_{12}O_6$), add 0.2 mL of ammonia TS and water to make exactly 100 mL, shake well to mix and allow to stand for 30 minutes, and measure optical rotation α_D at 20 ± 1 ℃ and layer length 100 mm.

Amount (mg) of glucose ($C_6H_{12}O_6$)
= α_D × 1895.4

Packaging and storage Preserve in hermetic containers. Plastic containers for aqueous injections may be used.

Glucuronolactone
글루쿠로노락톤



$C_6H_8O_6$: 176.12
D-Glucuronic acid *γ*-lactone; *D*-Glucofuranurono-6,3-lactone, [*32449-92-6*]

Glucuronolactone, when dried, contains NLT 99.0% and NMT 101.0% of glucuronolactone ($C_6H_8O_6$).

Description Glucuronolactone occurs as odorless, white crystals or crystalline powder, with a bitter taste.
It is freely soluble in water, sparingly soluble in methanol and slightly soluble in ethanol or acetic acid.

Identification (1) Add 2 or 3 drops of boiling Fehling's TS to the 10% aqueous solution of Glucuronolactone; a red precipitate is generated.

(2) Add 1 mL of the orcine-ferric chloride TS to 1 mL of the 10% aqueous solution of Glucuronolactone and heat for 10 minutes on a steam bath; the resulting solution appears green.

Optical rotation $[\alpha]_D^{20}$: Between +19° and +20° (5.19 g as dried, water, 100 mL, 100 mm).

Melting point Between 176 and 178 ℃ (Ethanol recrystalization).

Purity (1) ***Chloride***—Proceed with 1.0 g of Glucuronolactone according to the Chloride and perform the test. Prepare the control solution with 0.12 mL of 0.02 mol/L hydrochloric acid VS (NMT 0.011%).

(2) ***Sulfate***—Proceed with 1.0 g of Glucuronolactone according to the Sulfate and perform the test. Prepare the control solution with 0.15 mL of 0.01 mol/L sulfuric acid VS (NMT 0.015%).

Loss on drying NMT 0.5% (1 g, sulfuric acid desiccator, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Glucuronolactone, previous dried, dissolve in 5 mL of water and cool it in cold water. While shaking it well to mix, add 30.0 mL of 0.1 mol/L sodium hydroxide solution, pass nitrogen gas through it in cold water, and allow it to stand for 30 minutes. Reversely titrate the excess of the sodium hydroxide with 0.05 mol/L sulfuric acid VS (indicator: 3 drops of phenolphthalein TS) The endpoint is reached when the solution turns colorless. At this point, add 3 drops of the indicator again and warm until the solution shows no color. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 17.610 mg of $C_6H_8O_6$

Packaging and storage Preserve in tight containers.

L-Glutamic Acid, L-Alanine and Glycine Capsules
L-글루탐산·L-알라닌·글리신 캡슐

L-Glutamic Acid, L-Alanine and Glycine Capsules contain NLT 90.0% and NMT 130.0% L-glutamic acid ($C_5H_9NO_4$: 147.13), L-alanine ($C_3H_7NO_2$: 89.09) and glycine ($C_2H_5NO_2$: 75.07).

Method of preparation Prepared as directed under Capsules, with L-Glutamic Acid, L-Alanine and Glycine.

Identification Perform the test with the content of NLT 20 L-Glutamic Acid, L-Alanine and Glycine Capsules as directed under the Identification and Assay for Amino Acids.

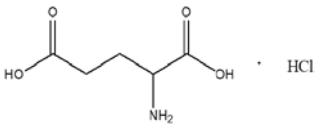
Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 L-Glutamic Acid, L-Alanine and Glycine Capsules and perform the test as directed under the Identification and Assay for Amino Acids.

Packaging and storage Preserve in tight containers.

Glutamic Acid Hydrochloride
글루탐산염산염



$C_5H_9NO_4 \cdot HCl$: 183.59
Glutamic acid hydrochloride, [*138-15-8*]

Glutamic Acid Hydrochloride, when dried, contains NLT 99.0% and NMT 101.0% of glutamic acid hydrochloride ($C_5H_9NO_4 \cdot HCl$: 183.59).

Description Glutamic Acid Hydrochloride occurs as a white, crystalline powder and its aqueous solution is acidic.

Identification (1) Dissolve 1 mL of the aqueous solution (1 in 3) of Glutamic Acid Hydrochloride in 1 mL of barium hydroxide solution (1 in 50), filter, add 10 mL of ethanol(95), and allow to stand; a crystalline precipitate of barium glutamate appears.

(2) Add 1 mL of ninhydrin TS and 0.1 g of sodium acetate to 1 mL of the aqueous solution (1 in 30) of Glutamic Acid Hydrochloride and boil for 10 minutes; the solution appears bluish purple.

Optical rotation $[\alpha]_D^{20}$: Between +23.5° and +25.5° (After drying, 3.125 g, 25 mL of 3 mol/L hydrochloric acid).

Purity (1) ***Sulfate***—Proceed with 0.5 g of Glutamic Acid Hydrochloride according to the Sulfate and perform the test. Prepare the control solution with 1 mL of 0.005 mol/L sulfuric acid VS (NMT 0.096%).

(2) ***Heavy metals***—Proceed with 1.0 g of Glutamic Acid Hydrochloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Loss on drying NMT 0.5% (1 g, 80 °C, 4 hours).

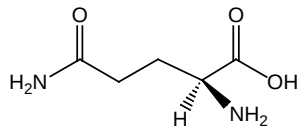
Residue on ignition NMT 0.25% (1 g).

Assay Weigh accurately about 0.2 g of Glutamic Acid Hydrochloride, previously dried, dissolve in 50 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: Bromothymol blue TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 9.180 mg of $C_5H_9NO_4 \cdot HCl$

Packaging and storage Preserve in tight containers.

Glutamine
글루타민



L-glutamine $C_5H_{10}N_2O_3$: 146.15
(*S*)-2,5-Diamino-5-oxopentanoic acid [*56-85-9*]

Glutamine, when dried, contains NLT 99.0% and NMT 101.0% of L-glutamine ($C_5H_{10}N_2O_3$).

Description Glutamine is white crystals or crystalline powder, with a characteristic taste.
It is freely soluble in formic acid, soluble in water, and practically insoluble in ethanol(95).

Identification Perform the test with Glutamine and L-glutamine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +6.3° and +7.3° (Weigh accurately 2 g of Glutamine, previously dried, and dissolve in 45 mL of water by warming at 40 ℃. After cooling, add water to make exactly 50 mL. Use this for measurement at the layer length of 100 mm within 60 minutes.)

pH Dissolve 1.0 g of Glutamine in 50 mL of water; the pH of this solution is between 4.5 and 6.0.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Glutamine in 20 mL of water; the resulting solution is clear and colorless.

(2) ***Chloride***—Perform the test with 0.5 g of Glutamine. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.021%).

(3) ***Sulfate***—Perform the test with 0.6 g of Glutamine. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid VS (NMT 0.028%).

(4) ***Ammonium***—Perform the test with 0.10 g of Glutamine. Use 10.0 mL of ammonium standard solution as the control solution (NMT 0.1%). However, perform the test as directed under the vacuum distillation method and set the water bath temperature to 45 ℃.

(5) ***Heavy metals***—Proceed with 1.0 g of Glutamine according to Method 1 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(6) ***Iron***—Prepare the test solution with 1.0 g of Glutamine according to Method 1 and perform the test according to Method A. Prepare the control solution with 1.0 mL of iron standard solution (NMT 10 ppm).

(7) ***Related substances***—Dissolve 0.10 g of Glutamine in 10 mL of water and use this solution as the test solution. Pipet 1 mL of this solution and add water to make exactly 10 mL. Pipet 1 mL of this solution, add water to make exactly 50 mL, and use this solution as the standard solution. With the solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of 1-butanol, water and acetic acid(100) (3 : 1 : 1) to a distance of about 10 cm, and dry the plate at 80 °C for 30 minutes. Evenly spray a mixture of methanol in ninhydrin, and acetic acid(100) (97 : 3) (1 in 100) to this and heat at 80 ℃ for 10 minutes; the spots other than the principal spot from the test solution are not darker than the spot from the standard solution (NMT 0.2%).

Loss on drying NMT 0.3% (1 g, 105 °C, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.15 g of Glutamine, dissolve in 3 mL of formic acid and 50 mL of acetic acid(100), and titrate with 0.1 mol/L of perchloric acid VS (potentiometric titration method under the Titrimetry). Separately, perform a blank test and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 14.615 mg of $C_5H_{10}N_2O_3$

Packaging and storage Preserve in tight containers.

Glutamine, Cyanocobalamin and DL-Phosphoserine Capsules
글루타민·시아노코발라민·DL-포스포세린 캡슐

Glutamine, Cyanocobalamin and DL-Phosphoserine Capsules contain NLT 90.0% and NMT 130.0% of Glutamine ($C_5H_{10}N_2O_3$: 146.15) and DL-phosphoserine ($C_3H_8NO_6P$: 185.08), and NLT 90.0% and NMT 150.0% of Cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$: 1355.37).

Method of preparation Prepare as directed under Capsules, with Glutamine, Cyanocobalamin and DL-Phosphoserine.

Identification (1) ***Glutamine*—**Weigh the content of Glutamine, Cyanocobalamin and DL-Phosphoserine Capsules to the amount equivalent to 30 mg of glutamine according to the labeled amount, dissolve it in acetic acid(100) to make 20.0 mL, and filter it. Use the filtrate as the test solution. Separately, weigh accurately about 30 mg of glutamine RS, dissolve it in 10 mL of acetic acid(100) and use it as the standard solution. With the solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Then, develop the plate with a mixture of benzene, methanol, acetic acid(100) and acetone (70 : 20 : 5 : 5) to a distance of about 10 cm and air-dry the plate. Spray ninhydrin TS evenly onto the plate; the spots from the test solution and the standard solution are the same in the R_f value and color tone.

(2) ***DL-Phosphoserine*—**Weigh accurately the content of Glutamine, Cyanocobalamin and DL-Phosphoserine Capsules to the amount equivalent to about 30 mg of DL-Phosphoserine according to the labeled amount, mix it with 10 mL of water by shaking well, and filter it. Use the filtrate as the test solution. Separately, weigh accurately about 30 mg of DL-phosphoserine RS, dissolve it in 10 mL of water and use it as the standard solution. With the solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Then, develop the plate with a mixture of ammonia, ethanol and water (125 : 100 : 25) to a distance of about 10 cm and air-dry the plate. Spray ninhydrin TS evenly onto the plate; the spots from the test solution and the standard solution are the same in the R_f value and color.

(3) ***Cyanocobalamin*—**Perform the test with the content of Glutamine, Cyanocobalamin and DL-Phosphoserine Capsules as directed under the Analysis for Vitamins.

Disintegration Meets the requirements.

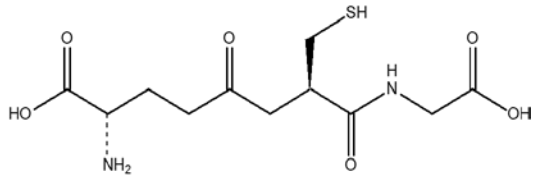
Uniformity of dosage units Meets the requirements.

Assay (1) ***Glutamine and DL-Phosphoserine*—**Weigh accurately the mass of the content of NLT 20 Glutamine, Cyanocobalamin and DL-Phosphoserine Capsules and perform the test as directed under the Identification and Assay for Amino Acids.

(2) ***Cyanocobalamin*—**Weigh accurately the mass of NLT 20 Glutamine, Cyanocobalamin and DL-Phosphoserine Capsules and perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in tight containers.

Glutathione (Reduced)
글루타티온(환원형)



$C_{10}H_{17}O_6N_3S$: 307.32
(2*S*)-2-Amino-4-[1-(carboxymethyl) carbamoyl-(2*R*)-2-sulfanylethylcarbamoyl]butanoic acid [*70-18-8*]

Glutathione (Reduced), when dried, contains NLT 98.0% and NMT 101.0% of glutathione ($C_{10}H_{17}O_6N_3S$).

Description Glutathione (Reduced) occurs as white crystals or a crystalline powder, with a characteristic odor and bitter taste.

Identification (1) Add 1 mL of ninhydrin TS to 5 mL of the aqueous solution (1 in 500) of Glutathione (Reduced) and heat; the solution appears bluish purple.

(2) Dry Glutathione (Reduced) and determine its absorption spectrum as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; it exhibits a maximum and a minimum at the same wavelength as in the RS.

Optical rotation $[\alpha]_D^{20}$: Between -15.5° and -17.5° (after drying, 2.0 g, water, 100 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Glutathione (Reduced) in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Glutathione (Reduced) according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Ammonium***—Proceed with 0.25 g of Glutathione (Reduced) according to the Ammonium and perform the test. Prepare the control solution with 5.0 mL of ammonium standard solution (NMT 0.020%).

(4) ***Sulfate***—Proceed with 0.5 g of Glutathione (Reduced) according to the Sulfate and perform the test. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid VS (NMT 0.50%).

(5) ***Iron***—Place 1.0 g of Glutathione (Reduced) in a separatory funnel and dissolve in 10 mL of diluted hydrochloric acid. Shake 10 mL of each of methyl isobutyl ketone for 3 minutes. Repeat the above procedure 3 times. Take the organic solvent layer, add 10 mL of water to it and shake for 3 minutes. It meets the requirement, when the test is performed with the water layer according to Method A under the Iron (NMT 10 ppm).

(6) ***Arsenic***—Proceed with 2.0 g of Glutathione (Reduced) according to Method 1 under the Arsenic and perform the test (NMT 1 ppm).

(7) ***Related substances***—Weigh accurately 50 mg of Glutathione (Reduced), dissolve in 100 mL of the mobile phase, and use this solution as the test solution. Pipet 2 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operation conditions, and determine the peak area of each solution according to the automatic integration method; the peak area for the test solution with the relative retention time to the glutathione of about 4 is not greater than 3/4 of the peak area of glutathione for the standard solution, and the sum of peak areas other than glutathione for the test solution is not greater than the peak area of glutathione for the standard solution.

Operating conditions

Detector: An Ultraviolet absorption spectrophotometer (wavelength: 210 nm).

Column: A stainless steel column of about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Dissolve 6.8 g of potassium dihydrogen phosphate and 2.02 g of sodium 1-heptanesulfonate in 980 mL of water and add phosphoric acid to adjust the pH to 3.0. Add water to make 1000 mL. To 970 mL of this solution, add 30 mL of methanol.

Flow rate: Adjust the flow rate to ensure that the retention time of glutathione is about 5 minutes.

Time span of measurement: About 6 times the retention time of glutathione after the solvent peak.

System suitability

Test for required detectability: Pipet 10 mL of the standard solution and add the mobile phase to make exactly 100 mL. Confirm that the peak area of glutathione obtained from 10 μL of this solution is equivalent to between 8 and 12% of the peak area of glutathione obtained from 10 μL of the standard solution.

System performance: Dissolve 50 mg of glutathione, 10 mg of D-phenylglycine and 50 mg of ascorbic acid in 100 mL of water, and proceed with 10 μL of this solution according to the above conditions; the ascorbic acid, glutathione and D-phenylglycine peaks are eluted in the mentioned order with the resolution of NLT 5.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak areas of glutathione is NMT 1.5%.

Loss on drying NMT 0.50% (1.0 g, 105 ℃, 3 hours).

Residue on ignition 0.1% (2 g).

Assay Weigh accurately about 0.5 g of Glutathione (Reduced), previously dried, dissolve in 50 mL of water, and titrate with 0.05 mol/L iodine VS (indicator: 3 mL of starch solution TS).

Each mL of 0.05 mol/L iodine VS
= 30.73 mg of $C_{10}H_{17}O_6N_3S$

Packaging and storage Preserve in tight containers.

Glutathione for Injection
주사용 글루타티온

Glutathione for Injection, as an injection that is dissolved upon use, contains NLT 95.0% and NMT 105.0% of glutathione ($C_{10}H_{17}N_3O_6S$: 307.32).

Method of preparation Prepare as directed under Injections, with Glutathione (reduced).

Description Glutathione for Injection occurs as a white, porous solid material.

pH Between 6.0 and 7.5 (2% aqueous solution).

Identification (1) Add 1 mL of ninhydrin TS to 5 mL of the 0.2% aqueous solution of Glutathione for Injection and heat; the solution appears bluish purple.

(2) Add 10 mL of ethanol to Glutathione for Injection that is in the amount equivalent to about 0.1 g of

glutathione, shake for 5 minutes for mixing, and filter it. Wash the residue and container with 5 mL of ethanol 3 times, combine it with the filtrate, carefully evaporate this solution to dryness on a steam bath by passing the nitrogen gas, and dissolve it in 100 mL of water. To 5 mL of this solution, add 10 mL of pH 7.6 phosphate buffer and 10 mL of alloxan solution (1 in 500), mix by occasional shaking, and allow to stand for 10 minutes. Add 10 mL of 1 mol/L sodium hydroxide TS and 15 mL of water to this and determine the absorption spectrum of the solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maximum absorption between 303 nm and 307 nm.

Sterility Meets the requirements.

Bacterial endotoxins Less than 1.5 EU/mg per mg of glutathione.

Particulate contamination: Visible particles in injections and ophthalmic solutions Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately an amount equivalent to about 2.5 mg of glutathione ($C_{10}H_{17}N_3O_6S$) according to the labeled amount of Glutathione for Injection, dissolve it in 0.005 mol/L tetrabutylammonium salt solution (pH 7.0), sonicate to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of glutathione RS and add 60 mL of 0.005 mol/L tetrabutylammonium salt solution (pH 7.0) to make exactly 100 mL. Take 5.0 mL of this solution, add 0.005 mol/L tetrabutylammonium salt solution (pH 7.0) to make exactly 50 mL and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution according to the following conditions under the Liquid Chromatography and determine the peak area, A_T and A_S, of glutathione in each solution.

$$\text{Amount of glutathione } (C_{10}H_{17}N_3O_6S) \text{ (mg)} = \text{Amount of glutathione RS (mg)} \times \frac{A_T}{A_S} \times \frac{1}{20}$$

Operating conditions

Detector: An Ultraviolet absorption spectrophotometer (wavelength: 215 nm).

Column: A stainless steel column of about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: 0.005 mol/L tetrabutylammonium salt solution (pH 7.0).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in well-closed containers.

Glutathione Tablets
글루타티온 정

Glutathione Tablets contain NLT 95.0% and NMT 105.0% of glutathione ($C_{10}H_{17}O_6N_3S$: 307.32).

Method of preparation Prepared as directed under Tablets, with Glutathione (reduced).

Identification (1) Weigh about 0.2 g of glutathione according to the labeled amount of Glutathione Tablets, add 100 mL of water, shake for 5 minutes to mix, and filter it. Add 1 mL of ninhydrin TS to 5 mL of the filtrate and heat; the solution appears bluish purple.

(2) Weigh about 0.1 g of glutathione according to the labeled amount of Glutathione Tablets, add 10 mL of ethanol, shake for 5 minutes to mix, and filter it. Wash the residue and container with 5 mL of ethanol 3 times, combine it with the filtrate, carefully evaporate this solution to dryness on a steam bath by passing the nitrogen gas, and dissolve it in 100 mL of water. To 5 mL of this solution, add 10 mL of phosphate buffer (pH 7.6) and 10 mL of alloxan solution (1 in 500), mix by occasional shaking, and allow to stand for 10 minutes. Add 10 mL of 1 mol/L sodium hydroxide TS and 15 mL of water to this and determine the absorption spectrum of the solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maximum absorption between 303 nm and 307 nm.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Glutathione Tablets and powder it. Weigh accurately the powder to the amount equivalent to about 2.5 mg of glutathione ($C_{10}H_{17}O_6N_3S$), dissolve it in 0.005 mol/L tetrabutylammonium salt solution (pH 7.0), sonicate to 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of glutathione RS, dissolve it in about 60 mL of 0.005 mol/L tetrabutylammonium salt solution (pH 7.0) to make 100 mL, dilute it 10-fold, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution according to the following conditions under the Liquid Chromatography and determine the peak area, A_T and A_S, of glutathione in each solution.

$$\text{Amount (mg) of glutathione } (C_{10}H_{17}O_6N_3S) = \text{Amount (mg) of glutathione RS} \times \frac{A_T}{A_S} \times \frac{1}{20}$$

Operating conditions

Detector: An Ultraviolet absorption spectrophotometer (wavelength: 215 nm).

Column: A stainless steel column of about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: 0.005 mol/L tetrabutylammonium phosphate solution (pH 7.0)

Flow rate: 1.0 mL/min

Packaging and storage Preserve in well-closed containers.

Glycerin
글리세린

Glycerol $C_3H_8O_3$: 92.09
Propane-1,2,3-triol [*56-81-5*]

Glycerin contains NLT 84.0% and NMT 87.0% of glycerol ($C_3H_8O_3$).

Description Glycerin occurs as a colorless, clear and viscous liquid with no odor and has a sweet taste.
It is miscible with water or ethanol.
It is hygroscopic.

Identification Perform the test as directed under the Identification of Concentrated Glycerin.

Refractive index n_D^{20}: Between 1.449 and 1.454.

Specific gravity d_{20}^{20}: Between 1.221 and 1.230.

Purity Perform the test as directed under the Purity of Concentrated Glycerin.

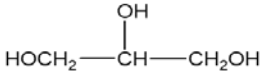
Water Between 13% and 17% (0.1 g, volumetric titration, direct titration).

Residue on ignition Perform the test as directed under the Residue on ignition of Concentrated Glycerin.

Assay Perform the test as directed under the Purity of Concentrated Glycerin.

Packaging and storage Preserve in tight containers.

Concentrated Glycerin
농글리세린



Concentrated Glycerol $C_3H_8O_3$: 92.09

Concentrated Glycerin contains NLT 98.0% and NMT 101.0% of glycerin ($C_3H_8O_3$), calculated on the anhydrous basis.

Description Concentrated Glycerin occurs as a colorless, clear and viscous liquid with a sweet taste.
It is miscible with water or ethanol(95).
It is hygroscopic.

Identification (1) Determine the absorption spectrum of Concentrated Glycerin and glycerin RS as directed under the liquid film method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of glycerin obtained from the test solution in the Purity (10) is the same as that of glycerin obtained from the standard solution.

Refractive index n_D^{20}: NLT 1.470.

Specific gravity d_{20}^{20}: NLT1.258.

Purity (1) ***Color*—**Put 50 mL of this solution into a Nessler tube and observe it from above. The color of the solution is not darker than that of the control solution below.

Control solution—Put 0.40 mL of iron(III) chloride hexahydrate colorimetric stock solution into a Nessler tube and add water to make 50 mL.

(2) ***Acidity or alkalinity*—**Mix 2 mL of Concentrated Glycerin with 8 mL of water. The resulting solution is neutral.

(3) ***Chloride*—**Weigh 10.0 g of Concentrated Glycerin and perform the test. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.001%).

(4) ***Sulfate*—**Weigh 10.0 g of Concentrated Glycerin and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid VS (NMT 0.002%).

(5) ***Ammonium*—**Add 5 mL of sodium hydroxide VS (1 in 10) to 5 mL of Concentrated Glycerin, and boil it. The evolving gas does not change the moistened red litmus paper to blue.

(6) ***Heavy metals*—**Weigh 5.0 g of Concentrated Glycerin and perform the test according to Method 1. Prepare the control solution with 2.5 mL of lead standard solution (NMT 5 ppm).

(7) ***Calcium*—**Add 3 drops of ammonium oxalate TS to 5 mL of the (2) solution; the resulting solution does not change.

(8) ***Arsenic*—**Weigh 1.0 g of Concentrated Glycerin and perform the test according to Method 1 (NMT 2 ppm).

(9) ***Acrolein, glucose or other reducing substances*—**Mix 1.0 g of Concentrated Glycerin with 1 mL of ammonia TS and warmed at 60 °C on a steam bath for 5 minutes; the resulting solution does not exhibit yellow. In

addition, add 3 drops of silver nitrate TS immediately after taking it out of the water bath, and allow to stand in the dark for 5 minutes. The resulting solution does not change color or become turbid.

(10) ***Ethylene glycol and diethylene glycol—***Weigh accurately an appropriate amount of Concentrated Glycerin and the internal standard, dissolve by adding methanol, and prepare a solution containing 50 mg of glycerin and 0.10 mg of the internal standard in 1 mL, Use this solution as the test solution. Separately, weigh appropriate amounts of each of glycerin RS, ethylene glycol RS, diethylene glycol RS and internal standard, dissolve in methanol, and prepare a solution containing 2.0 mg, 0.050 mg, 0.050 mg and 0.10 mg of the respective RS and internal standard in 1 mL. Use these solutions as standard solutions. Measure the peak area of each of the solutions by the automatic integration method with 1.0 μL of the test solution and test solution, respectively. The peak area ratio for the internal standard of diethylene glycol obtained from the test solution is not greater than the peak area ratio for the internal standard of diethylene glycol obtained from the standard solution (0.10%), and the peak area ratio for the internal standard of ethylene glycol obtained from the test solution is not greater than the peak area ratio for the internal standard of ethylene glycol obtained from the standard solution (0.10%).

Internal standard—2,2,2-trichloroethanol

Operating conditions

Detector: Flame ionization detector

Column: Coat the inside of a quartz glass column 0.53 mm in internal diameter and about 30 m in length with 3.0 μm thick cyanopropylphenyl dimethylpolysiloxane for gas chromatography (6:94).

Column temperature: Maintain the temperature at 100 °C for 4 minutes, then raise to 120 °C at a rate of 50 °C per minute, and maintain it for 10 minutes. Raise the temperature again to 220 °C at a rate of 50 °C per minute and maintain it at 220 °C for 6 minutes.

Sample injection port temperature: A constant temperature of about 220 °C.

Detector temperature: A constant temperature of about 250 °C.

Carrier gas: Helium

Flow rate: 4.5 mL/min

Split ratio: About 1:10.

System suitability

System performance: Perform the test under the above conditions with 1 μL of the standard solution; the resolution of diethylene glycol and glycerin is NLT 1.5. The relative retention time is 0.3 for ethylene glycol, 0.6 for 2,2,2-trichloroethanol (95), 0.8 for diethylene glycol and 1.0 for glycerin.

(11) ***Related substance—***Weigh accurately an appropriate amount of Concentrated Glycerin and dissolve in water to make a solution containing 50 mg of glycerin in 1 mL, and use this solution as the test solution. Perform the test according to the Gas Chromatography with 0.5 μL of the test solution under the following conditions, and measure the amount of related substances. The amount of each related substance is NMT 0.1% and the total amount of related substances is NMT 1.0%.

$$\text{Amount of related substances (\%)} = \frac{A_i}{A_S} \times 100$$

A_i: Peak area of each related substance obtained from the test solution (except for solvent and diethylene glycol peaks)

A_S: Sum area of all peaks obtained from the test solution

Operating Conditions

Detector: Flame ionization detector

Column: Coat the inside of a quartz glass column 0.53 mm in internal diameter and about 30 m in length with 3.0 μm thick cyanopropylphenyl dimethylpolysiloxane for gas chromatography (6:94).

Column temperature: Maintain a constant temperature of about 100 °C until injection, raise the temperature at a rate of 7.5 °C per minute until it reaches 220 °C, and keep the temperature for 4 minutes.

Sample injection port temperature: A constant temperature of about 220 °C.

Detector temperature: A constant temperature of about 250 °C.

Carrier gas: Helium

Flow rate: 38 cm/sec

Split ratio: About 1:10.

System suitability

System performance: Weigh accurately appropriate amounts of diethylene glycol RS and glycerin RS and dissolve in water to make a solution containing 0.5 mg of each RS in 1 mL, and use this solution as the system suitability solution. Perform the test with 0.5 μL of this solution under the above conditions; the resolution of diethylene glycol and glycerin is NLT 7.0.

(12) ***Chlorine compounds—***Weigh accurately about 5 g of glycerin, put it in a dry 100 mL round-bottom flask, add 15 mL of morpholine, connect the flask to a reflux condenser, and reflux quietly for 3 hours. Rinse the condenser with 10 mL of water, add the washings to the flask, and carefully acidify it with nitric acid. Put this solution in an appropriate colorimetric tube, add 0.50 mL of silver nitrate TS and water to make 50.0 mL, mix, and use this solution as the test solution. Separately, take 0.20 mL of 0.020 mol/L hydrochloric acid, omit the reflux procedure, proceed in the same manner as the test solution, and use this solution as the control solution. The turbidity of the test solution is not thicker than that of the control solution (NMT 0.003%).

(13) ***Fatty acid or fatty acid ester—***To 50 g of Concentrated Glycerin, exactly add 50 mL of freshly boiled and cooled water and 10 mL of 0.1 mol/L sodium hydroxide VS, boil for 15 minutes, cool, and then titrate the

excess sodium hydroxide with 0.1 mol/L hydrochloric acid. The consumption of 0.1 mol/L sodium hydroxide VS is NMT 3.0 mL (indicator: 3 drops of phenolphthalein TS). Perform a blank test in the same manner.

(14) ***Sulfuric acid for readily carbonizable substances***—Carefully add 5mL of sulfuric acid for readily carbonizable substances test to 5mL of Concentrated Glycerin, mix slowly at 18 – 20 ℃ and allow to stand at ordinary temperature for 1 hour. The color of the solution is not darker than that of the matching fluid H.

Water NMT 2.0% (6 g, volumetric titration, direct titration).

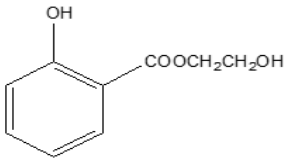
Residue on ignition Weigh accurately about 10 g of Concentrated Glycerin by putting in the crucible, heat to boiling, ignite immediately after boiling, and cool it down. Moisten the residue with 1 - 2 drops of sulfuric acid, and carefully ignite it until it reaches a constant weight. The remaining amount is NMT 0.01%.

Assay Weigh accurately about 0.2 g of Concentrated Glycerin, put it in an Erlenmeyer flask, and add 50 mL of water to mix. Add exactly 50 mL of sodium periodate TS, shake to mix, and allow to stand in a dark place at room temperature for about 30 minutes. Add 10 mL of a mixture of water and ethylene glycol (1:1) to this solution, allow to stand for about 20 minutes, put 100 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 2 drops of phenolphthalein TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 9.209 mg of $C_3H_8O_3$

Packaging and storage Preserve in tight containers.

Glycol Salicylate
살리실산글리콜



$C_9H_{10}O_4$: 182.17
2-Hydroxybenxoic acid 2-hydroxy ethyl ester, [*87-28-5*]

Glycol Salicylate contains NLT 98.5% and NMT 101.0% of glycol salicylate ($C_9H_{10}O_4$), calculated on the anhydrous basis.

Description Glycol Salicylate occurs as a colorless, transparent and viscous liquid.
It is odorless.
It is miscible with methanol, ethanol(95), ether, or chloroform.
It is practically insoluble in water.

Identification (1) Add a drop of Glycol Salicylate to 5 mL of water, shake well to mix for 1 minute, and add a drop of ferric chloride TS; the resulting solution shows a purple color.

(2) Dissolve about 3 drops of Glycol Salicylate in 5 mL of methanol, add 0.5 mL of hydroxylamine TS and 0.4 mL of potassium hydroxide-ethanol TS, and heat on a steam bath until boiling. After cooling, add 0.7 mL of 2 mol/L hydrochloric acid TS to the resulting solution to make it acid, and add a drop of ferric chloride TS; the solution shows a purple color.

(3) Dissolve about 3 drops of Glycol Salicylate in 5 mL of methanol and 0.4 mL of potassium hydroxide-ethanol TS and heat on a steam bath until boiling. After cooling, neutralize it with 0.7 mL of dilute sulfuric acid. Add 10 mL of potassium periodate TS and 1 drop of nitric acid to the resulting solution, shake well to mix, and filter it. Add 1 to 2 drops of silver nitrate TS to the filtrate; a white precipitate is formed immediately.

(4) Determine the absorption spectrum of a solution of Glycol Salicylate in methanol (3 in 250000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 235 nm and 239 nm and between 304 nm and 308 nm.

Refractive index n_D^{20}: Between 1.546 and 1.550.

Specific gravity d_{20}^{20}: Between 1.240 and 1.255.

Purity (1) ***Acidity***—To 5.0 mL of Glycol Salicylate, add 25 mL of freshly boiled and cooled water and 1.0 mL of 0.1 mol/L sodium hydroxide solution, and shake well to mix for 1 minute. Add 2 drops of phenol red TS, and titrate the resulting solution with 0.1 mol/L hydrochloric acid VS until the red color of the solution turns to yellow (NMT 0.45 mL of 0.1 mol/L sodium hydroxide consumed).

(2) ***Heavy metals***—Proceed with 2.0 g of Glycol Salicylate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 0.1 g of Glycol Salicylate in 100 mL of ethanol(95) and use this solution as the test solution. Pipet 1 mL of the resulting solution, add ethanol(95) to make 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate and n-hexane (27 : 20) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Allow the plate to stand for 2 hours in a container full of iodine vapor; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Water NMT 0.20% (5 g).

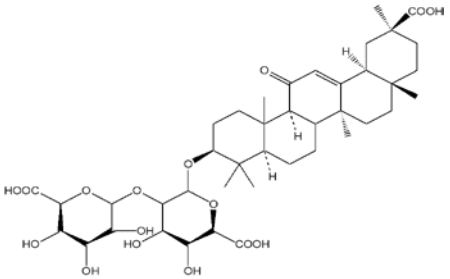
Residue on ignition NMT 0.1% (1.0 g).

Assay Weigh accurately about 2 g of Glycol Salicylate, add 50.0 mL of 0.5 mol/L potassium hydroxide-ethanol, and heat on a steam bath for 90 minutes under a reflux condenser. After cooling, titrate the resulting solution with 0.5 mol/L hydrochloric acid VS (indicator: 3 drops of phenolphthalein TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.5 mol/L potassium hydroxide-ethanol VS
= 91.085 mg of $C_9H_{10}O_4$

Packaging and storage Preserve in tight containers.

Glycyrrhizic Acid
글리시리진산



$C_{42}H_{62}O_{16}$: 822.93
(3β,20β)-20-Carboxy-11-oxo-30-norolean-12-en-3-yl-2-*O*-β-D-glucopyranuronosyl-α-D-glucopyranosiduronic acid, [*1405-86-3*]

Glycyrrhizic Acid, when dried, contains NLT 98.0% and NMT 101.0% of glycyrrhizic acid ($C_{42}H_{62}O_{16}$: 822.93).

Description Glycyrrhizic Acid occurs as a white crystalline or crystalline powder with a sweet taste.
It is practically insoluble in ethanol(95) and practically insoluble in chloroform or ether.

Melting point—Between 219 and 230 °C.

Identification Dissolve 0.2 g of Glycyrrhizic Acid in 5 mL of water and 3 mL of hydrochloric acid, and add 2 to 3 drops of 2,4-dinitrophenylhydrazine TS; an orange or reddish orange precipitate forms upon boiling on a steam bath.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Glycyrrhizic Acid in 10 mL of ethanol(95); the solution appears almost colorless, clear, or slightly yellow.

(2) ***Heavy metals***—Proceed with the residue obtained from the Residue on Ignition and perform the test according to Method 1. Prepare the control solution with 1.0 mL of the lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Glycyrrhizic Acid and perform the test according to Method 4 (NMT 4 ppm).

Loss on drying NMT 6.0% (1 g, 105 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay After drying Glycyrrhizic Acid and glycyrrhizic acid RS under reduced pressure in a vacuum desiccator at 80 ℃ for 15 hours, weigh accurately about 20 mg and dissolve it by 50% to make exactly 100 mL. Pipet 10 mL of this solution, add 50% ethanol to make 25 mL, and use this as the test solution and standard solution. Perform the test using the test solution and the standard solution according to the Ultraviolet-visible Spectroscopy, and measure the absorbance A_T and A_S at a wavelength of 252 nm.

Amount of glycyrrhizic acid ($C_{42}H_{62}O_{16}$) (mg)
= Amount of glycyrrhizic Acid RS (mg) × (A_T / A_S)

Packaging and storage Preserve in tight containers.

Gramicidin
그라미시딘

[*1405-97-6*]

Gramicidin is a mixture of peptide compounds with antibacterial activity, which is obtained by culturing *Bacillus brevis Dubos*.

Gramicidin contains NLT 900 μg (potency) per mg of gramicidin, calculated on the dried basis.

Description Gramicidin occurs as a white to pale yellow crystalline powder.
It is freely soluble in methanol, ethanol(99.5) and practically insoluble in water.

Identification (1) To 10 mg of gramicidin, add 2 mL of 6 mol/L hydrochloric acid TS and heat on a steam bath for 30 minutes while shaking occasionally. After cooling, neutralize with 6 mol/L sodium hydroxide TS, add 1 mL of ninhydrin-acetic acid TS and 0.5 mL of pyridine, and heat for 2 minutes; the resulting solution turns bluish violet to purple.

(2) Determine the absorption spectra of solutions of Gramicidin and gramicidin RS in methanol (1 in 20000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Crystallinity Meets the requirements.

Melting point NLT 229 ℃ (after drying).

Loss on drying NMT 3.0% (0.1 g, in vacuum, 60 ℃, 3

hours).

Ignition residue NMT 1.0% (1 g).

Assay ***Turbidmetry***—(1) Medium: (i) Agar medium for transferring test organisms.

Peptone, casein	5.0 g
Monobasic potassium phosphate	2.0 g
Yeast extract	20.0 g
Polysorbate 80	0.1 g
Glucose	10.0 g
Agar	15.0 g

Weigh the above, mix all the components, add purified water to make 1000 mL, sterilize, and adjust the pH to 6.7 - 6.8.

(ii) Liquid medium for suspending the test organism: Use the culture medium described in (iii) (2) (ii) under the Microbial Assays for Antibiotics.

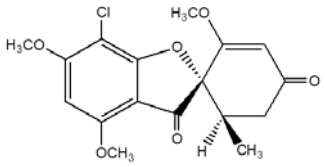
(2) Test organism and preparation of test organism suspension: Use *Enterococcus hirae* ATCC 10541 as the test organism. Stab-culture the test organism in an agar medium made deep enough for transferring the test organism, subculture NLT 3 times at 36.5 - 37.5 ℃ for 20 to 24 hours, and keep at 1 - 5 ℃. Transfer this organism into 10 mL of the liquid medium for suspending the test organism and incubate at 36.5 - 37.5 ° C for 20 to 24 hours, and use this as the stock suspension. Before use, add the liquid medium for suspending the test organism to this stock suspension so that the transmittance becomes 50 - 60% at the wavelength of 580 nm, and to 1 mL of this solution, add 200 mL of the liquid medium for suspending the test organism to prepare the test suspension.

(3) Weigh accurately an appropriate amount of Gramicidin equivalent to about 10 mg (potency) of Gramicidin and dissolve it in ethanol(99.5) to make exactly 100 mL. Take an appropriate amount of this solution and dilute it with a solvent so that each mL contains 0.02 μg (potency), and use this solution as the test solution. Separately, weigh accurately an appropriate amount of gramicidin RS (previously dried at 60 ° C for 3 hours in vacuum at a pressure not exceeding 0.67 kPa), equivalent to about 10 mg (potency) of Gramicidin and dissolve it in ethanol(99.5) to make exactly 100 mL, and use it as the standard stock solution. Keep the standard solution at a temperature not exceeding 5 °C and use it within 30 days. Before use, take a suitable amount of this solution and dilute it with a solvent so that each mL contains 0.02 μg (potency), and use this solution as the standard solution. Take 0.155 mL, 0.125 mL, 0.100 mL, 0.080 mL, 0.065 mL of the standard solution, 0.100 mL of the test solution, and 0.100 mL of the solvent for dilution, put them into test tubes, add 10 mL of the test suspension to each test tube, and stopper the test tubes. Then, incubate them at 37.5 ° C for 180 to 270 minutes and add 0.5 mL of formaldehyde solution (1 in 3) to each test tube. Perform the test according to (C) (6) under the Microbial Assays for Antibiotics. In this case, use the wavelength of 530 nm for measurement.

Diluted solvent—Add 210 mL of a mixture of ethanol(99.5) and acetone (9 : 1) to 390 mL of propylene glycol, and put distilled water to make 1000 mL.

Packaging and storage Preserve in tight containers.

Griseofulvin
그리세오풀빈



$C_{17}H_{17}ClO_6$: 352.77

(1′*S*,6′*R*)-7-Chloro-2',4,6-trimethoxy-6'-methyl-3*H*-spiro[benzofuran-2,1'-cyclohex[2]ene]-3,4'-dione [*126-07-8*]

Griseofulvin is a compound with an antifungal activity, which is obtained by culturing *Penicillium griseofulvum* or *Penicillium janczewskii*.

Griseofulvin contains NLT 960 μg and NMT 1020 μg (potency) of griseofulvin ($C_{17}H_{17}ClO_6$) per mg, calculated on the dried basis.

Description Griseofulvin occurs as white crystals or a crystalline powder.
It is soluble in *N*,*N*-dimethylformamide, sparingly soluble in acetone, slightly soluble in methanol or ethanol(95) and practically insoluble in water.

Identification (1) Determine the absorption spectra of Griseofulvin and griseofulvin RS in ethanol(95) solution (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Griseofulvin and griseofulvin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{25}$: Between +350° and +364° (0.25 g, calculated on the dried basis, 25 mL of *N*,*N*-dimethylformamide, 200 mm).

Melting point Between 218 and 222 ℃.

Purity (1) ***Acid***—Dissolve about 0.25 g of Griseofulvin in 20 mL of neutralized ethanol, and add 2 drops of phenolphthalein TS and 1.0 mL of 0.02 mol/L sodium hydroxide solution; the resulting solution exhibits red.

(2) ***Heavy metal***—Proceed with 1.0 g of Griseoful-

vin according to Method 2 and perform the test. Prepare the control solution with 2.5 mL of lead standard solution (NMT 25 ppm).

(3) ***Arsenic***—Prepare the test solution with 1.0 g of Griseofulvin according to Method 3 and perform the test. (NMT 2 ppm).

(4) ***Petroleum ether soluble body***—Add about 1.0 g of Griseofulvin to 20 mL of petroleum ether, shake to mix, and boil for 10 minutes with a reflux condenser. After cooling, filter with a dry filter paper, wash the filter paper twice with 15 mL of petroleum ether each time, combine the filtrate and the solution used for washing, transfer the combined solution on a steam bath to evaporate petroleum ether, and dry the residue at 105 ° C for 1 hour; the residue is NMT 0.2%.

(5) ***Related substances***—Add exactly 1 mL of internal standard solution to about 0.10 g of Griseofulvin, dissolve in acetone to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately 5.0 mg of griseofulvin RS, add 1 mL of internal standard solution, dissolve in acetone to make 10 mL, and use this solution as the standard solution. Perform the test with 2 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, measure the peak area of each solution according to the automatic integration method, and determine Q_1, which is the ratio of the peak area of dechlorogriseofulvin to that of the internal standard from the test solution, Q_2, which is the ratio of the peak area of dechlorogriseofulvin to that of the internal standard from the standard solution, and Q_S, which is the ratio of the peak area of Griseofulvin to that of the internal standard from the standard solution: Q_1/Q_S is NMT 0.6 (NMT 3.0%) and Q_2/Q_S is NMT 0.15 (NMT 0.75%).

Internal standard solution—9,10-diphenylanthracene solution in acetone (1 in 500).

Operating conditions

Detector: A flame ionization detector

Column: A glass column about 4 mm in internal diameter and about 1 m in length, packed with 25% phenyl - 25% cyanopropylmethyl silicone polymer for gas chromatography coated with 150 μm to 180 μm diatomaceous earth for gas chromatography at a rate of 1%.

Column temperature: A constant temperature of about 250 °C.

Sample injection port temperature: A constant temperature of about 270 °C.

Detector temperature: A constant temperature of about 300 °C.

Carrier gas: Nitrogen

Flow rate: Adjust the flow rate so that the retention time of Griseofulvin is about 10 minutes.

System suitability

Test for required detectability: Take exactly 1 mL of the standard solution and add the acetone solution (1 in 10) of the internal standard solution to make exactly 10 mL. Confirm that the ratio of the peak area of Griseofulvin to that of the internal standard substance obtained from 2 μL of this solution is equivalent to 7 to 13% of the ratio of the peak area of Griseofulvin to that of the internal standard substance obtained from 2 mL of the standard solution.

System performance: Proceed with 2 μL of the standard solution under the above conditions; the internal standard and Griseofulvin are eluted in this order with the resolution between these peaks being NLT 5.

System reproducibility: Repeat the test 6 times with 2 μL each of the standard solutions under the above conditions; the relative standard deviation of the ratio of the peak area of Griseofulvin to that of the internal standard is NMT 5.0%.

Relative retention time: The relative retention times of dechlorogriseofulvin and dehydrogriseofulvin relative to griseofulvin are about 0.6 and 1.2, respectively.

Abnormal toxicity Dissolve 0.1 g of Griseofulvin in 0.5 mL to 1 mL of distilled water and administer orally to 5 healthy mice weighing 17 to 22 g. Use animals in which no abnormalities are observed for NLT 5 days prior to the test. No animal dies during the 48-hour post-dosage observation. If one animal dies, repeat the test with 5 animals; no animal dies during the 24-hour post-dosage observation.

Loss on drying NMT 1.0% (1.0 g, in vacuum at the pressure not exceeding·0.67 kPa, 60 °C, 3 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 50 mg (potency) each of Griseofulvin and griseofulvin RS, dissolve in 50 mL of *N*,*N*-dimethylformamide, add exactly 20 mL of the internal standard solution to each, and add water to make exactly 250 mL. Use these solutions as the test solution and the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak area of Griseofulvin to that of the internal standard, Q_T and Q_S.

$$\text{Potency (μg) of griseofulvin } (C_{17}H_{17}ClO_6) = \text{Potency (μg) of griseofulvin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of butylparaben in acetonitrile (1 in 400).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of

about 25 °C.

Mobile phase: A mixture of water and acetonitrile (3 : 2).

Flow rate: Adjust the flow rate so that the retention time of Griseofulvin is about 6 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution under the above conditions; Griseofulvin and the internal standard are eluted in this order with the resolution between these peaks being NLT 4.

System reproducibility: Repeat the test 6 times with 10 μL of the standard solution under the above conditions; the relative standard deviation of the ratio of the peak area of Griseofulvin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Griseofulvin Tablets
그리세오풀빈 정

Griseofulvin Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of griseofulvin ($C_{17}H_{17}ClO_6$: 352.77).

Method of preparation Prepare as directed under Tablets, with Griseofulvin.

Identification Powder Griseofulvin Tablets, weigh an appropriate amount, equivalent to 15 mg (potency) of griseofulvin, according to the labeled amount, add 100 mL of ethanol(95), vigorously shake to mix, and filter. Add ethanol(95) to 1 mL of the filtrate to make 10 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 250 nm and 254 nm, between 255 nm and 259 nm, and between 261 nm and 265 nm.

Loss on drying NMT 5.0% (0.1 g (as very fine powder), 0.7 kPa, 60 ℃, 3 hours).

Dissolution Perform the test with 1 tablet of Griseofulvin Tablets at 75 revolutions per minute according to Method 2 under the Dissolution using 1000 mL of a solution containing 40.0 mg of sodium lauryl sulfate per mL. Take the dissolved solution after 90 minutes from the start of the test and filter. Discard the first 10 mL of the filtrate, take exactly *V* mL of the subsequent filtrate, add methanol-water (4 : 1) solution to make exactly *V ′* mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of griseofulvin RS, dissolve in the dissolution medium, make it as the same concentration as the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution using the dissolution medium as the control as directed under the Liquid Chromatography and determine absorption A_T and A_S at the absorbance maximum wavelength around 291 nm. It meets the requirements when the dissolution rate in 90 minutes is NLT 75% (Q).

Dissolution rate (%) with respect to the labeled amount of griseofulvin ($C_{17}H_{17}ClO_6$)

$$= Cs \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 100000$$

Cs: Concentration [mg (potency)/mL] of the standard solution

C: Labeled amount [mg (potency)] of griseofulvin ($C_{17}H_{17}ClO_6$) in 1 tablet

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following method. Take 1 tablet of Griseofulvin Tablets, add *V*/5 mL of water to disintegrate using ultrasonic wave, add 50 mL of *N*,*N*-dimethylformamide to 5*V*/8 mL, shake vigorously for 20 minutes, add *N*,*N*-dimethylformamide to make *V* mL of a solution containing exactly 1.25 mg (potency) of griseofulvin in each mL, and centrifuge. Take exactly 8 mL of the supernatant, add exactly 20 mL of the internal standard solution, add water to make 100 mL, and filter through a membrane filter with a pore size of NMT 0.5 μm. Discard the first 5 mL of the filtrate and use the subsequent filtrate as the test solution. Hereinafter, proceed as directed under the Assay.

Amount [mg (potency)] of griseofulvin ($C_{17}H_{17}ClO_6$)

$$= Ws \times \frac{Q_T}{Q_S} \times \frac{V}{32}$$

W_S: Amount [mg (potency)] of Griseofulvin RS

Internal standard solution—A solution of butylparaben in acetonitrile (1 in 2000).

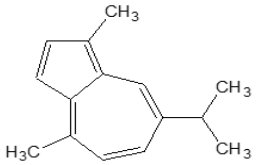
Assay Weigh accurately NLT 20 Griseofulvin Tablets and powder them. Weigh accurately an appropriate amount, equivalent to about 0.5 g (potency) of griseofulvin, according to the labeled potency, add water, sonicate, and add 100 mL of *N*,*N*-dimethylformamide. Then shake the resulting solution vigorously for 20 minutes, add *N*,*N*-dimethylformamide to make exactly 250 mL, and filter. Take exactly 5 mL of this filtrate, add exactly 20 mL of internal standard solution, add water to make exactly 100 mL, and filter through a membrane filter with a pore size of NMT 0.5 μm. Discard the first 5 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 40 mg (potency) of griseofulvin RS and dissolve in *N*,*N*-dimethylformamide to make exactly 20 mL. Take exactly 5 mL of this solution, add exactly 20 mL of the internal standard solution, add water to make exactly 100 mL, and use this solution as the standard solution. Hereinafter, proceed as directed under the Assay of Griseofulvin.

Potency (μg) of griseofulvin ($C_{17}H_{17}ClO_6$)
= Potency (μg) of griseofulvin RS $\times \frac{Q_T}{Q_S} \times \frac{25}{2}$

Internal standard solution—A solution of butylparaben in acetonitrile (1 in 2000).

Packaging and storage Preserve in tight containers.

Guaiazulene
구아야줄렌



$C_{15}H_{18}$: 198.30
1,4-Dimethyl-7-(1-methylethyl)azulene; 7-Isopropyl-1,4-dimethylazulene, [*489-84-9*]

Guaiazulene contains NLT 97.0% and NMT 102.5% of guaiazulene ($C_{15}H_{18}$), calculated on the anhydrous basis.

Description Guaiazulene is dark blue crystals and liquids. It has a slight characteristic odor.
It is freely soluble in ethanol, ether and chloroform, sparingly soluble in petroleum benzene and practically insoluble in water.
It is gradually decomposes by light.

Identification (1) Dissolve about 0.1 g of Guaiazulene in 10 mL of ethanol, add 6 mL of ethanol solution of picric acid (1 in 50) (1 in 50) of picric acid, concentrate by evaporation on a steam bath, and allow to stand. Filter the created bluish purple crystals, wash with a small amount of ethanol, and dry in a desiccator (in vacuum, silica gel) for 2 hours; the melting point is NLT 121 ℃ and NMT 125 ℃ (with decomposition).

(2) Determine the absorption spectrum of petroleum benzene solution of Guaiazulene (1 in 2000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits maximum between 604 nm and 608 nm.

Melting point Between 29 and 32 ℃ (Method 2).

Purity (1) ***Heavy metals***—Proceed with about 1.0 g of Guaiazulene according to Method 2 and perform the test. Add 2.0 mL of lead standard solution in the control solution (NMT 20 ppm).

(2) ***Arsenic***—Prepare the test solution with 1.0 g of Guaiazulene according to Method 3 and perform the test (NMT 2 ppm).

(3) ***Related substances***—Weigh 0.2 g of Guaiazulene, dissolve in ether to make 5.0 mL, and use this solution as the test solution. Proceed with 3 μL of the test solution and perform the test as directed under the Gas Chromatography according to the following conditions, and measure the peak area as directed in the automatic integration method; the sum of peak area other than the solvent and major peak is NMT 2% for the major peak area.

Operating conditions

Detector: A flame-ionization detector (FID)

Column: A stainless steel column with an inside diameter of about 3 mm to 4 mm and a length of about 1.5 m, filled with diatomaceous earth for gas chromatography (177 to 250 μm) coated with 5% polyethylene glycol 6000.

Column temperature: A constant temperature of about 180 °C.

Carrier gas: Nitrogen

Flow rate: Adjust the flow rate of nitrogen so that the peak of Guaiazulene shows about 17 minutes.

Detection sensitivity: Adjust the sensitivity so that the peak height of Guaiazulene chromatogram measured with diluted test solution (1 in 100) is about 1/2 of the total marking of the data collection device.

Water NMT 0.5% (2 g, volumetric titration, direct titration).

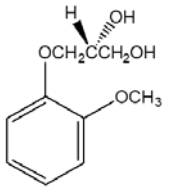
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 20 mg of Guaiazulene, dissolve in ethanol to make 100 mL. Determine the absorbance *A* of this solution at a wavelength 605 nm with ethanol as a contrast as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of guaiazulene ($C_{15}H_{18}$)
$= \frac{A}{22.10} \times 1000$

Packaging and storage Preserve in light-resistant, tight containers.

Guaifenesin
구아이페네신



and enantiomer

Guaiacol Glyceryl Ether $C_{10}H_{14}O_4$: 198.22
(*RS*)-3-(2-Methoxyphenoxy)propane-1,2-diol [*93-14-1*]

Guaifenesin, when dried, contains NLT 98.0% and NMT 102.0% of guaifenesin ($C_{10}H_{14}O_4$).

Description Guaifenesin occurs as white crystals or a crystalline powder.
It is freely soluble in hot water or ethanol(95), soluble in chloroform, sparingly soluble in water and slightly soluble in ether.
Its solution in ethanol(95) (1 in 20) shows no optical rotation.

Identification (1) Pipet 5 mL of Guaifenesin, add 1 mL of formaldehyde solution-sulfuric acid TS; a purple color develops.

(2) Determine the absorption spectra of solutions of Guaifenesin and guaifenesin RS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Guaifenesin and guaifenesin RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 80 and 83 °C.

pH The pH of a solution obtained by dissolving 1.0 g of Guaifenesin in 100 mL of water is between 5.0 and 7.0.

Purity (1) ***Solubilized state***—Dissolve about 0.20 g of Guaifenesin in 10 mL of water; the solution is clear and colorless.

(2) ***Chloride***—Weigh about 0.7 g of Guaifenesin, dissolve in 25 mL of water, and warm the solution. After cooling it down, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid (NMT 0.020%).

(3) ***Heavy metals***—Weigh about 2.0 g of Guaifenesin, dissolve in 25 mL of water, and warm the solution. After cooling it down, add 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Proceed with 1.0 g of Guaifenesin according to Method 3 and perform the test (NMT 2 ppm).

(5) ***Free guaiacol***—Weigh 1.0 g of Guaifenesin, add exactly 25 mL of water, dissolve by waring, and cool. Use this solution as the test solution. Separately, dissolve 0.10 g of guaiacol in water to make exactly 1000 mL. Pipet 3 mL of the solution, add water to make exactly 25 mL, and use this solution as the standard solution. Add 1.0 mL of Potassium hexacyanoferrate trihydrate(III) TS and 5.0 mL of aminoantipyrine VS (1 in 200) respectively and mix by shaking for exactly 5 seconds. Add sodium bicarbonate VS (1 in 1200) to make exactly 100 mL. Determine the absorbances of the test solution and the standard solution at wavelength 500 nm exactly 15 minutes after adding 4-aminoantipyrine VS as directed under the Ultraviolet-visible Spectroscopy, using a solution prepared in the same manner with 25 mL of water as the control solution; the absorbance of the solution obtained from the test solution is not greater than that from the standard solution.

(6) ***Related substances***—Dissolve 1.0 g of Guaifenesin in 100 mL of ethanol(95) and use this solution as the test solution. Pipet 1 mL of the solution, add water to make exactly 200 mL, and use this solution as the standard solution. With the solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test and the standard solutions on a thin-layer chromatographic plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ether, ethanol(95) and ammonia water(28) (40 : 10 : 1) to a distance of about 10 cm and air-dry the plate. Spray evenly 4-dimethylaminobenzaldehyde TS for spray on the plate and heat the plate at 110 ℃ for 10 minutes; the spots other than the main spot from the test solution are not more concentrated than the spot from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, 60 ºC, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 60 mg of Guaifenesin and guaifenesin RS, previously dried, and dissolve by adding water to make exactly 100 mL. Pipet 5 mL of the solution, add water to make exactly 100 mL, and use these solutions as the test and standard solutions. Immediately determine the absorbance, A_T and A_S, of the test solution and the standard solution, at the absorbance maximum wavelength around 273 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount of guaifenesin } (C_{10}H_{14}O_4)\text{ (mg)} = \frac{A_T}{A_S} \times W_S$$

W_S: Amount of guaifenesin RS (mg)

Packaging and storage Preserve in tight containers.

Guaifenesin, Dextromethorphan Hydrobromide and Pseudoephedrine Hydrochloride Syrup
구아이페네신·덱스트로메토르판 브롬화수소산염·슈도에페드린염산염 시럽

Guaifenesin, Dextromethorphan Hydrobromide and Pseudoephedrine Hydrochloride Syrup contains NLT 90.0% and NMT 110.0% of the labeled amount of guaifenesin ($C_{10}H_{14}O_4$: 198.22), dextromethorphan hydrobromide ($C_{18}H_{25}NO \cdot HBr$: 352.31) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$: 201.70).

Method of preparation Prepared as directed under Syrups, with Guaifenesin, Dextromethorphan Hydrobromide and Pseudoephedrine Hydrochloride.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

pH Between 3.5 and 5.5.

Assay With Guaifenesin, Dextromethorphan Hydrobromide and Pseudoephedrine Hydrochloride Syrup, weigh accurately an amount, equivalent to about 100 mg of guaifenesin ($C_{10}H_{14}O_4$) [about 10 mg of dextromethorphan hydrobromide ($C_{18}H_{25}NO \cdot HBr$) and about 30 mg of pseudoephedrine hydrochloride ($C_{10}H_{15}$], add 50% methanol to make exactly 100 mL. Then, sonicate for 5 minutes, pass through a 0.45 μm membrane filter, and use this solution as the test solution. Separately, weigh accurately about 100 mg of guaifenesin RS, about 10 mg of dextromethorphan hydrobromide hydrate RS (previously measure water) and about 30 mg of pseudoephedrine hydrochloride RS, add 50% methanol to make exactly 100 mL, and use this solution as the standard solution. With 10 μL each of the test and standard solution, calculate the peak areas of test and standard solutions A_{T1}, A_{T2}, A_{T3}, A_{S1}, A_{S2} and *AS3 by* performing the test according to the following conditions as directed under the Liquid Chromatography.

Amount (mg) of guaifenesin ($C_{10}H_{14}O_4$)
= Amount (mg) of guaifenesin RS × (A_{T1} / A_{S1})

Amount (mg) of dextromethorphan hydrobromide ($C_{18}H_{25}NO \cdot HBr$) (mg)
= Amount of dextromethorphan hydrobromide RS, calculated on the anhydrous basis (mg) × (A_{T2} / A_{S2})

Amount (mg) of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) (mg)
= Amount (mg) of pseudoephedrine hydrochloride RS (mg) × (A_{T3} / A_{S3})

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in inside diameter and about 15 cm in length, packed with 5 μm of octadecylsilanized silica gel for liquid chromatography.

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Control the gradient by mixing the mobile phases A and B as directed under the following table.

Mobile phase A: Put water into a 1000-mL volumetric flask, add 1 mL of trifluoroacetic acid, and adjust the volume with water.

Mobile B: Put methanol into a 1000-mL volumetric flask, add 1 mL of trifluoroacetic acid, and adjust the volume with methanol.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0.0 - 3.0	95	5
3.0 - 15.0	95 → 30	5 → 70
15.0 - 16.0	30 → 0	70 → 100
16.0 - 16.1	0 → 95	100 → 5
16.1 - 26.0	95	5

Flow rate: 1.0 mL/min

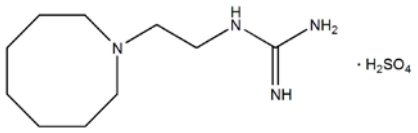
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operation conditions; pseudoephedrine hydrochloride, guaifenesin, and dextromethorphan hydrobromide are eluted in this order with the resolution between the peaks of guaifenesin and dextromethorphan hydrobromide being NLT 9.2.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak area of guaifenesin is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Guanethidine Sulfate
구아네티딘황산염



$C_{10}H_{22}N_4 \cdot H_2SO_4$: 296.39

2-[2-(Azocan-1-yl)ethyl]guanidine;sulfuric acid [*645-43-2*]

Guanethidine Sulfate, when dried, contains NLT 98.5% and NMT 101.0% of guanethidine sulfate ($C_{10}H_{22}N_4 \cdot H_2SO_4$).

Description Guanethidine Sulfate is white crystals or crystalline powder. It is odorless or has a slight characteristic odor and a bitter taste.

It is very soluble in formic acid, freely soluble in water, and practically insoluble in ethanol(95) or ether.

Melting point—Between 251 and 256 °C (a capillary tube in vacuum, decomposition).

Identification (1) Pipet 4 mL of Guanethidine Sulfate aqueous solution (1 in 4000), add 2 mL of 1-naphthol TS, 1 mL of diacetyl TS and 15 mL of water and allow to stand for 30 minutes. The resulting solution exhibits a red color.

(2) Determine the infrared spectra of Guanethidine Sulfate and guanethidine sulfate RS, previously dried, as directed in the potassium bromide disk method under

Mid-infrared Spectroscopy. Both exhibits similar intensities of absorption at the same wavenumbers.

(3) A solution of Guanethidine Sulfate (1 in 10) responds to the Qualitative Analysis for sulfate.

pH Dissolve 1.0 g of Guanethidine Sulfate in 50 mL of water. The pH of the solution is between 4.7 and 5.7.

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Guanethidine Sulfate in 50 mL of water. The resulting solution is clear and colorless.

(2) ***Heavy metals*—**Proceed with 2.0 g of Guanethidine Sulfate according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Methylisothiourea sulfate*—**Dissolve 2.0 g of Guanethidine Sulfate in 80 mL of sodium hydroxide TS and allow to stand for 10 minutes. Then dissolve 60 mL of hydrochloric acid, 2 g of sodium bromide, and water to make 200 mL. To this solution, add 0.70 mL of 1/60 mol/L potassium bromate VS and 2 mL of zinc iodide-starch TS: a blue color is observed.

Loss on drying NMT 0.5% (1 g, 105 °C, 4 hours).

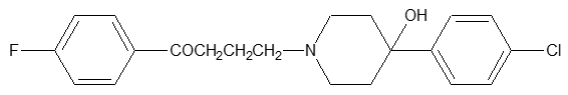
Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.5 g of Guanethidine Sulfate, previously dried, dissolve in 2 mL of formic acid, add 70 mL of a mixture of acetic anhydride and acetic acid(100) (6 : 1), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration, Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid
= 29.639 mg of $C_{10}H_{22}N_4 \cdot H_2SO_4$

Packaging and storage Preserve in light-resistant, tight containers.

Haloperidol
할로페리돌



Haloperidol $C_{21}H_{23}ClFNO_2$: 375.86
4-[4-(4-Chlorophenyl)-4-hydroxy-1-piperidyl]-1-(4-fluorophenyl)-butan-1-one [*151-67-7*]

Haloperidol, when dried, contains NLT 99.0% and NMT 101.0% of haloperidol ($C_{21}H_{23}ClFNO_2$).

Description Haloperidol occurs as white to pale yellow crystals or a powder.
It is freely soluble in acetic acid(100), sparingly soluble in methanol, slightly soluble in 2-propanol or ethanol(99.5), and practically insoluble in water.

Identification (1) Dissolve 30 mg each of Haloperidol and haloperidol RS in 100 mL of 2-propanol. To 5 mL of these solutions, add 10 mL of 0.1 mol/L hydrochloric acid TS and 2-propanol to make 100 mL. Determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy: both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Determine the infrared spectra of Haloperidol and haloperidol RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 149 and 153 °C.

Purity (1) ***Sulfate*—**To 1.0 g of Haloperidol, add 50 mL of water, shake to mix, and filter. To 25 mL of the filtrate, add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid (NMT 0.048%).

(2) ***Heavy metals***—Proceed with 1.0 g of Haloperidol according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve 25 mg of Haloperidol in 50 mL of mobile phase, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the peak area other than haloperidol obtained from the test solution is not greater than 2 times the peak area of haloperidol from the standard solution. However, the peak area with a relative retention time to haloperidol of about 0.5, the peak area with a relative retention time of about 1.2, and the peak area with a relative retention time of about 2.6 are determined by multiplying the area determined as directed in the automatic integration method by correction factors of 0.75, 1.47, and 0.76, respectively.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 2.95 g of sodium citrate hydrate in 900 mL of water, add dilute hydrochloric acid

to adjust the pH to 3.5, and add water to make 1000 mL. To 300 mL of this solution, add 700 mL of methanol, and dissolve in 1.0 g of sodium lauryl sulfate.

Flow rate: Adjust the flow rate so that the retention time of haloperidol is about 9 minutes.

System suitability

Test for required detectability: Weigh exactly 5 mL of the standard solution, and add the mobile phase to make 25 mL. Confirm that the peak area of haloperidol obtained from 10 μL of this solution is equivalent to 15% to 25% of the peak area of haloperidol obtained from the standard solution.

System performance: Proceed with 10 μL of the standard solution under the above conditions; the number of theoretical plates and the symmetry factor of the peak of haloperidol are NLT 4000 and NMT 2.0, respectively.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of haloperidol is NMT 2.0%.

Time span of measurement: A range of about 3 times the retention time of the peak area of haloperidol after the solvent peak.

Loss on drying NMT 0.5% (1 g, in vacuum, 60 ℃, phosphorus pentoxide, 3 hours).

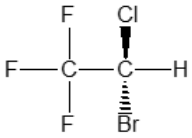
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.6 g of Haloperidol, previously dried, dissolve in 40 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 1 drop of methylrosanilinium chloride TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 37.587 mg of $C_{21}H_{23}ClFNO_2$

Packaging and storage Preserve in light-resistant, tight containers.

Halothane
할로탄



and enantiomer

Halothane $C_2HBrClF_3$: 197.38
2-Bromo-2-chloro-1,1,1-trifluoroethane [*151-67-7*]

Halothane contains NLT 0.008% and NMT 0.012% of Thimerosal as a stabilizer.

Description Halothane occurs as a colorless, clear, and fluid liquid.
It is miscible with ethanol(95), ether or isooctane.
It is slightly soluble in water.
It is volatile, non-flammable, and does not burn when its heated gas is ignited.
It is affected by light.

Refractive index n_D^{20}: Between 1.369 and 1.371.

Identification Transfer 3 μL each of Halothane and halothane RS into a gas cell with the optical path of 10 cm, and determine as directed under the gas sampling method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Specific Gravity d_{20}^{20}: Between 1.872 and 1.877.

Purity (1) ***Acid or alkali***—To 60 mL of Halothane, add 60 mL of freshly boiled and cooled water, shake vigorously for 3 minutes to mix, take the water layer separately, and use this solution as the test solution. To 20 mL of the test solution, add 1 drop of bromocresol purple TS and 0.10 mL of 0.01 mol/L sodium hydroxide TS; the resulting solution exhibits a purple color. Also, to 20 mL of the test solution, add 1 drop of bromocresol purple TS and 0.6 mL of 0.01 mol/L hydrochloric acid; the resulting solution exhibits a yellow color.

(2) ***Halide and halogen***—To 5 mL of the test solution from (1), add 1 drop of nitric acid and 0.20 mL of silver nitrate TS; the resulting solution is not turbid. Also, to 10 mL of the test solution from (1), add 1 mL of potassium iodide TS and 2 drops of starch TS, and allow to stand for 5 minutes; the resulting solution does not exhibit a blue color.

(3) ***Phosgen***—Transfer 50 mL of Halothane to a dried 300-mL Erlenmeyer flask, stopper the flask, lower a phosgene paper strip vertically from the stopper, and suspend the tip 10 mm above the surface of the liquid. Allow to stand in a dark place for 20 to 24 hours; the test paper does not change to yellow.

(4) ***Residue on evaporation***—Take exactly 50 mL of Halothane to evaporate on a steam bath, and dry the residue at 105 ºC for 2 hours; the weight of the residue is NMT 1.0 mg.

(5) ***Volatile related substances***—Take 100 mL of Halothane, add exactly 5.0 μL of internal standard, and use this solution as the test solution. Perform the test with 5 μL of the test solution as directed under the Gas Chromatography according to the following conditions, and determine the peak areas from the respective solutions according to the automatic integration method; the sum of the peak areas other than halothane and the internal standard is not greater than the peak area of the internal standard.

Internal standard—1,1,2-Trichloro-1,2,2-trifluoroethane

Operating conditions

Detector: A flame ionization detector

Column: A column about 3 mm in inside diameter, 3 m in length, packed with diatomaceous earth for gas chromatography (180 μm to 250 μm in particle diameter), coated with polyethylene glycol 400 for gas chromatography at the ratio of 30% in 2 m of the injection site. The remaining 1 m is packed with diatomaceous earth for gas chromatography (180 μm to 250 μm in particle diameter), coated with dinonyl phthalate at the ratio of 30%.

Column temperature: A constant temperature of about 50 °C.

Carrier gas: Nitrogen

Flow rate: Adjust the flow rate so that the retention time of the internal standard is between 2 and 3 minutes.

System suitability

System performance: Mix 3 mL of Halothane with 1 mL of the internal standard. Proceed with 1 μL of this solution under the above conditions; the internal standard and halothane are eluted in this order with the resolution being NLT 10.

Detection sensitivity: Adjust the sensitivity so that the peak height of the internal standard from 5 μL of the test solution is between 30% and 70% of the full scale.

Time span of measurement: About 3 times the retention time of halothane.

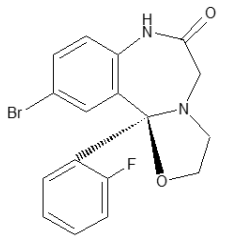
Distilling range Between 49 and 51 ℃ ± 1 ℃, NLT 95 vol%.

Thimerosal content To 0.50 mL of Halothane, add 5.0 mL of isooctane and 5.0 mL of titanium(IV) oxide TS, shake vigorously for 30 seconds to mix, and allow to stand; the color of the upper layer is more intense than the control solution A and not more intense than the control solution B.

Control solution—Dissolve 0.225g of thimerosal RS in isooctane to make exactly 100 mL. Pipet 10 mL each of these solutions, and add isooctane to make 150 mL and 100 mL. Proceed with 0.50 mL each of these solutions in the same manner as Halothane, and use the upper layer as the control solution A, and the control solution B.

Packaging and storage Preserve in light-resistant, tight containers below 30 ℃.

Haloxazolam
할록사졸람



and enantiomer

Haloxazolam $C_{17}H_{14}BrFN_2O_2$: 377.21

10-Bromo-11*b*-(2-fluorophenyl)-2,3,7,11*b*-tetrahydrobenzo[f]oxazolo[3,2-d][1,4]diazepin-6(5*H*)-one [*59128-97-1*]

Haloxazolam, when dried, contains NLT 99.0% and NMT 101.0% of haloxazolam ($C_{17}H_{14}BrFN_2O_2$).

Description Haloxazolam occurs as white crystals or a crystalline powder. It is odorless and tasteless.

It is freely soluble in acetic acid(100), sparingly soluble in acetonitrile, methanol, or anhydrous ethanol, slightly soluble in ether, and practically insoluble in water.

Melting point—About 183 °C (with decomposition).

Identification (1) Dissolve 10 mg of Haloxazolam in 10 mL of methanol, add 1 drop of hydrochloric acid, and examine under ultraviolet light (main wavelength: 365 nm); the resulting solution exhibits a yellowish green fluorescent. To this solution, add 1 mL of sodium hydroxide TS; the fluorescence of the solution immediately disappears.

(2) Weigh 50 mg of Haloxazolam, and burn as directed under the Oxygen Flask Combustion, using a mixture of 20 mL of dilute sodium hydroxide TS and 1 mL of strong hydrogen peroxide water as the absorbent to obtain the test solution. The test solution responds to the Qualitative Analysis for bromide and fluoride.

(3) Determine the absorption spectra of solutions of Haloxazolam and haloxazolam RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared spectra of Haloxazolam and biperiden haloxazolam RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Absorbance $E_{1cm}^{1\%}$ (247 nm): Between 390 and 410 (10 mg, methanol, 1000 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Haloxazolam in 20 mL of anhydrous ethanol; the resulting solution is colorless and clear.

(2) ***Soluble halide***—Take 1.0 g of Haloxazolam,

add 50 mL of water, allow to stand for 1 hour with occasional shaking to mix, and filter. Pipet 25 mL of the filtrate, and add 6 mL of dilute nitric acid and water to make 50 mL. Use this as the test solution and perform the test as directed under Chloride. Prepare the control solution with 0.10 mL of 0.01 mol/L hydrochloric acid (Cl: NMT 0.0071%).

(3) ***Heavy metals***—Proceed with 1.0 g of Haloxazolam according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic***—Transfer 1.0 g of Haloxazolam into a decomposition flask, add 5 mL of nitric acid and 2 mL of sulfuric acid, put a small funnel in on top of the flask, and heat carefully until the white smoke is produced. After cooling, add another 2 mL of nitric acid, and heat. Repeat the procedure 2 times, add 2 mL of strong hydrogen peroxide water several times, and heat until the solution changes to a colorless to pale yellow color. After cooling, add 2 mL of saturated ammonium oxalate solution, and heat again until the white smoke is produced. After cooling, add water to make 5 mL. Use this solution as the test solution and perform the test; it is not more intense than the following reference color (NMT 2 ppm).

Reference color—Proceed in the same manner without using Haloxazolam, add 2.0 mL of arsenic standard solution and water to make 5 mL, and proceed in the same manner as the test with test solution.

(5) ***Related substances***—Dissolve 0.10 g of Haloxazolam in 100 mL of acetonitrile, and use this solution as the test solution. Pipet 1 mL of this solution, add acetonitrile to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas in each solution as directed in the automatic integration method; the sum of peak areas other than the major peak from the test solution is not greater than that of the major peak areas from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 250 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Dissolve 6.2 g of boric acid and 7.5 g of potassium chloride in 900 mL of water, adjust pH to 8.5 with triethylamine, and add water to make 1000 mL. To 3 volumes of this solution, add 2 volumes of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of haloxazolam is about 10 minutes.

System suitability

Test for required detectability: Weigh accurately 5 mL of the standard solution and add the acetonitrile to make exactly 50 mL. Confirm that the peak area of haloxazolam obtained from 10 μL of this solution is equivalent to 8 to 12% of the peak area of haloxazolam obtained from the standard solution.

System performance: Dissolve 10 mg each of Haloxazolam and cloxazolam in 200 mL of acetonitrile. Proceed with 10 μL of this solution according to the above conditions; haloxazolam and cloxazolam are eluted in this order with the resolution being NLT 1.5.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of haloxazolam is NMT 1.0%.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

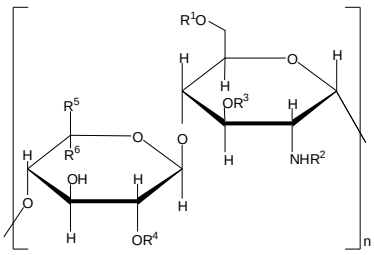
Residue on ignition NMT 0.1% (1 g, platinum crucible).

Assay Weigh accurately about 0.5 g of Haloxazolam, previously dried, and dissolve in 50 mL of acetic acid(100). Titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 37.721 mg of $C_{17}H_{14}BrFN_2O_2$

Packaging and storage Preserve in light-resistant, tight containers.

Heparin Sodium
헤파린나트륨



R^1, R^3, R^4=SO_3Na, or H

R^2=SO_3Na or 

R^5=CO_2Na, R6 = H or R^5 = H, R^6 = CO_2Na

Heparin Sodium

Sodum (3*S*,4*S*,5*R*,6*R*)-6-(((2*R*,3*S*,4*R*,5*R*)-4,6-dihydroxy-5-(sulfonatoamino)-2-((sulfonatooxy)methyl)tetrahydro-2*H*-pyran-3-yl)oxy)-3,4-dihydroxy-5-(sulfonatooxy) tetrahydro-2*H*-pyran-2-carboxylate [*9041-08-1*]

Heparin Sodium is obtained from the liver, lungs, or intestinal mucous membranes of healthy edible animals and has the effect of delaying blood coagulation. Heparin

Sodium is the sodium salt of heparin, composed of sulfated glycosaminoglycans in disaccharide units of D-glucosamine and uronic acid (L-iduronic acid or D-glucuronic acid). Plasma protein antithrombin and heparin cofactor II form a complex that inactivates thrombin (blood coagulation factor IIa), thereby delaying blood coagulation, and also inhibits the activity of other coagulation factors such as activated blood clotting factor X (blood coagulation factor Xa). The ratio of the anticoagulant potency against blood coagulation factor IIa to the anticoagulant potency against blood coagulation factor Xa is between 0.9 and 1.1. Heparin Sodium contains NLT 180 heparin units (international unit) per mg, calculated on the dried basis.

Heparin Sodium should be labeled with the species of animals used as raw materials and the organs involved.

Description Heparin Sodium occurs as a white to grayish brown powder or grain and is odorless.
It is soluble in water and practically insoluble in ethanol(95) or ether.
It is hygroscopic.

Identification (1) Perform the test as directed under the Assay; it meets the requirements.

(2) Dissolve 20 mg each of Heparin Sodium and heparin sodium RS in 0.60 mL of a solution of 3-(trimethylsilyl)propionic acid-d4 sodium salt for nuclear magnetic resonance spectroscopy in deuterium oxide for nuclear magnetic resonance spectroscopy (1 in 10000), and use these solutions as the test solution and the standard solution. Perform the test with the test solution and the standard solution according to the operating conditions in Purity (6) as directed under the Nuclear Magnetic Resonance Spectroscopy (^{1}H), using the 3-(trimethylsilyl)propionic acid-d4 sodium salt for nuclear magnetic resonance spectroscopy as the reference material; the test solution and the standard solution exhibit signals of equal area intensity at δ 2.03 ppm to 2.07 ppm, δ 3.25 ppm to 3.31 ppm, δ 5.20 ppm to 5.26 ppm, and δ 5.39 ppm to 5.45 ppm.

(3) Dissolve 1 mg each of Heparin Sodium and heparin sodium RS in 1 mL of water, and use these solutions as the test solution and the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions; the retention times of major peaks obtained from each solution are the same.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 202 nm).

Column: A stainless steel column, 2.0 mm in internal diameter and 7.5 cm in length, packed with synthetic polymer with diethylaminoethyl groups for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: Dissolve 0.4 g of sodium dihydrogen phosphate dihydrate in 1000 mL of water, and add diluted phosphoric acid (1 in 10) to adjust the pH to 3.0.

Mobile phase B: Dissolve 0.4 g of sodium dihydrogen phosphate dihydrate and 106.4 g of lithium perchlorate in 1000 mL of water, and add diluted phosphoric acid (1 in 10) to adjust the pH to 3.0.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 3	90	10
3 - 15	90 → 0	10 → 100

Flow rate: 0.2 mL/min

System suitability

System performance: Dissolve 0.10 mg of oversulfated chondroitin sulfate RS in 0.20 mL of water, and use this solution as the standard oversulfated chondroitin sulfate solution. Dissolve 1.0 mg of dermatan sulfate in 2.0 mL of water, and use this solution as the standard dermatan sulfate solution. Dissolve 1.0 mg of heparin sodium RS in 0.60 mL of water, and use this solution as the standard heparin sodium solution. Mix 90 μL of standard heparin sodium solution, 30 μL of standard oversulfated chondroitin sulfate solution, and 30 μL of standard dermatan sulfate solution, and use this solution as the system suitability solution. Perform the test with 20 μL of this solution according to the above conditions; dermatan sulfate, heparin, and over-sulfated chondroitin sulfate are eluted in this order, with the resolution between dermatan sulfate and heparin being NLT 1.0 and the resolution between heparin and oversulfated chondroitin sulfate being NLT 1.5.

(4) The ratio of the anticoagulant potency against blood coagulation factor IIa to the anticoagulant potency against blood coagulation factor Xa Anticoagulant potency against blood coagulation factor Xa

(i) Substrate solution: Dissolve *N*-benzoyl-*L*-isoleucyl-*L*-glutamyl (γ-OR)-glycyl-*L*-arginine-*p*-nitroanilide hydrochloride in water to make a 1 mmol/L solution.

(ii) Antithrombin solution: Dissolve human antithrombin III in pH 8.4 buffer solution to make a solution containing 1.0 international units of antithrombin per mL.

(iii) Blood coagulation factor Xa solution: Dissolve bovine blood coagulation factor Xa in pH 8.4 buffer solution. Instead of using a standard solution or a test solution, take 30 mL of pH 8.4 buffer solution, and determine the absorbance at a wavelength of 405 nm according to the Assay to make the absorbance between 0.65 and 1.25.

(iv) pH 8.4 buffer solution: Dissolve 2-amino-2-hydroxymethyl-1,3-propanediol, disodium dihydrogen

ethylenediaminetetraacetate and sodium chloride each in water containing 0.1% polyethylene glycol 6000 to make solutions having 0.050 mol/L, 0.0075 mol/L, and 0.175 mol/L of concentration, respectively. If necessary, add hydrochloric acid or sodium hydroxide solution to adjust the pH to 8.4.

(v) Reaction stop solution: To 20 mL of acetic acid(100), add water to make 100 mL.

(vi) Standard heparin solution: Dissolve heparin sodium RS in an appropriate amount of water, and use this solution as the standard stock solution. Pipet a certain volume of the standard stock solution, and add pH 8.4 buffer solution to make at least 5 solutions with each concentration between 0.03 units and 0.375 units per mL. Prepare at least 2 of each standard solution with the same concentration to use.

(vii) Test solution: Pipet an appropriate amount of Heparin Sodium according to the labeling unit, dissolve in pH 8.4 buffer solution to make the solution with the same concentration as the standard solution, and use this solution as the test solution. Prepare at least 2 of each test solution with the same concentration to use.

(viii) Procedure: Prepare the test tubes on a steam bath at 37 °C to maintain a constant temperature, add 120 μL of pH 8.4 buffer solution to each test tube, and add 30 μL each of the test solution or the standard solution of each concentration, respectively. Add 150 μL each of antithrombin solution, previously warmed at 37°C for 15 minutes, to each test tube, and allow to stand for 2 minutes. Add 300 μL each of blood coagulation factor Xa solution, previously warmed at 37°C for 15 minutes, to each test tube, mix, and allow to stand for 2 minutes. Add 300 μL each of the substrate solution, previously warmed at 37°C for 15 minutes, to each test tube, mix, and allow to stand for 2 minutes. Add 150 μL each of the reaction stop solution to each test tube, and shake each test tube to mix. Separately prepare the control solution by previously adding 150 μL of the reaction stop solution in the test tube and mixing each of the above solutions in the reverse order. Determine the absorbance of the test solution and the standard solution at the wavelength of 405 nm as directed under the Ultraviolet-visible Spectroscopy using the control solution.

(ix) Calculation: Plot log absorbance in the y-axis and plot heparin concentration, calculated on the dried basis, of the standard heparin solution or the test solution in the x-axis to prepare the graph. Calculate the anticoagulant potency against blood coagulation factor Xa of Heparin Sodium according to the following equation. Calculate the ratio (r) of the anticoagulant potency against blood coagulation factor IIa to the anticoagulant potency against blood coagulation factor Xa of Heparin Sodium obtained from the Assay; it is between 0.9 and 1.1.

$$\text{Anticoagulant potency against blood coagulation factor Xa (heparin unit/mg) of Heparin Sodium} = \text{Potency of Heparin sodium RS (heparin unit/mg)} \times \frac{S_T}{S_S}$$

S_T: Slope of the test solution
S_S: Slope of the standard solution

$$r = \frac{\text{Anticoagulant potency (heparin unit/mg) against blood coagulation factor Xa}}{\text{Anticoagulant potency (heparin unit/mg) against blood coagulation factor IIa}}$$

(5) Heparin Sodium responds to the Qualitative Analysis (1) for sodium salt.

pH Dissolve 1.0 g of Heparin Sodium in 100 mL of water; the pH of this solution is between 5.0 and 7.5.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Heparin Sodium in 20 mL of water; the resulting solution is colorless to pale yellow and is clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Heparin Sodium according to Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(3) ***Barium***—Dissolve 30 mg of Heparin Sodium in 3.0 mL of water, and use this solution as the test solution. To 1.0 mL of the test solution, add 3 drops of sulfuric acid, and allow to stand for 10 minutes; the solution does not become turbid.

(4) ***Total nitrogen***—Weigh accurately about 100 mg of Heparin Sodium, previously dried in vacuum at 60 °C for 3 hours, and perform the test according to the Nitrogen Determination; the amount of nitrogen (N : 14.01) is 1.3% to 2.5%.

(5) ***Protein***—Weigh accurately an appropriate amount of Heparin Sodium, dissolve in water to make a solution containing 5 mg per mL, and use this solution as the test solution (prepare 3 identical test solutions, and use these solutions as the test solutions (1), (2) and (3), respectively). Separately, weigh an appropriate amount of bovine serum albumin, dissolve in water to make a solution containing 0.100 mg per mL, take an appropriate amount of this solution, and dilute with water to make at least 5 solutions with each concentration between 0.005 mg and 0.100 mg per mL. Use these solutions as the standard solutions. To 1 mL of each concentration standard solutions, the test solutions (1), (2), (3) and water (blank test solution), add 5 mL each of the reaction solution, and allow to stand at room temperature for 10 minutes. To these solutions, add 0.5 mL each of diluted Folin TS, immediately mix, and allow to stand at room temperature for 30 minutes. Determine the absorption of these solutions at the wavelength of 750 nm as directed under the Ultraviolet-visible Spectroscopy using the blank test solution as the blank, and calculate the protein content of the test solution from the calibration curve created using the absorbance of the standard solution.

Reaction solution—Weigh accurately an appropriate amount of sodium hydroxide, and dissolve in water to make a solution containing 10 g in 1000 mL. Separately,

dissolve sodium carbonate decahydrate in water to make a solution containing 50 g in 1000 mL. Take the same amounts of each 2 solutions, and mix them. Mix 4 volumes of this solution and 1 volume of water, and use this solution as the solution A. Dissolve an appropriate amount of sodium tartrate dihydrate in water to make a solution containing 29.8 g in 1000 mL. Separately, dissolve an appropriate amount of copper(II) sulfate pentahydrate in water to make a solution containing 12.5 g in 1000 mL. Take the same amounts of each 2 solutions, and mix them. Mix 4 volumes of this solution and 1 volume of water, and use this solution as the solution B. Mix 50 volumes of the solution A and 1 volume of the solution B proportionately.

Diluted Folin TS—Add water to the Folin TS to be diluted about 2 to 4 times to make the pH 10.25 ± 0.25 after adding the reaction solution and Folin TS to the test solution and the standard solution in the above procedure.

(6) ***Oversulfated chondroitin sulfate***—(i) Nuclear magnetic resonance spectrum: Dissolve 20 mg each of Heparin Sodium and heparin sodium RS in 0.60 mL of a solution of 3-(trimethylsilyl)propionic acid-d4 sodium salt for nuclear magnetic resonance spectroscopy in deuterium oxide for nuclear magnetic resonance spectroscopy (1 in 10000), and use these solutions as the test solution and the standard solution. Perform the test with the test solution and the standard solution as directed under the Nuclear Magnetic Resonance Spectroscopy (^{1}H) according to the following conditions, using the 3-(trimethylsilyl)propionic acid-d4 sodium salt for nuclear magnetic resonance spectroscopy as the reference material; it exhibits no signal of over-sulfated chondroitin sulfate at δ 2.13 ppm to 2.17 ppm (it exhibits the hydrogen signal of the *N*-acetyl group of oversulfated chondroitin sulfate at δ 2.13 ppm to 2.17 ppm).

Operating conditions

Device: ^{1}H-pulse Fourier transform nuclear magnetic resonance spectrum measurement device.

Device frequency: NLT 400 MHz

Measurement temperature: 25 ℃

Spectrum Range: ± 6.0 ppm focusing on the signal of DHO.

Pulse angle: 90°

Pulse repetition time: 20 seconds

Number of repetitions: 4 times

Signal-to-noise ratio: NLT 1000 at the hydrogen signal (around 2 ppm) of the *N*-acetyl group of heparin.

Window function: Exponential function (linewidth broadening factor = 0.2 Hz).

System suitability

Dissolve 0.10 mg of oversulfated chondroitin sulfate RS in 1.0 mL of a solution of 3-(trimethylsilyl)propionic acid-d4 sodium salt for nuclear magnetic resonance spectroscopy in deuterium oxide for nuclear magnetic resonance spectroscopy (1 in 10000), and use this solution as the oversulfated chondroitin sulfate standard solution. Separately, dissolve 20 mg of heparin sodium RS in 0.40 mL of deuterium oxide for nuclear magnetic resonance spectroscopy solution, add 0.20 mL of oversulfated chondroitin sulfate standard solution to the solution, and use this solution as the system suitability solution. Perform the test with this solution according to the above conditions; it exhibits the signal of the *N*-acetyl group of heparin at δ 2.02 ppm to 2.06 ppm, and the signal of the *N*-acetyl group of oversulfated chondroitin sulfate at δ 2.13 ppm to 2.17 ppm.

(ii) Liquid Chromatography: Perform the test according to the Identification (3); it exhibits no oversulfated chondroitin sulfate peak.

(7) ***Galactosamine***—Weigh accurately about 2.4 mg of Heparin Sodium, dissolve in 1.0 mL of diluted hydrochloric (5 in 12), and use this solution as the test stock solution. Separately, weigh accurately 8.0 mg each of *D*-glucosamine hydrochloride and *D*-galactosamine hydrochloride, dissolve in diluted hydrochloric acid (5 in 12) to make exactly 10 mL, and use these solutions as standard glucosamine solution and galactosamine standard solution, respectively. To 99 volumes of standard glucosamine solution, add 1 volume of galactosamine standard solution, and use this solution as the standard stock solution. Transfer 500 μL each of the test stock solution and the standard stock solution into two stoppered test tubes, close the stopper, and heat at 100 ℃ for 6 hours. Cool this solution to room temperature, take 100 μL each, and dry in vacuum. To each residue, add 50 μL each of methanol, dry in vacuum at room temperature, and dissolve each residue in 10 μL of water. To each of the solutions, add 40 μL each of aminobenzoic acid derivatization TS, mix well, and heat at 80 ℃ for 1 hour. Cool these solutions to room temperature, and dry in vacuum. To each residue, add 200 μL each of water and ethyl acetate, shake vigorously, and centrifuge for 1 minute. After removing the upper layer, to each lower layer, add 200 μL each of ethyl acetate, shake vigorously, and centrifuge for 1 minute. Use the obtained lower layers as the test solution and the standard solution, respectively. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions; The ratio of the peak area of glucosamine to the peak area of galactosamine in the test solution is not greater than the ratio of the peak area of glucosamine to the peak area of galactosamine in the standard solution.

Operating conditions

Detector: A fluorometer (excitation wavelength: 305 nm, fluorescence wavelength: 360 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 45 ℃.

Mobile phase: To a mixture of water and trifluoroa-

cetic acid (1000 : 1), add 100 mL of acetonitrile. To 140 mL of this solution, add 860 mL of a mixture of water and trifluoroacetic acid (1000 : 1).

Flow rate: 1.0 mL/min

System suitability

Test for required detectability: Dissolve 8.0 mg of D-mannosamine hydrochloride in 10 mL of diluted hydrochloric acid (5 in 12), and use this solution as the standard mannosamine solution. Transfer 500 μL of a mixture of the standard stock solution and the standard mannosamine solution (100 : 1) into a stoppered test tube, close the stopper, heat at 100 ℃ for 6 hours, and cool to room temperature. Take 100 μL of this solution, and dry in vacuum. To the residue, add 50 μL of methanol, dry in vacuum at room temperature, dissolve the residue in 10 μL of water, and mix with 40 μL of aminobenzoic acid derivatization TS. Heat this solution at 80 ℃ for 1 hour, cool to room temperature, and dry in vacuum. To the residue, add 200 μL each of water and ethyl acetate, shake vigorously, and centrifuge for 1 minute. After removing the upper layer, take the lower layer, add 200 μL of ethyl acetate, shake vigorously, and centrifuge for 1 minute. Use the obtained lower layer as the system suitability solution. Proceed with 5 μL of this solution according to the above conditions; confirm that the ratio of the peak area of glucosamine to the peak area of galactosamine is between 0.7% and 2.0%.

System performance: Perform the test with 5 μL of the system suitability solution according to the above conditions; glucosamine, mannoseamine, and galactosamine are eluted in this order, and the resolution between glucosamine and mannoseamine, and between mannoseamine and galactosamine, is NLT 1.5, respectively.

System repeatability: Repeat the test 6 times with 5 μL each of the system suitability solutions according to the above conditions, the relative standard deviation of peak area ratios of galactosamine to glucosamine is NMT 4.0%.

Time span of measurement: 50 minutes

(8) ***Hexane related substances***—Weigh accurately 40 mg of Heparin Sodium, dissolve in 10 mL of water, and perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at the wavelength of 260 nm is NMT 0.20.

Loss on drying NMT 5.0% (in vacuum, 60 ℃, 3 hours).

Residue on ignition Between 28.0% and 41.0% (20 mg after drying).

Bacterial endotoxins Less than 0.03 EU per heparin unit of Heparin Sodium.

Sterility It meets the requirements when used in the manufacturing of sterile preparations.

Assay ***Anticoagulant potency against blood coagulation factor IIa***—(i) Substrate solution: Dissolve *D*-phenylalanyl-*L*-pipecolinic-*L*-arginine-*p*-nitroanilide dihydrochloride in water to make a 1.25 mmol/L solution.

(ii) Antithrombin solution: Dissolve human antithrombin III in an appropriate amount of water to make a solution containing 5 international units of antithrombin per mL, take a certain amount of this solution, and dissolve in pH 8.4 buffer solution to make a solution containing 0.125 international units of antithrombin per mL.

(iii) Human antithrombin solution: To human antithrombin (blood coagulation factor IIa), add water to make a solution containing 20 international units of thrombin per mL, take a certain amount of this solution, and dilute in pH 8.4 buffer solution to make a solution containing 5 international units of thrombin per mL. Use this solution as the human antithrombin solution.

(iv) pH 8.4 buffer solution: Weigh 6.10 g of 2-amino-2-hydroxymethyl-1,3-propanediol, 2.80 g of disodium dihydrogen ethylenediaminetetraacetate, 10.20 g of sodium chloride, and NMT 10.00 g of polyethylene glycol 6000 and (or) 2.00 g of bovine serum albumin, dissolve in 800 mL of water, adjust the pH to 8.4 with hydrochloric acid, and add water to make 1000 mL.

(v) Reaction stop solution: Add water to 20 mL of acetic acid(100) to make 100 mL.

(vi) Standard heparin solution: Dissolve heparin sodium RS in an appropriate amount of water, and use this solution as the standard stock solution. Pipet a certain volume of the standard stock solution, and add pH 8.4 buffer solution to make at least 4 solutions with each concentration between 0.005 units to 0.03 units per mL. Use these solutions as the standard solutions. Prepare NLT 2 of each standard solution with the same concentration.

(vii) Test solution: Take an appropriate amount of Heparin Sodium according to the labeling unit, dissolve in pH 8.4 buffer solution to make the solution with the same concentration as the standard solution, and use this solution as the test solution. Prepare NLT 2 of each test solution with the same concentration.

(viii) Procedure: Prepare test tubes on a steam bath at 37°C to maintain a constant temperature. Transfer each of a certain amount (50 μL to 100 μL) of pH 8.4 buffer solution (blank test solution), previously warmed at 37 ℃ to maintain the constant temperature, test solutions of each concentration, and standard solutions into each test tube. To each solution, add 2 times the above volume (100 μL to 200 μL) of antithrombin, previously warmed at 37 ℃, carefully mix the solutions to prevent foaming, and allow to stand at 37 ℃ for at least 1 minute. Add 25 μL to 50 μL each of human thrombin solutions, previously warmed at 37 ℃, and allow to stand for at least 1 minute. To each solution, add 50 μL to 100 μL of substrate solution, previously warmed at 37 ℃, mix, and allow to stand for at least 1 minute. Add 50 μL to 100 μL of the reaction stop solution, shake each test tube to mix, and complete the test after at least 1 minute. With these solutions, determine the absorbance of the test solution and the standard solution at the wavelength of 405 nm as directed under the Ultraviolet-visible Spectroscopy using

the blank test solution as the control solution. However, prepare an appropriate amount of blank test solutions and measure just before measuring the absorbance of each test solution and standard solution in the dilutions, and the relative standard deviation of the measured values for the blank test solution at this point is NMT 10%.

(ix) Calculation: Plot log absorbance in the y-axis and plot heparin concentration, calculated on the dried basis, of the standard heparin solution or the test solution in the x-axis to prepare the graph. Calculate the heparin unit (international unit) per mg of Heparin Sodium according to the following equation.

$$\text{Heparin unit in each mg of Heparin Sodium} = \text{Potency (heparin unit/mg) of heparin sodium RS} \times \frac{S_T}{S_S}$$

S_T: Slope of the test solution
S_S: Slope of the standard solution

Packaging and storage Preserve in tight containers.

Heparin Sodium Injection
헤파린나트륨 주사액

Heparin Sodium Injection, as an aqueous injection, contains NLT 90.0% and NMT 110.0% of the labeled heparin unit.

Heparin Sodium Injection is labeled to indicate the animal species and organ from which Heparin Sodium used for manufacturing is derived.

Method of preparation Prepare as directed under Injections, with a solution of Heparin Sodium dissolved in Isotonic Sodium Chloride Injection.

Description Heparin Sodium Injection occurs as colorless to pale yellow, clear liquid.

pH Between 5.5 and 8.0.

Purity (1) ***Barium***—Measure exactly a volume of Heparin Sodium Injection, equivalent to 3000 units of Heparin Sodium according to the labeled unit. Add water to make 3.0 mL and use this solution as the test solution. To 1.0 mL of the test solution, add 3 drops of dilute sulfuric acid and allow to stand for 10 minutes: no turbidity is produced.

(2) ***Protein***—Perform the test as directed under the Purity (5) under Heparin Sodium.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.0030 EU per heparin unit of Heparin Sodium Injection.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Perform the test as directed under the Assay under Heparin sodium. For (vii) Test solution and (ix) Calculation, proceed as below:

(vii) Test solution*:* Pipet Heparin Sodium Injection in a suitable quantity according to the labeling unit, add pH 8.4 buffer solution to make a solution having the same concentration as the standard stock solution, and use this solution as the test stock solution. Pipet suitable quantities of this solution, add pH 8.4 buffer solution to each, dilute in the same manner as its respective standard solution, and use each as the respective test solution. Prepare at least 2 test solutions having the same concentration for use.

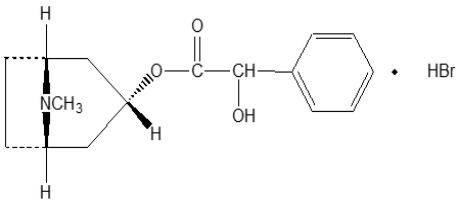
(ix) Calculation: Prepare a graph having the x axis for the log absorbance and the y axis for the concentration of heparin, calculated on the dried basis, contained in each standard heparin solution or test solution, for each solution. Determine the heparin unit (international unit) contained in 1 mL of Heparin Sodium Injection according to the following formula:

$$\text{Heparin unit contained in 1 mL of Heparin Sodium Injection} = \text{Concentration (heparin unit/mL) of the standard stock solution} \times \frac{S_T}{S_S} \times \frac{b}{a}$$

S_T: Gradient of the test solution
S_S: Slope of the standard solution
a: Amount (mL) of Heparin Sodium Injection taken
b: Total volume (mL) when the test stock solution was prepared

Packaging and storage Preserve in light-resistant, hermetic containers.

Homatropine Hydrobromide
호마트로핀브롬화수소산염



$C_{16}H_{21}NO_3 \cdot HBr$: 356.26
(1*R*,3*R*,5*S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-

hydroxy-2-phenylacetate hydrobromide [*51-56-9*]

Homatropine Hydrobromide contains NLT 99.0% and NMT 101.0% of homatropine hydrobromide ($C_{16}H_{21}NO_3 \cdot HBr$), calculated on the dried basis.

Description Homatropine Hydrobromide occurs as white crystals or a crystalline powder. It is odorless.
It is freely soluble in water, sparingly soluble in ethanol(95), slightly soluble in acetic anhydride, and practically insoluble in ether.
It is affected by light.

Melting point—About 214 °C (with decomposition).

Identification (1) Determine the infrared spectra of Homatropine Hydrobromide and homatropine hydrobromide RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Homatropine Hydrobromide (1 in 20) responds to the Qualitative Analysis for bromide.

pH Dissolve 1.0 g of Homatropine Hydrobromide in 50 mL of water; the pH of this solution is between 5.7 and 7.0.

Purity (1) ***Acid***—Dissolve 1.0 g of Homatropine Hydrobromide in 20 mL of water, and add 0.40 mL of 0.01 mol/L sodium hydroxide TS and 1 drop of methyl red-methylene blue TS; the resulting solution exhibits a green color.

(2) ***Atropine, hyoscyamine, or scopolamine***—To 10 mg of Homatropine Hydrobromide, add 5 drops of nitric acid, and evaporate to dryness on a steam bath. After cooling, dissolve the residue in 1 mL of *N*,*N*-dimethylformamide, and add 5 to 6 drops of tetrabutylammonium hydroxide TS; the resulting solution does not exhibit a purple color.

(3) ***Other alkaloid***—Dissolve 0.15 g of Homatropine Hydrobromide in 3 mL of water, and use this solution as the test solution.

(i) To 1 mL of the test solution, add 2 to 3 drops of tannic acid TS; a precipitate does not form.

(ii) To 1 mL of the test solution, add 2 to 3 drops each of dilute hydrochloric acid and hexachloroplatinic(IV) acid TS; a precipitate does not form.

Loss on drying NMT 1.5% (0.5 g, 105 ℃, 2 hours).

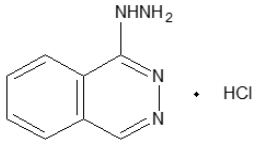
Residue on ignition NMT 0.2% (0.2 g).

Assay Weigh accurately about 0.4 g of Homatropine Hydrobromide, and dissolve in 60 mL of a mixture of acetic anhydride and acetic acid(100)(7:3) by warming. After cooling, titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 35.626 mg of $C_{16}H_{21}NO_3 \cdot HBr$

Packaging and storage Preserve in light-resistant, tight containers.

Hydralazine Hydrochloride
히드랄라진염산염



$C_8H_8N_4 \cdot HCl$: 196.64
1-Hydrazinylphthalazine hydrochloride [*304-20-1*]

Hydralazine Hydrochloride, when dried, contains NLT 98.0% and NMT 101.0% of hydralazine hydrochloride ($C_8H_8N_4 \cdot HCl$).

Description Hydralazine Hydrochloride occurs as a white crystalline powder, which is odorless and has a bitter taste.
It is soluble in water, slightly solution in ethanol(95) and practically insoluble in ether.

Melting point—About 275 °C (with decomposition).

Identification (1) Determine the absorption spectra of aqueous solutions of Hydralazine Hydrochloride and hydralazine hydrochloride RS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Hydralazine Hydrochloride and hydralazine hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Hydralazine Hydrochloride (1 in 50) responds to the Qualitative Analysis for chloride.

pH Dissolve 1.0 g of Hydralazine Hydrochloride in 50 mL of water; the pH of this solution is between 3.5 and 4.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Hydralazine Hydrochloride in 50 mL of water; the resulting solution is clear, and colorless to pale yellow.

(2) ***Heavy metals***—Proceed with 1.0 g of Hydralazine Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Weigh accurately about 25

mg of Hydralazine Hydrochloride, add 30 mL of 0.1 mol/L acetic acid, sonicate to dissolve, cool it, and add 0.1 mol/L acetic acid to make 50 mL. Use this solution as the test solution. Perform the test with 20 μL of the test solution as directed under the Liquid Chromatography according to the following operating conditions. Determine the area of each peak other than solvent as directed in the automatic integration method and calculate each amount as directed under the percentage peak area method; the total amount of related substances is NMT 1.0%.

$$\text{Content (\%) of each related substance} = 100 \times \frac{A_\text{i}}{A_\text{S}}$$

A_i: Peak area of each related substance obtained from the test solution

A_S: Total area of all peaks other than the solvent peak from the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4 mm in internal diameter and 25 cm in length, packed with cyanopropylsilyl silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: Dissolve 1.44 g of sodium dodecyl sulfate and 0.75 g of tetra n-butylammonium bromide in 770 mL of water and add 230 mL of acetonitrile. To this solution, add 0.1 mol/L sulfuric acid to adjust the pH to 3.0.

Flow rate: About 1 mL/min.

System suitability

System performance: Dissolve 25 mg of hydralazine hydrochloride RS and 5 mg of phthalazine in 100 mL of 0.1 mol/L acetic acid. Pipet 5 mL of this solution, add 0.1 mol/L acetic acid to make 50 mL, and use it as the system suitability solution. Proceed the system suitability solution according to the above operating conditions; the relative retention time of phthalazine with respect to hydralazine hydrochloride is about 0.65 with the resolution between these peaks being NLT 4.0.

(4) ***Hydrazine***—Weigh accurately about 20 mg of Hydralazine Hydrochloride, dissolve in 1.0 mL of water, add 4 mL of benzaldehyde solution, and shake for 20 minutes with a suitable instrument. Pipet 2.0 mL of this solution and pass through the solid-phase extraction (SPE) column to put into a 5 mL volumetric flask. Wash the column twice with 1.5 mL of a mixture of water and acetonitrile (3 : 7), add the washings to the effluent, add a mixture of water and acetonitrile (3 : 7) to make 5 mL, and use this solution as the test solution. Separately, weigh accurately about 65 mg of hydrazine dihydrochloride and add water to make 100 mL. To 1 mL of this solution, add water to make 100 mL. To 1 mL of this solution, add water again to make 20 mL. Pipet 1.0 mL of this solution, add 4 mL of benzaldehyde solution, and shake for 20 minutes with a suitable instrument. Pipet 2.0 mL of this solution, add a mixture of water and acetonitrile (3 : 7) to make 5 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas from the solutions as directed in the automatic integration method to obtain the peak areas of hydrazine, A_T and A_S.

$$\text{Amount (ppm) of hydrazine} = 1000 \times \frac{32.05}{104.97} \times \frac{C_\text{S}}{C_\text{T}} \times \frac{A_\text{T}}{A_\text{S}}$$

32.05: Molecular weight of hydrazine

104.97: Molecular weight of hydrazine dihydrochloride

C_S: Concentration (μg/mL) of hydrazine dihydrochloride $(NH_2)_2 \cdot 2HCl$ in the standard solution

C_T: Concentration (mg/mL) of hydralazine hydrochloride in the test solution

A_T: Peak area of hydrazine obtained from the test solution

A_S: Peak area of hydrazine obtained from the standard solution

Benzaldehyde solution—Pipet 1.0 mL of benzaldehyde and dilute in a mixture of methanol and water (9 : 1) to make 100 mL.

Solid-phase extraction (SPE) column—Fill the column with a benzenesulfonic acid-based strong acidic cation exchange cartridge having the ratio of absorbent mass to column volume of 0.5 g/3 mL or equivalent. Wash the column twice with 2.0 mL of hexane in advance, immediately dry in vacuum for 2 minutes, then wash twice each with 2.0 mL of methanol, 2.0 mL of water, and 2.0 mL of phosphate buffer solution (pH 7.0) before use.

Phosphate buffer solution (pH 7.0)—Dissolve 5.82 g of sodium hydrogen phosphate and 3.81 g of potassium dihydrogen phosphate in 1000 mL of water, and adjust to the pH to 7.0±0.1 with 1 mol/L sodium hydroxide solution or 1 mol/L phosphoric acid.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 310 nm).

Column: A stainless steel column about 4 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: Dissolve 0.3 g of ethylenediaminetetraacetic acid disodium salt dihydrate in 300 mL of water and add acetonitrile to make 1000 mL.

Flow rate: About 1.0 mL/min.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above operating condi-

tions; the relative retention time of hydrazine derivative with respect to hydralazine derivative is about 1.5.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation is NMT 2.0%.

Loss on drying NMT 0.5% (0.5 g, in vacuum, phosphorus pentoxide, 8 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.15 g of Hydralazine Hydrochloride, previously dried, place in a stoppered flask, and dissolve in 25 mL of water. Add 25 mL of hydrochloric acid, cool to room temperature, add 5 mL of chloroform, shake to mix, and titrate with 0.05 mol/L potassium iodate VS until the purple color of the chloroform layer disappears. The endpoint is when the purple color of the chloroform layer does not reappear within 5 minutes after it is decolorized.

Each mL of 0.05 mol/L potassium iodate VS
= 9.832 mg of $C_8H_8N_4 \cdot HCl$

Packaging and storage Preserve in tight containers.

Hydralazine Hydrochloride for Injection
주사용 히드랄라진염산염

Hydralazine Hydrochloride for Injection is a preparation for injection which is reconstituted before use. Hydralazine Hydrochloride contains NLT 99.0% and NMT 113.0% of the labeled amount of hydralazine hydrochloride ($C_8H_8N_4 \cdot HCl$: 196.64).

Method of preparation Prepare as directed under Injections, with Hydralazine Hydrochloride.

Description Hydralazine Hydrochloride for Injection occurs as a white to pale yellow powder or a mass. It is odorless and has a bitter taste.

Identification Determine the absorption spectrum of an aqueous solution of Hydralazine Hydrochloride for Injection (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima at the wavelengths of 238 nm to 242 nm, 258 nm to 262 nm, 301 nm to 305 nm and 313 nm to 317 nm.

pH Dissolve 1.0 g of Hydralazine Hydrochloride for Injection in 50 mL of water; the pH of the solution is 3.5 to 4.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 5.0 EU per mg of hydralazine hydrochloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements of the mass variation test.

Assay Take NLT 10 samples of Hydralazine Hydrochloride for Injection and weigh accurately the mass. Weigh accurately about 0.15 g of Hydralazine Hydrochloride for Injection, place in a stoppered flask, dissolve in 25 mL of water, and add 25 mL of hydrochloric acid. Cool to the room temperature, add 5 mL of chloroform, and shake to mix. While mixing, titrate with 0.05 mol/L potassium iodate VS until the violet color of the chloroform layer disappears. The endpoint is when the purple color of the chloroform layer does not reappear within 5 minutes after it is decolorized.

Each mL of 0.05 mol/L potassium iodate VS
= 9.832 mg of $C_8H_8N_4 \cdot HCl$

Packaging and storage Preserve in hermetic containers.

Hydralazine Hydrochloride Tablets
히드랄라진염산염 정

Hydralazine Hydrochloride Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of hydralazine hydrochloride ($C_8H_8N_4HCl$: 196.64).

Method of preparation Prepare as directed under Tablets, with Hydralazine Hydrochloride.

Identification Powder Hydralazine Hydrochloride Tablets, weigh an amount of the powder equivalent to 25 mg of Hydralazine Hydrochloride according to the labeled amount, add 100 mL of water, mix, and filter it, if necessary. Add water to 2 mL of the filtrate to make 50 mL. Determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry; it exhibits maxima between 238 nm and 242 nm, between 258 nm and 262 nm, between 301 nm and 305 nm and between 313 nm and 317 nm.

Dissolution Perform the test with 1 tablet of Hydralazine Hydrochloride Tablets at 50 revolutions per minute according to Method 2, using 900 mL of water as the dissolution medium. Take NLT 30 mL of the dissolution medium 45 minutes after starting the test, and filter through a membrane filter with a pore size of NMT 0.8 μm. Discard the first 10 mL of the filtrate, pipet the subsequent V mL, add water to make exactly V' mL, so that Each mL

of the filtrate contains about 11 μg of hydralazine hydrochloride ($C_8H_8N_4$·HCl) according to the labeled amount and use this solution as the test solution. Separately, weigh accurately about 50 mg of Hydralazine Hydrochloride RS, previously dried at 105 ℃ for 3 hours and dissolve in water to make exactly 50 mL. Pipet 1 mL of the resulting solution, add water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 260 nm as directed under the Ultraviolet-visible Spectroscopy. Meets the requirements if the dissolution rate of Hydralazine Hydrochloride Tablets in 45 minutes is NLT 80%.

Dissolution rate (%) for the labeled amount of hydralazine hydrochloride (C_8H_8 N $_4$·HCl)

$$= W_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 18$$

*W*s: Amount (mg) of reference standards
C: Labeled amount (mg) of hydralazine hydrochloride ($C_8H_8N_4$·HCl) per tablet

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Hydralazine Hydrochloride Tablets, and powder. Weigh accurately an amount of the powder, equivalent to about 0.15 g of hydralazine hydrochloride ($C_8H_8N_4$·HCl), put into a stoppered flask, and perform the test according to the Assay of Hydralazine Hydrochloride.

Each mL of 0.05 mol/L potassium iodate VS
= 9.832 mg of $C_8H_8N_4$·HCl

Packaging and storage Preserve in tight containers.

Hydrochloric Acid
염산

Chlorane [*7647-01-0*]

Hydrochloric Acid contains NLT 35.0% and NMT 38.0% of hydrogen chloride (HCl: 36.46).

Description Hydrochloric Acid occurs as a colorless fluid having a pungent odor.
It is fuming but ceases to fume when it is diluted with 2 volumes of water.

Specific gravity—d_{20}^{20}: About 1.18.

Identification (1) Allow a glass stick wet with ammonia TS to come near the surface of Hydrochloric Acid; remarkable white fumes evolves.

(2) An aqueous solution of Hydrochloric Acid (1 in 100) changes blue litmus paper to red, and responds to the Qualitative Analysis for chloride.

Purity (1) ***Sulfates***—To 15 mL of Hydrochloric Acid, add water to make 50 mL, and use this solution as the test solution. To 3.0 mL of the test solution, add 5 mL of water and 5 drops of barium chloride TS, and allow to stand for 1 hour; the solution does not become turbid.

(2) ***Sulfite***—To 3.0 mL of the test solution obtained in (1), add 5 ml of water and 1 drop of iodine TS; the color of iodine TS does not disappear.

(3) ***Bromide and iodide***—Place 0.10 g of Hydrochloric Acid in a stoppered test tube, add 1 mL of chloroform and 1 drop of 0.002 mol/L potassium permanganate solution, and shake well to mix; the chloroform layer remains colorless.

(4) ***Bromine and chlorine***—Place 0.10 g of Hydrochloric Acid in a stoppered test tube, add 5 drops of potassium iodide TS and 1 drop of 1 mL of chloroform, and shake for 1 minute to mix; the chloroform layer does not exhibit a purple color.

(5) ***Heavy metals***—Evaporate 5 mL of Hydrochloric Acid on a steam bath to dryness, and add 2mL of dilute acetic acid and water to the residue to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 3.0 mL of lead standard solution, 2 mL of dilute acetic acid and water to make 50 mL (NMT 20 ppm).

(6) ***Mercury***—Dilute 20 mL of Hydrochloric Acid with water to make exactly 100 mL, and use the solution as the test solution. Perform the test with the test solution as directed under the Atomic Absorption Spectroscopy (cold vapor method). Place the test solution in a sample bottle of the atomic absorption spectrophotometer, add 10 mL of tin(II) chloride-sulfuric acid TS, connect the bottle immediately to the spectrophotometer, and circulate air. Measure the absorbance when the reading of the data collection device has risen rapidly and indicate a constant value at a wavelength of 253.7 nm, and determine this absorbance as A_T. Separately, take 8 mL of standard mercury solution, and add water to make 100 mL. Determine the absorbance A_S of a solution obtained by proceeding with this solution by the same procedure as in the test solution; A_T is smaller than A_S (NMT 0.04 ppm).

(7) ***Arsenic***—Take 1.7 mL of Hydrochloric Acid, proceed according to Method 1, and perform the test (NMT 1 ppm).

Residue on ignition Pipet 10 mL of Hydrochloric Acid, add 2 drops of sulfuric acid, evaporate to dryness, and ignite; the reside is NMT 1.0 mg.

Assay Add 20 mL of water to a glass-stoppered flask and weigh accurately its mass. Add about 3 mL of Hydrochloric Acid, weigh accurately again, add 25 mL of water, and titrate with 1 mol/L sodium hydroxide VS (indicator: 2 to 3 drops of methyl red TS).

Each mL of 1 mol/L sodium hydroxide VS
= 36.461 mg of HCl

Packaging and storage Preserve in tight containers.

Dilute Hydrochloric Acid
묽은염산

Dilute Hydrochloric Acid contains NLT 9.5 w/v% and NMT 10.5 w/v% of hydrogen chloride (HCl: 36.46).

Description Dilute Hydrochloric Acid occurs as a colorless liquid, which is odorless and has a strong acid taste.

Specific gravity—d_{20}^{20} : About 1.05.

Identification An aqueous solution of Dilute Hydrochloric Acid (1 in 30) changes blue litmus paper to red and responds to the Qualitative Analysis for chloride.

Purity (1) ***Bromide or iodide***—Take 10 mL of Dilute Hydrochloric Acid into a test tube with a stopper, add 1 mL of chloroform and 1 drop of 0.002 mol/L potassium permanganate TS and shake well to mix; the chloroform layer remains colorless.

(2) ***Bromine or chlorine***—Take 10 mL of Dilute Hydrochloric Acid into a test tube with a stopper, add 5 drops of potassium iodide TS and 1 mL of chloroform, and shake for 1 minute to mix; the chloroform layer does not exhibit a violet color.

(3) ***Sulfite***—Add 5 mL of water and 1 drop of iodine TS to 3.0 mL of Dilute Hydrochloric Acid; the color of the test solution does not disappear.

(4) ***Sulfate***—Add 5 mL of water and 5 drops of barium chloride TS to 3.0 mL of Dilute Hydrochloric Acid and allow to stand for 1 hour; the solution has no turbidity.

(5) ***Heavy metals***—Evaporate 9.5 mL of Dilute Hydrochloric Acid on a steam bath to dryness, add 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution as follows; to 3.0 mL of the lead standard solution, add 2 mL of dilute acetic acid and water to make 50 mL (NMT 3 ppm).

(6) ***Mercury***—Proceed 80 mL of Dilute Hydrochloric Acid, add water to make exactly 100 mL and use this solution as the test solution. Perform the test with this test solution as directed under the Atomic Absorption Spectroscopy (cold vapor type). Put the test solution into the sample bottle for the atomic absorption spectrophotometer, add 10 mL of tin(II) chloride-sulfuric acid TS, then immediately connect it to the atomic absorption spectrophotometer, and circulate air. Measure the absorbance when the reading of the data collection device rises rapidly and reaches a constant value at a wavelength of 253.7 nm, and determine this absorbance as A_T. Separately, pipet 8 mL of standard mercury solution and add water to make exactly 100 mL. With this solution, determine the absorbance, A_S, of the solution obtained by proceeding in the same manner as in the preparation of the test solution; A_T is smaller than A_S (NMT 0.01 ppm).

(7) ***Arsenic***—Proceed with 4.0 mL of Dilute Hydrochloric Acid as directed under Method 1 and perform the test (NMT 0.5 ppm).

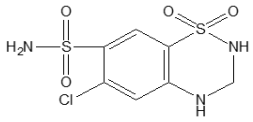
Residue on ignition Pipet 10 mL of Dilute Hydrochloric Acid, add 2 drops of sulfuric acid, evaporate it to dryness, and ignite; the weight of the residue is NMT 1.0 mg.

Assay Pipet 10 mL of Dilute Hydrochloric Acid and add 20 mL of water. Titrate with 1 mol/L sodium hydroxide VS (indicator: 2 to 3 drops of methyl red TS).

Each mL of 1 mol/L sodium hydroxide VS
= 36.461 mg of HCl

Packaging and storage Preserve in tight containers.

Hydrochlorothiazide
히드로클로로티아지드



$C_7H_8ClN_3O_4S_2$: 297.74

6-Chloro-1,1-dioxo-3,4-dihydro-2*H*-benzo[1,2,4]thiadiazine-7-sulfonamide [*58-93-5*]

Hydrochlorothiazide contains NLT 99.0% and NMT 101.0% of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$), calculated on the dried basis.

Description Hydrochlorothiazide occurs as white crystals or a crystalline powder, which is odorless and has a slightly bitter taste.

It is freely soluble in acetone, sparingly soluble in acetonitrile, very slightly soluble in water or ethanol(95) and practically insoluble in ether.

It dissolves in sodium hydroxide TS.

Melting point—About 267 °C (with decomposition).

Identification (1) Add 5 mL of Chromotropic acid TS to 5 mg of Hydrochlorothiazide and stand for 5 minutes; the resulting solution exhibits a violet color.

(2) Add 0.5 g of sodium carbonate decahydrate to 0.1 g of Hydrochlorothiazide and mix carefully to liquefy; the gas produced changes the moistened red litmus paper to blue. Crush the cooled fused mass with a glass rod, add 10 mL of water, stir to mix, and filter. Take 4 mL of the filtrate and add 2 drops of hydrogen peroxide(30), 5 mL of diluted hydrochloric acid (1 in 5) and 2 to 3 drops of barium chloride TS; a white precipitate is formed.

(3) Take 4 mL of the filtrate of (2) and add 5 mL of dilute nitric acid and 3 drops of silver nitrate TS; a white precipitate is formed.

(4) Dissolve 12 mg of Hydrochlorothiazide and hy-

drochlorothiazide RS in 100 mL of sodium hydroxide TS. To 10 mL each of these solutions, add water to make 100 mL respectively, and determine the absorption spectra of the solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Purity (1) ***Chloride***—Dissolve 1.0 g of Hydrochlorothiazide in 30 mL of acetone, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Add 30 mL of acetone, 6 mL of dilute nitric acid and water to 1.0 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.036%), and use this solution as the control solution.

(2) ***Sulfate***—Dissolve 1.0 g of Hydrochlorothiazide in 30 mL of acetone and add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid, add 30 mL of acetone, 1 mL of dilute hydrochloric acid and water to 50 mL (NMT 0.048%).

(3) ***Heavy metals***—Proceed with 2.0 g of Hydrochlorothiazide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Primary aromatic amine***—Weigh 80 mg of Hydrochlorothiazide and dissolve in acetone to make exactly 100 mL. Pipet 1 mL of this solution, add 3.0 mL of dilute hydrochloric acid, 3.0 mL of water and 0.15 mL of sodium nitrite TS, shake to mix, and allow to stand for 1 minute. To this solution, add 1.0 mL of ammonium sulfamate, shake to mix, allow to stand for 3 minutes, add 1.0 mL of N-(1-naphthyl)-N'-diethyl-ethylenediamine oxalate TS, shake to mix, and allow to stand for 5 minutes. Perform the test as directed under the Ultraviolet-visible Spectroscopy using the solution prepared with 1.0 mL of acetone in the same manner as the control solution; the absorbance at 525 nm is NMT 0.10.

(5) ***Related substances***—Weigh accurately 32 mg of Hydrochlorothiazide, add 70 mL of diluent, sonicate for 10 minutes, cool at the room temperature, add the diluent to make exactly 100 mL, filter through a filter with pore size of NMT 0.45 μm, and use the filtrate as the test solution. Take 10 μL of the test solution and perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution as directed in the automatic integration method, and calculate the amount of related substances; hydrochlorothiazide related substance I RS {4-amino-6-Chloro-1,3-benzenedesulfoneamide} is NMT 1.0%, and the amount of each related substance is NMT 0.5%. The sum of all related substances except hydrochlorothiazide related substance I is NMT 0.9%. However, the peak areas of hydrochlorothiazide related substance I and chlorothiazide are determined by dividing the peak areas obtained from the automatic integration method by the correction factors 0.54 and 0.63, respectively.

$$\text{Content (\%) of each related substance} = 100 \times \frac{A_i}{A_S}$$

A_i: Peak area of each related substance obtained from the test solution

A_S: Peak area of all substances from the test solution

Diluent—A mixture of sodium phosphate solution and acetonitrile (7 : 3).

Sodium phosphate solution—Dissolve 2.76 g of sodium dihydrogen phosphate monohydrate in 990 mL of water, adjust the pH to 2.7 with phosphoric acid, and add water to make 1000 mL.

Operating conditions

Proceed as directed under the operating conditions under the Assay.

System suitability

System performance: Weigh an appropriate amount of hydrochlorothiazide RS, chlorothiazide RS and hydrochlorothiazide related substances I and dissolve in chloroform to make the solution containing 0.32 mg, 0.0032 mg and 0.0032 mg per mL respectively, filter through 0.45 μm filters, and use these solutions as the system suitability solutions. Proceed with 10 μL of the system suitability solution according to the above conditions; the resolution between the peak of hydrochlorothiazide related substances I and the peak of chlorothiazide is NLT 2.0; the resolution between the peak of chlorothiazide and the peak of hydrochlorothiazide is NLT 1.5; the symmetry factor for each peak is NMT 1.5.

System repeatability: Repeat the test 6 times with 10 μL each of the system suitability solution according to the above conditions; the relative standard deviation of hydrochlorothiazide related substances I and chlorothiazide is NMT 5.0% Also, dissolve a suitable amount of hydrochlorothiazide RS in diluent to prepare the solution containing 0.16 μg per mL, and repeat the test 6 times with 10 μL of this solution under the above operating conditions; the relative standard deviation of the peak area is NMT 2.5%.

Loss on drying NMT 1.0% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 32 mg of Hydrochlorothiazide and hydrochlorothiazide RS, add 70 mL of diluent, sonicate for 10 minutes, cool at the room temperature, add the diluent to make exactly 100 mL, filter through a filter with pore size of 0.45 μm, and use the filtrate as the test solution and the standard solution respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of hydrochlorothiazide, A_T and A_S, in each solution.

Amount (mg) of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$)
= Amount (mg) of hydrochlorothiazide RS× $\frac{A_T}{A_S}$

Diluent—A mixture of sodium phosphate solution and acetonitrile (7 : 3).

Sodium phosphate solution—Dissolve 2.76 g of sodium dihydrogen phosphate monohydrate in 990 mL of water, adjust the pH to 2.7 with phosphoric acid, and add water to make 1000 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 275 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3.5 μm in particle diameter).

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: A mixture of acetonitrile and methanol (3 : 1).

Mobile phase B: An anhydrous formic acid aqueous solution (5 in 1000).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 5	3	97
5 - 14	3 → 36	97 → 64
14 - 18	36 → 3	64 → 97
18 - 20	3	97

Flow rate: About 1.0 mL/min.

Column temperature: A constant temperature of about 35 °C.

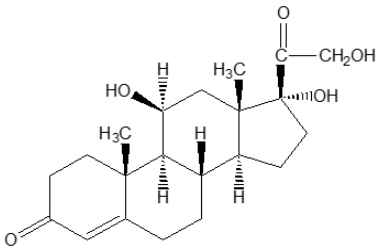
System suitability

System performance: Weigh an appropriate amount of hydrochlorothiazide RS, chlorothiazide RS and hydrochlorothiazide related substances I and dissolve in chloroform to make the solution containing 0.32 mg, 0.0032 mg and 0.0032 mg per mL respectively, filter through 0.45 μm filters, and use these solutions as the system suitability solutions. Proceed with 10 μL of the system suitability solution according to the above conditions; the relative retention time of hydrochlorothiazide related substances I and chlorothiazide to hydrochlorothiazide is about 0.5 and 0.8 respectively. The resolution between the peak of hydrochlorothiazide related substances I and the peak of chlorothiazide is NLT 2.0; the resolution between the peak of chlorothiazide and the peak of hydrochlorothiazide is NLT 1.5; the symmetry factor for each peak is NMT 1.5.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Hydrocortisone
히드로코르티손



Hydrocortisone $C_{21}H_{30}O_5$: 362.46
(8*S*,9*S*,10*R*,11*S*,13*S*,14*S*,17*R*)-11,17-Dihydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[a]phenanthren-3(2*H*)-one [*50-23-7*]

Hydrocortisone, when dried, contains NLT 97.0% and NMT 102.0% of hydrocortisone ($C_{21}H_{30}O_5$).

Description Hydrocortisone occurs as a white crystalline powder, which is odorless.
It is sparingly soluble in methanol, ethanol(95) or 1.4-dioxane, slightly soluble in chloroform, and practically insoluble in water or ether.

Melting point—Between 212 and 220 °C (with decomposition).

Identification (1) To 2 mg of Hydrocortisone, add 2 mL of sulfuric acid; the resulting solution exhibits a yellowish green fluorescence immediately, and changes gradually from orange to dark red. Add carefully 10 mL of water to this solution; the color changes from yellow to orange-yellow with a green fluorescence, and a small amount of flocculent precipitate is produced.

(2) Dissolve 0.01 g of Hydrocortisone in 1 mL of methanol, add 1 mL of Fehling's TS, and heat; a red precipitate is produced.

(3) Determine the infrared spectra of Hydrocortisone and hydrocortisone RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the spectra, dissolve Hydrocortisone and hydrocortisone RS in ethanol(95), respectively, then evaporate the ethanol to dryness, and perform the test with the residues in the same manner.

Optical rotation $[\alpha]_D^{20}$: Between +162° and +168° (after drying, 0.2 g, methanol, 25 mL, 100 mm).

Purity ***Related substances***—Dissolve 20 mg of Hydro-

cortisone in 10 mL of a mixture of chloroform and methanol (9 : 1), and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of chloroform and methanol (9 : 1) to make exactly 50 mL and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform and ethanol(95) (17 : 3) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 1.0% (0.5 g, 105 °C, 3 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately about 50 mg of Hydrocortisone and hydrocortisone RS, dissolve each in 20 mL of a mixture of chloroform and methanol (9 : 1), add exactly 10 mL of the internal standard solution to each, and add a mixture of chloroform and methanol (9 : 1) to each to make exactly 50 mL. Use these solutions as the test solution and the standard solution, respectively. Perform the test with 5 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios of the peak area, Q_T and Q_S, of hydrocortisone that of internal standard, respectively.

$$\text{Amount (mg) of hydrocortisone } (C_{21}H_{30}O_5) = \text{Amount (mg) of hydrocortisone RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of prednisone in a mixture of chloroform and methanol (9 : 1) (9 in 10000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 20 °C.

Mobile phase: A mixture of chloroform, methanol and acetic acid(100) (1000 : 20 : 1).

Flow rate: Adjust the flow rate so that the retention time of hydrocortisone is about 15 minutes.

System suitability

System performance: Proceed with 5 μL of the standard solution according to the above operating conditions; the internal standard and hydrocortisone are eluted in this order with the resolution being NLT 7.

System repeatability: Repeat the test 6 times with 5 μL of the standard solution according to the above operating conditions; the relative standard deviation of the ratios of the peak area of hydrocortisone to that of the internal standard is NMT 1.0.

Packaging and storage Preserve in tight containers.

Hydrocortisone Tablets
히드로코르티손 정

Hydrocortisone Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of hydrocortisone ($C_{21}H_{30}O_5$: 362.46).

Method of preparation Prepare as directed under Tablets, with Hydrocortisone.

Identification Powder Hydrocortisone Tablets, weigh the amount of powder equivalent to 50 mg of hydrocortisone according to the labeled amount, add 15 mL of hexane, shake to mix for 15 minutes, and then remove the hexane. To the residue, add 10 mL of hexane again, and shake to mix for 15 minutes. Remove the hexane, add 10 mL of ether without peroxide, and shake to mix for 15 minutes. Remove the ether, add 25 mL of ethanol(99.5), shake to mix for 15 minutes. Then, filter the resulting solution, evaporate to dryness on a steam bath. Perform the test with the residue according to the Identification (3) of Hydrocortisone.

Dissolution Perform the test with 1 tablet of Hydrocortisone Tablets at 50 revolutions per minute according to Method 2, using 900 mL of water as the dissolution medium. Take the dissolved solution after 30 minutes from starting of the test, filter, dilute with the dissolution solution, if necessary and use this solution as the test solution. Separately, weigh accurately a portion of Hydrocortisone RS, previously dried at 105 ºC for 3 hours, add the dissolution solution to make the same concentration as the test solution and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as a control solution, and determine the absorbances at the absorbance maximum wavelength of about 248 nm.

It meets the requirements if the dissolution rate of Hydrocortisone Tablets in 30 minutes is NLT 70%.

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following method.

Transfer 1 tablet of Hydrocortisone Tablets to a suitable container and add about 0.3 mL of water directly on the tablet. Allow the tablet to stand for about 5 minutes. Shake the container to break up the tablet and sonicate to

ensure complete disintegration. Add 4 to 5 small glass beads and 50.0 mL of the internal standard solution to the container. After shaking the container for about 30 minutes, pipet *V* mL of the clear supernatant, add exactly a certain amount of the internal standard solution to make a solution containing 0.1 mg of hydrocortisone per mL, and use this solution as the test solution. Separately, weigh accurately a portion of Hydrocortisone RS, previously dried at 105 ºC for 3 hours, dissolve in the internal standard solution to obtain a solution having a known concentration of 0.1 mg per mL and use this solution as the standard solution. Perform the test with 10 µL each of the test solution and the standard solution as directed under Liquid Chromatography according to the following conditions and calculate the ratios, Q_T and Q_S, of the peak area of Hydrocortisone to that of the internal standard for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of hydrocortisone } (C_{21}H_{30}O_5) = 50 \times \frac{V'}{V} \times C \times \frac{Q_T}{Q_S}$$

V': Final amount (mL) of the test solution
C: Concentration (mg/mL) of the standard solution

Internal standard solution—A solution of prednisone in a saturated chloroform in water (6 in 100000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, having porous silica gel for liquid chromatography (3 µm to 10 µm in particle diameter).

Mobile phase: A mixture of butyl chloride, water saturated butyl chloride, ethanol, acetic acid(100) and tetrahydrofuran (95 : 95 : 7 : 6 : 4).

System suitability

System performance: Proceed with 10 µL of the standard solution according to the above operating conditions; the resolution between peaks of hydrocortisone and the internal standard is NLT 3.0.

System repeatability: Repeat the test 6 times with 10 µL of the standard solution under the above operating conditions; the relative standard deviation of the ratios of the peak areas of hydrocortisone to those of the internal standard is NMT 2.0%.

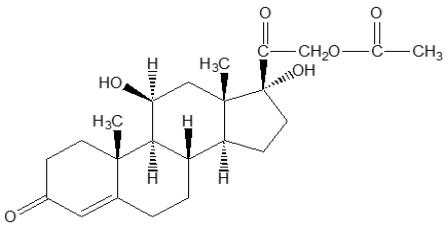
Assay Weigh accurately the mass of NLT 20 tablets of Hydrocortisone Tablets, and reduce to powder. Equivalent to about 5 mg of hydrocortisone ($C_{21}H_{30}O_5$), transfer to a centrifuge and add 50 mL of the internal standard solution. Shake vigorously to mix for 30 minutes, centrifuge the solution, and use the clear supernatant as the test solution. Proceed as directed under the Uniformity of Dosage Units under Hydrocortisone

$$\text{Amount (mg) of hydrocortisone } (C_{21}H_{30}O_5) = 50 \times C \times \frac{Q_T}{Q_S}$$

C: Concentration (mg/mL) of the standard solution

Packaging and storage Preserve in well-closed containers.

Hydrocortisone Acetate
히드로코르티손아세테이트



$C_{23}H_{32}O_6$: 404.50

2-((8*S*,9*S*,10*R*,11*S*,13*S*,14*S*,17*R*)-11,17-dihydroxy-10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl acetate [*50-03-3*]

Hydrocortisone Acetate, when dried, contains NLT 97.0% and NMT 102.0% of hydrocortisone acetate ($C_{23}H_{32}O_6$).

Description Hydrocortisone Acetate occurs as white crystals or a crystalline powder and is odorless.
It is sparingly soluble in 1,4-dioxane, slightly soluble in methanol, ethanol(95) or acetone, very slightly soluble in ether and practically insoluble in water.

Melting point—About 220 °C (with decomposition).

Identification (1) Dissolve 2 mg of Hydrocortisone Acetate in 2 mL of sulfuric acid; the solution exhibits a yellowish green fluorescence initially, and the color gradually turns orange to dark red. Under the ultraviolet rays, the solution exhibits a intense pale green fluorescence. Add carefully 10 mL of water to this solution; the solution changes yellow to orange-yellow color and shows pale green fluorescence, and a amber cotton-shaped precipitate is formed.

(2) Dissolve about 10 mg of Hydrocortisone Acetate in 1 mL of methanol by warming, add 1 mL of Fehling's TS, and heat; the resulting solution exhibits a orange to red color and precipitate.

(3) Add 2 mL of potassium hydroxide-ethanol TS to 50 mg of Hydrocortisone Acetate and heat on a steam bath for 5 minutes. After cooling, add 2 mL of diluted sulfuric acid (2 in 7) and heat gently for 1 minute; it gives the odor of ethyl acetate.

(4) Determine the infrared spectra of Hydrocortisone Acetate and hydrocortisone acetate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit

similar intensities of absorption at the same wavenumbers. If any difference appears between the two spectra, dissolve each in ethanol(95), evaporate, and perform the test with the residue in the same manner.

Optical rotation $[\alpha]_D^{20}$: Between +144° and +151° (25 mg after drying, acetone, 10 mL, 100 mm).

Purity ***Related substances***—Weigh about 40 mg of Hydrocortisone Acetate, dissolve in 25 mL of the mixture of chloroform and methanol (9 : 1), and use this solution as the test solution. Pipet 2 mL of this solution, add a mixture of chloroform and methanol (9 : 1) to make exactly 100 mL, and use the solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Develop the plate with the mixture of dichloromethane, ether, methanol, and water (160 : 30 : 8 : 1) as the developing solvent to a distance of about 12 cm and air-dry the plate. Spray evenly alkaline blue tetrazolium TS on the plate; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 1.0% (0.5 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Dissolve about 20 mg each of Hydrocortisone Acetate and hydrocortisone acetate RS, previously dried and accurately weighed, in methanol, add exactly 10 mL each of the internal standard solution, add methanol to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under Liquid Chromatography according to the following conditions and calculate the ratios, Q_T and Q_S, of the peak area of hydrocortisone acetate to that of the internal standard, for the test solution and the standard solution, respectively.

$$\text{Amount (mg) hydrocortisone acetate } (C_{23}H_{32}O_6) = \text{Amount (mg) of hydrocortisone acetate RS} \times \frac{A_T}{A_S}$$

Internal standard solution—A solution of benzyl p-hydroxybenzoate in methanol (1 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: A mixture of water and acetonitrile (13 : 7).

Flow rate: Adjust the flow rate so that the retention time of hydrocortisone acetate is about 8 minutes.

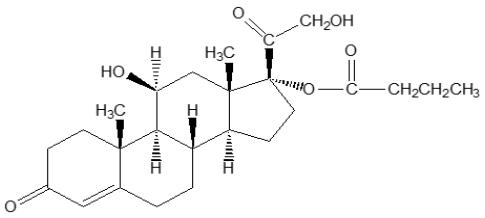
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above operating conditions; hydrocortisone acetate and the internal standard are eluted in this order with the resolution between their peaks being NLT 4.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio of hydrocortisone acetate to the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Hydrocortisone Butyrate
히드로코르티손부티레이트



$C_{25}H_{36}O_6$: 432.55

(8*S*,9*S*,10*R*,11*S*,13*S*,14*S*,17*R*)-11-hydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl butanoate [*13609-67-1*]

Hydrocortisone, when dried, contains NLT 96.0% and NMT 104.0% of hydrocortisone ($C_{25}H_{36}O_6$).

Description Hydrocortisone Butyrate occurs as a white powder, which is odorless.

It is freely soluble in tetrahydrofuran, chloroform or 1,2-dichloroethane, soluble in methanol, sparingly soluble in ethanol(99.5), slightly soluble in ether, and practically insoluble in water.

Melting point—About 200 °C (with decomposition).

Identification (1) Dissolve 2 mg of Hydrocortisone Butyrate in 2 mL of sulfuric acid; the resulting solution exhibits a yellowish green fluorescence initially, and changes gradually to orange to dark red. Examine this solution under ultraviolet light (main wavelength: 254 nm); the solution shows a strong pale green fluorescence. Add carefully 10 mL of water to this solution; the color changes from yellow to orange-yellow with a pale green fluorescence, and a yellowish brown flocculent precipitate is produced.

(2) To 10 mg of Hydrocortisone Butyrate, add 1 mL of methanol, dissolve by warming, add 1 mL of Fehling's TS, and heat; an orange to red precipitate is produced.

(3) To 50 mg of Hydrocortisone Butyrate, add 2 mL

of potassium hydroxide-ethanol TS, and heat on a steam bath for 5 minutes. After cooling, add 2 mL of dilute sulfuric acid (2 in 7), and boil gently for 1 minute; the odor of ethyl butyrate is perceptible.

(4) Determine the infrared spectrum of Hydrocortisone Butyrate and hydrocortisone Butyrate RS, previously dried, as directed in the potassium bromide disk method under Mid Infrared Spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +48° and +52° (after drying, 0.1 g, chloroform, 10 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Hydrocortisone Butyrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Weigh and dissolve 25 mg of Hydrocortisone Butyrate in 5 mL of tetrahydrofuran and use this solution as the test solution. Pipet 2 mL of this solution and add tetrahydrofuran to make exactly 50 mL. Pipet 5 mL of this solution, add tetrahydrofuran to make exactly 20 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of toluene, acetic acid(95) and water (200 : 30 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray evenly alkaline blue tetrazolium TS on the plate; the number of the spot other than the principal spot from the test solution is NMT one and it is not more intense than the spot from the standard solution.

Loss on drying NMT 1.0% (1 g, 105 °C, 3 hours).

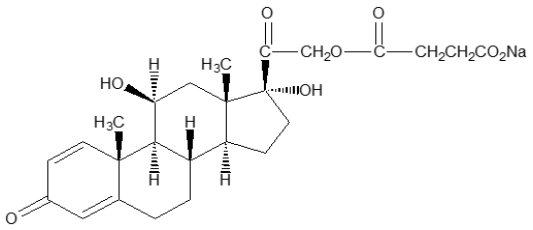
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg of Hydrocortisone Butyrate and dissolve in ethanol(99.5) to make exactly 100 mL. Pipet 2 mL of this solution and add ethanol(99.5) to make exactly 50 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance of this solution, *A*, at the absorbance maximum wavelength (λmax) of about 241 nm.

$$\text{Amount (mg) of hydrocortisone butyrate } (C_{25}H_{36}O_6) = \frac{A}{375} \times 25000$$

Packaging and storage Preserve in tight containers.

Hydrocortisone Sodium Succinate
히드로코르티손숙시네이트나트륨



$C_{25}H_{33}NaO_8$: 484.51

Sodium 4-[2-[(8*S*,9*S*,10*R*,11*S*,13*S*,14*S*,17*R*)-11,17-dihydroxy-10,13-dimethyl-3-oxo-2,6,7,8,9,11,12,14,15,16-decahydro-1*H*-cyclopenta[a]phenanthren-17-yl]-2-oxoethoxy]-4-oxobutanoate [*125-04-2*]

Hydrocortisone Sodium Succinate contains NLT 97.0% and NMT 103.0% of hydrocortisone sodium succinate ($C_{25}H_{33}NaO_8$), calculated on the dried basis.

Description Hydrocortisone Sodium Succinate occurs as a white powder or a mass, which is odorless.
It is freely soluble in water, methanol or ethanol(95), and practically insoluble in ether.
It is hygroscopic.
It is gradually colored by light.

Identification (1) Dissolve 0.2 g of Hydrocortisone Sodium Succinate in 20 mL of water, stir to mix, and add 0.5 mL of dilute hydrochloric acid; a white precipitate is produced. Filter the precipitate, wash twice each with 10 mL of water, and dry for 3 hours at 105 °C. To 3 mg of the dried matter, add 2 mL of sulfuric acid; the resulting solution exhibits a yellowish green fluorescence immediately, and changes gradually from orange-yellow to dark red. Examine this solution under ultraviolet light; the solution shows a very pale green fluorescence. Add carefully 10 mL of water to this solution; the color changes from yellow to orange with a pale green fluorescence, and a yellowish brown flocculent precipitate is produced.

(2) Dissolve 10 mg of the dried matter obtained in (1) in 1 mL of methanol, add 1 mL of Fehling's TS, and heat; an orange to red precipitate is produced.

(3) Dissolve 0.1 g of the dried matter obtained in (1) in 2 mL of sodium hydroxide TS, and allow to stand for 10 minutes. Filter the precipitated produced, mix the filtrate with 1 mL of dilute hydrochloric acid, shake to mix, and filter if necessary. Adjust the filtrate to the pH of about 6 with dilute ammonia TS (1 in 10), and add 2 to 3 drops of iron(III) chloride TS; a brown precipitate is produced.

(4) Determine the infrared spectra of the dried matter obtained in (1) and hydrocortisone succinate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the spectra, dissolve Hydro-

cortisone Sodium Succinate and hydrocortisone succinate RS in methanol, respectively, then evaporate the methanol to dryness, and repeat the test on the residues.

(5) Hydrocortisone Sodium Succinate responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between +135° and +145° (0.1 g as a calculated dried basis, ethanol(95), 10 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Hydrocortisone Sodium Succinate in 10 mL of water; the solution is colorless and clear.

(2) ***Related substances***—Weigh 25 mg of Hydrocortisone Sodium Succinate, dissolve in methanol to make exactly 10 mL, and use this solution as the test solution. Separately, dissolve 25 mg of hydrocortisone RS in methanol to make exactly 10 mL. Pipet 1 mL of this solution, add methanol to make exactly 20 mL, and use this solution as the standard solution (1). Pipet 6 mL of the standard solution (1), add methanol to make exactly 10 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 3 µL each of the test solution, the standard solution (1) and (2) on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform, ethanol(99.5) and formic acid (150 : 10 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the spot obtained from the test solution equivalent to the location of spot from the standard solution (1) is not more intense than the spot from the standard solution (1). Any spot other than the principal spot and the above spot from the test solution is NMT one, and is not more intense than the spot from the standard solution (2).

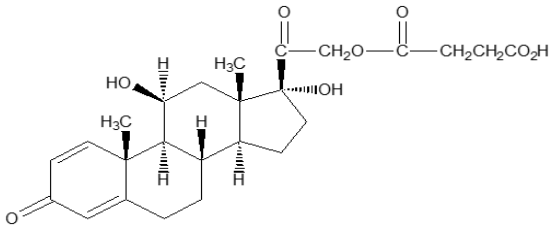
Loss on drying NMT 2.0% (0.5 g, 105 °C, 3 hours).

Assay Weigh accurately about 10 mg of Hydrocortisone Sodium Succinate and dissolve in methanol to make exactly 100 mL. Pipet 5 mL of this solution, add methanol to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of hydrocortisone succinate RS, previously dried at 105 °C for 3 hours, and proceed with it in the same manner as the test solution. Use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 240 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of hydrocortisone sodium succinate } (C_{25}H_{33}NaO_8) = \text{Amount (mg) of hydrocortisone succinate RS} \times \frac{A_T}{A_S} \times 1.0475$$

Packaging and storage Preserve in light-resistant, tight containers.

Hydrocortisone Succinate
히드로코르티손숙시네이트



$C_{25}H_{34}O_8$: 462.53

4-[2-[(8*S*,9*S*,10*R*,11*S*,13*S*,14*S*,17*R*)-11,17-dihydroxy-10,13-dimethyl-3-oxo-2,6,7,8,9,11,12,14,15,16-decahydro-1*H*-cyclopenta[a]phenanthren-17-yl]-2-oxoethoxy]-4-oxobutanoic acid [*2203-97-6*]

Hydrocortisone Succinate, when dried, contains NLT 97.0% and NMT 103.0% of hydrocortisone succinate ($C_{25}H_{34}O_8$).

Description Hydrocortisone Succinate occurs as a white crystalline powder, which is odorless.
It is very soluble in methanol, freely soluble in ethanol(99.5), sparingly soluble in ethanol(95), very slightly soluble in ether, and practically insoluble in water.

Identification (1) Dissolve 3 mg of Hydrocortisone Succinate in 2 mL of sulfuric acid; the resulting solution exhibits a yellowish green fluorescence initially, and changes gradually to orange to dark red. Examine this solution under ultraviolet light; the solution shows a very pale green fluorescence. Add carefully 10 mL of water to this solution; the color changes from yellow to orange with a pale green fluorescence, and a yellowish brown flocculent precipitate is produced.

(2) Determine the infrared spectrum of Hydrocortisone Succinate and hydrocortisone succinate RS as directed in the potassium bromide disk method under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the spectra, dissolve Hydrocortisone Succinate and hydrocortisone succinate RS in methanol, respectively, then evaporate the methanol to dryness, and repeat the test on the residues.

Optical rotation $[\alpha]_D^{20}$: Between +147° and +153° (after drying, 0.1 g, ethanol(99.5), 10 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Hydrocortisone Succinate in 10 mL of water; the solution is colorless and clear.

(2) ***Related substances***—Weigh 25 mg of Hydrocortisone Succinate, dissolve in methanol to make exactly

10 mL, and use this solution as the test solution. Separately, dissolve 25 mg of hydrocortisone RS in methanol to make exactly 10 mL. Pipet 1 mL of this solution, add methanol to make 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 3 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform, ethanol(99.5) and formic acid (150 : 10 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 2.0% (0.5 g, 105 °C, 3 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately about 50 mg each of Hydrocortisone Succinate and hydrocortisone succinate RS, previously dried, and dissolve in methanol to make exactly 50 mL. Pipet 5 mL each of these solutions, add exactly 5 mL each of the internal standard solution, add methanol to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios of the peak area, Q_T and Q_S, of hydrocortisone succinate to that of internal standard, respectively.

$$\text{Amount (mg) of hydrocortisone succinate } (C_{25}H_{34}O_8) = \text{Amount (mg) of hydrocortisone succinate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of butyl p-hydroxybenzoate in methanol (1 in 2500).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of acetic acid-sodium acetate buffer solution (pH 4.0) and acetonitrile (3 : 2).

Flow rate: Adjust the flow rate so that the retention time of hydrocortisone succinate is about 5 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; hydrocortisone succinate and internal standard are eluted in this order with the resolution being NLT 9.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above operating conditions; the relative standard deviation of the ratios of peak area of hydrocortisone succinate to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Hydrogen Peroxide Solution
과산화수소수

[*7722-84-1*]

Hydrogen Peroxide Solution contains NLT 2.5 w/v% and NMT 3.5 w/v% of hydrogen peroxide (H_2O_2: 34.02).
It contains NMT 0.05% of suitable preservatives.

Description Hydrogen Peroxide Solution occurs as a clear, colorless liquid. It is odorless or has an ozone-like odor.
It is acidic and forms bubbles on the mouth of the container.
It rapidly decomposes when in contact with oxidizing agents or reducing agents.
It can be decomposed by heating.
It is affected by light.

Specific gravity—d_{20}^{20}: About 1.01.

Identification Add 10 mL of water with 1 drop of dilute sulfuric acid to 1 mL of Hydrogen Peroxide Solution, shake, add 2 mL of ether, and add 1 drop of potassium dichromate TS; the water layer exhibits a light blue color. Shake well to mix and allow to stand; the light blue color is moved to the etheric layer.

Purity (1) ***Acid***—Pipet 25.0 mL of Hydrogen Peroxide Solution, add 2 drops of phenolphthalein TS and 2.5 mL of 0.1 mol/L sodium hydroxide TS; the resulting solution exhibits red color.

(2) ***Heavy metals***—Pipet 5.0 mL of Hydrogen Peroxide Solution, add 20 mL of water and 2 mL of ammonia TS, evaporate to dryness on a steam bath, dissolve the residue in 2 mL of dilute acetic acid by heating, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 2 mL of dilute acetic acid and water to 2.5 mL of lead standard solution to make 50 mL (NMT 5 ppm).

(3) ***Arsenic***—Pipet 1.0 mL of Hydrogen Peroxide Solution, add 1 mL of ammonia TS and evaporate to dryness on a steam bath. Proceed with the residue according to Method 1 and perform the test (NMT 2 ppm).

(4) ***Barium***—Pipet 10 mL of Hydrogen Peroxide Solution, add 2 drops of dilute sulfuric acid; no turbidity or precipitate is produced within 10 minutes.

(5) ***Preservative***—Pipet 100 mL of Hydrogen Peroxide Solution, previously shaken well, and extract with

50 mL, 25 mL and 25 mL of a chloroform-ether mixture (3 : 2). Combine all the extracts, put them in a tared container, evaporate at room temperature, and dry the residue in a desiccator (silica gel) for 2 hours; the mass of residue is NMT 50 mg.

(6) ***Evaporation residue*—**Evaporate to dryness 20.0 mL of Hydrogen Peroxide Solution on a steam bath and dry the residue at 105 ℃ for 1 hour; the mass of the residue is NMT 20 mg.

Assay Pipet 2 mL of Hydrogen Peroxide Solution, put it into a flask containing 20 mL of water, add 20 mL of dilute sulfuric acid, and titrate with 0.02 mol/L potassium permanganate VS.

Each mL of 0.02 mol/L potassium permanganate VS
= 1.701 mg of H_2O_2

Packaging and storage Preserve in light-resistant, tight containers, at below 30 ℃.

Hydrogen Peroxide Solution 35%
과산화수소수35%

H_2O_2 : 34.01

Hydrogen Peroxide Solution 35% is an aqueous solution, and contains an appropriate stabilizer. Hyrdogen Peroxide Solution 35% contains NLT 34.5% and NMT 35.5% of hydrogen peroxide (H_2O_2 : 34.01).

Description Hyrdogen Peroxide Solution 35% occurs as clear and colorless liquid. It is odorless or has an ozon-like odor.

Identification 1 ml of Hyrdogen Peroxide Solution 35% responds to the Qualitative Analysis.

pH Between 2.0 and 3.7.

Specific gravity d_{20}^{20}: Between 1.132 and 1.137 (Method 1).

Purity (1)***Acid***—Take 30.0 g of Hydrogen Peroxide Solution 35%, and add 150 mL of newly boiled and cooled water, 2 drops of methyl red TS and 0.60 mL of 0.1 mol/L sodium hydroxide solution. Then, the resulting solution exhibits a yellow color.

(2) ***Heavy metals***—Take 5 mL of Hydrogen Peroxide Solution 35%, add 20 mL of water and 2 mL of ammonia TS and evaporate on a steam bath to dryness. Dissolve the residue in 2 mL of dilute acetic acid by heating and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 2.5 mL of lead standard solution (NMT 5 ppm).

(3) ***Arsenic***—Add 1.0 g of Hydrogen Peroxide Solution 35% in 1 mL of ammonia TS, evaporate on a steam bath to dryness, and dissolve the residue in 10 mL of water. Use this solution as the test solution and perform the test (NMT 2 ppm).

(4) ***Organic Stabilizer***—With 100 g of Hydrogen Peroxide Solution 35%, extract using 50 mL, 25 mL, and 25 mL of a mixture of ether and chloroform (2:3), add all the extracted solutions and heat on a steam bath to evaporate ether and chloroform, and dry the residue in a desiccator (silica gel) to a constant mass (NMT 50 mg).

(5) ***Residue on evaporation***—Evaporate about 20.0 g of Hydrogen Peroxide Solution 35% on a steam bath to dryness and dry the residue at 105 ℃ for 1 hour (NMT 20 mg).

Assay Weigh accurately about 1 g of Hydrogen Peroxide Solution 35%, dissolve in water to make exactly 100 mL. Take 10 mL of this solution, add 10 mL of dilute sulfuric acid, and titrate with 0.02 mol/L potassium permanganate VS. The endpoint of the titration is when the color of the solution is red and persists for 30 seconds. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.02 mol/L potassium permanganate VS
= 1.7007 mg of H_2O_2

Packaging and storage Preserve in light-resistant, tight containers, at below 30 ℃.

Hydrotalcite Granules
히드로탈시트 과립

Hydrotalcite Granules contain NLT 90.0% and NMT 110.0% of the labeled amount hydrotalcite [$Al_2Mg_6(OH)_{16}CO_3 \cdot 4H_2O$: 603.98].

Method of preparation Prepare as directed under Granules, with Hydrotalcite.

Identification Weigh an appropriate amount of Hydrotalcite Granules, equivalent to 1.0 g of hydrotalcite, according to the labeled amount, add 20 mL of 2 mol/L hydrochloric acid, shake vigorously to mix, and filter. Add 30 mL of water to the resulting mixture, filter, and heat. Add 2 mol/L ammonia until it turns alkaline verifying with methyl red, heat for 2 minutes, and filter. Wash the precipitate with 50 mL of warm 2 w/v% ammonium chloride TS, and dissolve with 15 mL of 2 mol/L hydrochloric acid. To 2 mL of this solution, add about 0.5 mL of 7.3 w/v% hydrochloric acid and 0.5 mL of thioacetamide TS; no precipitate forms. To this solution, drop 8.5 w/v% sodium chloride solution; a white gel precipitate forms, and it dissolves when more 8.5 w/v% sodium chloride solution is added. To this solution, slowly add 10.7 w/v% ammonium chloride solution; the white precipitate appears again.

Acid-neutralizing capacity Perform the test as directed under the Acid-neutralizing Capacity with Hydrotalcite Granules.
Hydrotalcite Granules, equivalent to each g of hydrotalcite consumes NLT 260 mL of 0.1 mol/L hydrochloric acid VS.

Particle size estimation by analytical sieving Meets the requirements.

Disintegration Meets the requirements.

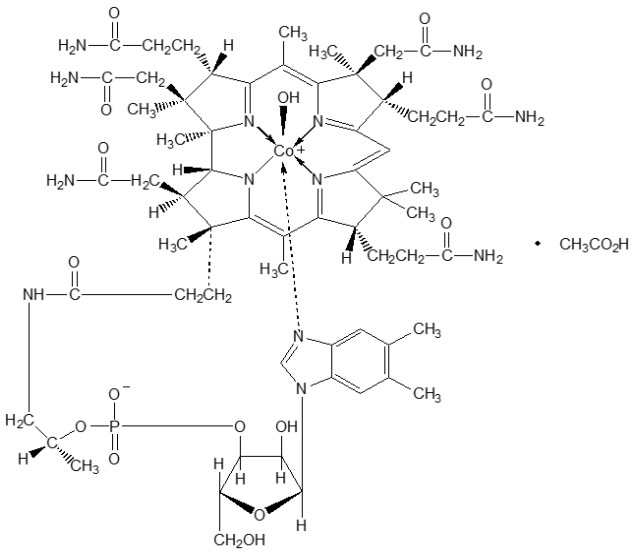
Uniformity of dosage units (distribution) Meets the requirements.

Assay Weigh accurately an amount of pulverized Hydrotalcite Granules equivalent to about 300 mg of hydrotalcite $Al_2Mg_6(OH)_{16}CO_3 \cdot 4H_2O$], add 2 mL of 7 mol/L hydrochloric acid, heat on a steam bath for 15 minutes, and cool. Add exactly 250 mL of water and 50 mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt solution. Neutralize this solution with 1 mol/L sodium hydroxide VS (indicator: methyl red TS), heat on a steam bath for 30 minutes, and cool. Add 3 g of hexamine, and titrate excess 0.05 mol/L ethylenediaminetetraacetic acid disodium salt with 0.05 mol/L lead nitrate VS (indicator: xylenol orange TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 15.09 mg of $Al_2Mg_6(OH)_{16}CO_3 \cdot 4H_2O$

Packaging and storage Preserve in well-closed containers.

Hydroxocobalamin Acetate
히드록소코발라민아세트산염



$C_{62}H_{89}CoN_{13}O_{15}P \cdot C_2H_4O_2$: 1406.41
Cobaltous [(2*R*,3*S*,4*R*,5*S*)-5-(5,6-dimethylbenzimidazol-1-yl)-4-hydroxy-2-(hydroxymethyl)tetrahydrofuran-3-yl] [(1*R*)-1-methyl-2-[3-[(2*R*,3*R*,4*Z*,7*S*,9*Z*,12*S*,13*S*,14*Z*,17*S*,18*S*,19*R*)-2,13,18-tris(2-amino-2-oxo-ethyl)-7,12,17-tris(3-amino-3-oxo-propyl)-3,5,8,8,13,15,18,19-octamethyl-2,7,12,17-tetrahydro-1*H*-corrin-21-id-3-yl]propanoylamino]ethyl] phosphate hydrate [*22465-48-1*]

Hydroxocobalamin Acetate contains NLT 95.0% and NMT 101% of hydroxocobalamin acetate ($C_{62}H_{89}CoN_{13}O_{15}P \cdot C_2H_4O_2$), calculated on the dried basis.

Description Hydroxocobalamin Acetate is deep red crystals or a powder which is odorless.
It is freely soluble in water, slightly solution in ethanol(95) and practically insoluble in ether.
It is hygroscopic.

Identification (1) Determine the absorption spectra of a solution of Hydroxocobalamin Acetate in pH 4.5 acetic acid-sodium acetate buffer solution (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Add 50 mg of potassium hydrogen sulfate to 1 mg of Hydroxocobalamin Acetate to mix and fuse by igniting. After cooling, crush the fused mass with a glass rod, dissolve in 3 mL of water by boiling, and add 1 drop of phenolphthalein TS. Put sodium hydroxide TS dropwise until the solution shows pale light red, and add 0.5 g of add trihydrate, 0.5 mL of dilute acetic acid and 0.5 mL of 1-nitroso-2-naphthol-3,6-disulfonic acid disodium (1 in 500); the resulting solution exhibits red to orange immediately. Then add 0.5 mL of hydrochloric acid and boil

for 1 minute; the red color of the solution does not disappear.

(3) To 20 mg of Hydroxocobalamin Acetate, add 0.5 mL of ethanol(99.5) and 1 mL of sulfuric acid, and heat; it gives the odor of ethyl acetate.

Purity ***Cyanocobalamin and colored related substances*—**Prepare 2 test tube with 50 mg of Hydroxocobalamin Acetate, and add exactly 5 mL of acetic acid-sodium acetate buffer solution, pH 5.0, in each tube. Add 0.15 mL of potassium thiocyanate TS in one tube, allow to stand for 30 minutes, and use this solution as the test solution (1). Add 0.10 mL of potassium thiocyanate TS in the other tube, allow to stand for 30 minutes, and use this solution as the test solution (2). Separately, weigh about 3.0 mg of cyanocobalamin RS, add exactly 10 mL of pH 5.0 acetic acid-sodium acetate buffer solution, pH 5.0, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution (1), (2) and the standard solution onto a thin-layer chromatographic plate made of silica gel for thin-layer chromatography, with a spacing of approximately 10 mm and a length of 25 mm each, following the original line. Next, develop the plate with water-saturated n-butanol as the developing solvent, tilted at an angle of about 15°, for 18 hours, and air-dry the plate. The spots obtained from the test solution (1) at the positions corresponding to the standard solution's spots are not more intense than the spots obtained from the standard solution; spots other than the principal spot obtained from the test solution (2) are not more intense than the spots obtained from the standard solution.

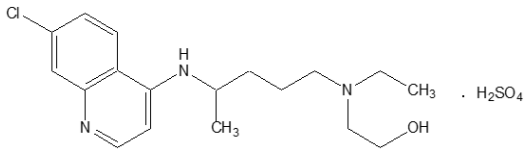
Loss on drying NMT 12.0% (50 mg, NMT 0.67 kPa, phosphorus pentoxide, 100 °C, 6 hours).

Assay Weigh accurately about 20 mg of Hydroxocobalamin Acetate and dissolve in acetic acid-sodium acetate buffer solution, pH 5.0 to make exactly 50 mL. Pipet 2 mL of this solution in a volumetric flask of 50 mL, add 1 mL of potassium cyanide solution (1 in 1000), allow to stand at ordinary temperature for 30 minutes, add acetic acid-sodium acetate buffer solution, pH 5.0 to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of cyanocobalamin RS (previously measure for loss on drying) and dissolve in water to make exactly 50 mL. Take exactly 2 mL of this solution, add acetic acid and sodium acetate buffer solution, pH 5.0, to make exactly 50 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 361 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of Hydroxocobalamin acetate ($C_{62}H_{89}CoN_{13}O_{15}P \cdot C_2H_4O_2$)
= Amount (mg) of cyanocobalamin RS, calculated on the dried basis $\times \frac{A_T}{A_S} \times 1.0377$

Packaging and storage Preserve in light-resistant, tight containers in a cold place.

Hydroxychloroquine Sulfate
히드록시클로로퀸황산염



$C_{18}H_{26}ClN_3O \cdot H_2SO_4$: 433.95

2-[4-[(7-Chloroquinolin-4-yl)amino]pentylethylamino]ethanol;sulfuric acid [*747-36-4*]

Hydroxychloroquine Sulfate contains NLT 98.0% and NMT 102.0% of hydroxychloroquine sulfate ($C_{18}H_{26}ClN_3O \cdot H_2SO_4$), calculated on the dried basis.

Description Hydroxychloroquine Sulfate occurs as a white crystalline powder, which is odorless and has a bitter taste.
It is freely soluble in water and practically insoluble in ethanol(95), chloroform or ether.
It shows polymorphism.
The typical form of Hydroxychloroquine Sulfate melts at about 240 ℃, while other forms melt at approximately 198 ℃.

Identification (1) Determine the absorption spectra of solutions of Hydroxychloroquine Sulfate and hydroxychloroquine sulfate RS in diluted hydrochloric acid (1 in 100) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit the same intensities of absorption at the same wavelengths.

(2) Determine the infrared spectrum of Hydroxychloroquine Sulfate and hydroxychloroquine sulfate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) An aqueous solution of Hydroxychloroquine Sulfate (1 in 100) responds to the Qualitative Analysis for sulfate.

Purity ***Related substances*—**Dissolve 0.10 g of Hydroxychloroquine Sulfate in a mixture of methanol and water (90: 10) to make exactly 10 mL, and use this solution as the test solution. Separately, weigh exactly a suitable amount of hydroxychloroquine sulfate RS, dissolve in a mixture of methanol and water (90 : 10) to make a solution containing 0.01, 0.05, 0.1 and 0.2 mg, per mL respectively, and use these solutions as the standard solu-

tions. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of ethanol(95), water and ammonia water(28) (80 : 16 : 4) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm and 366 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

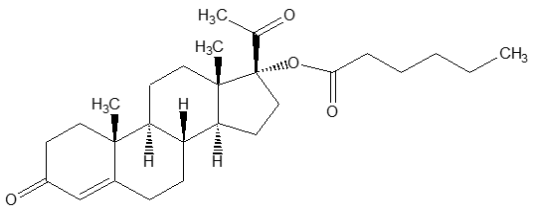
Loss on drying NMT 2.0% (1 g, 105 ℃, 2 hours).

Assay Weigh accurately about 0.1 g each of Hydroxychloroquine Sulfate and hydroxychloroquine sulfate RS, dissolve in 5 mL of water, and add diluted hydrochloric acid (1→ 100) to make exactly 100 mL, respectively. Pipet 1.0 mL each of these solutions, add diluted hydrochloric acid (1→ 100) to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength of around 343 nm, as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) hydroxychloroquine sulfate } (C_{18}H_{26}ClN_3O\cdot H_2SO_4) = \text{Amount (mg) of hydroxychloroquine sulfate RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in light-resistant, well-closed containers.

Hydroxyprogesterone Caproate
히드록시프로게스테론카프로에이트



$C_{27}H_{40}O_4$: 428.60

(8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-Acetyl-10,13-dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl hexanoate [*630-56-8*]

Hydroxyprogesterone Caproate contains NLT 97.0% and NMT 103.0% of hydroxyprogesterone caproate ($C_{27}H_{40}O_4$), calculated on the anhydrous basis.

Description Hydroxyprogesterone Caproate occurs as a white to milky white crystalline powder and is odorless. It is soluble in ether and practically insoluble in water.

Identification Determine the infrared spectra of Hydroxyprogesterone Caproate and hydroxyprogesterone caproatee RS, previously dried in a desiccator (in vacuum, silica gel) for 4 hours, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit the maxima at the same wavenumbers.

Specific optical rotation $[\alpha]_D^{20}$: Between +58° and +64° (0.1 g calculated on the anhydrous basis, chloroform, 10 mL, 100 mm).

Melting point Between 120 and 124 ℃.

Purity (1) ***Free n-caproic acid***—Dissolve 0.20 g of Hydroxyprogesterone Caproate in 25 mL of ethanol, neutralized before by adding 2 to 3 drops of phenolphthalein TS until a red color exhibits, and titrate with 0.02 mol/L sodium hydroxide VS; the consumption is NMT 0.50 mL (NMT 0.58%).

(2) ***Related substances***—Weigh 0.1 g of Hydroxyprogesterone Caproate, dissolve in 10 mL of chloroform, and use this solution as the test solution. Separately, weigh accurately about 10 mg of hydroxyprogesterone caproate RS, previously dried in a desiccator (vacuum, silica gel) for 4 hours, and dissolve in chloroform to make exactly 10 mL. Pipet 0.1 mL, 0.5 mL, 1 mL and 2 mL of this solution and add chloroform to each to make exactly 10 mL, and use these solutions as the standard solutions (1),(2), (3) and (4). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solutions (1), (2), (3) and (4), on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform and ethyl acetate (3 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. On the plate, spray evenly the solution, prepared by adding 10 mL of sulfuric acid to 90 mL of ethanol(95) in an ice bath, and heat the plate until it carbonizes. After cooling, expose to ultraviolet light (main wavelength: 366 nm), and compare the intensities of any spot other than the principal spot from the test solution with those from the standard solution; the relative intensity is NMT 2.0%.

Water NMT 0.1% (5 g, volume titration, direct titration).

Assay Weigh accurately about 50 mg each of Hydroxyprogesterone Caproate and hydroxyprogesterone caproatee RS (previously vacuum dried in a silica gel desiccator for 4 hours), separately dissolve in ethanol(95) to make exactly 100 mL, and shake to mix. Pipet 2 mL each of these solutions, add ethanol(95) to make exactly 100 mL and use these solutions as the test solution and the standard solution, respectively. Determine the absorbances, A_T and A_S, of the test solution and the standard solution,

respectively, at the absorbance maximum wavelength of around 240 nm, as directed under the Ultraviolet-visible Spectroscopy, using ethanol(95) to as the control solution.

$$\text{Amount (mg) of hydroxyprogesterone caproate}(C_{27}H_{40}O_4) = \text{Amount (mg) of hydroxyprogesterone caproate RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in light-resistant, well-closed containers.

Hydroxyprogesterone Caproate Injection
히드록시프로게스테론카프로에이트 주사액

Hydroxyprogesterone Caproate Injection is an oily injection. Hydroxyprogesterone Caproate Injection contains NLT 90.0% and NMT 110.0% of the labeled amount of hydroxyprogesterone caproate ($C_{27}H_{40}O_4$: 428.60).

Method of preparation Prepare as directed under Injections, with Hydroxyprogesterone Caproate.

Description Hydroxyprogesterone Caproate Injection occurs as a colorless to pale yellow, clear, oily liquid.

Identification (1) Take Hydroxyprogesterone Caproate Injection in the amount equivalent to 0.125 g of hydroxyprogesterone caproate according to the labeled amount, place it in a 60-mL separatory funnel containing 10 mL of hexane, 8 mL of methanol and 2 mL of water. Stopper the funnel, shake well for 2 minutes to mix, allow to stand until separated. Take 3 mL of the lower layer, add sulfuric acid dropwise until it exhibits a color, and add 3 mL of methanol; the solution exhibits a violet color. Examine the solution under the long-wavelength ultraviolet light; the solution exhibits a pale yellow fluorescence.

(2) Evaporate 4 mL of the test solution of the Assay to dryness by heating on a steam bath. Dissolve the residue in 0.5 mL of chloroform and use this solution as the test solution. Dissolve a suitable amount of Hydroxyprogesterone Caproate RS in a suitable amount of chloroform so as to contain 400 μg of hydroxyprogesterone caproate per mL. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform and ethyl acetate (3 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly a mixture of sulfuric acid and ethanol(95) (1 : 3) onto the plate, and heat the plate at 105 ℃ for 5 minutes; the principal spots obtained from the test solution and the standard solution exhibit a yellowish green color and have the same R_f value.

Water NMT 0.2% (5 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

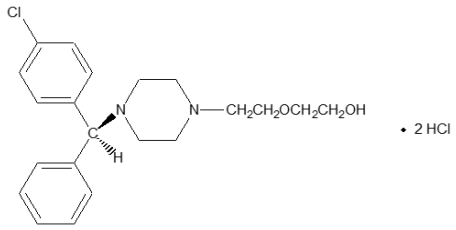
Assay Pipet Hydroxyprogesterone Caproate Injection in the amount equivalent to about 0.25 g of hydroxyprogesterone caproate ($C_{27}H_{40}O_4$) according to the labeled amount, add methanol to make exactly 250 mL, and mix. Pipet 5 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of hydroxyprogesterone caproate RS, and add methanol to make exactly 50 mL. Pipet 5 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. Pipet 5 mL each of the test solution and the standard solution, place in a respective stoppered flask, add 10.0 mL of isoniazid solution to each, and shake to mix. Allow each to stand in a 30 ℃ water bath for about 45 minutes. With these solutions, perform the test as directed under the Ultraviolet-visible Spectroscopy, using a mixture of methanol and isoniazid solution (1 : 2) as a control solution, and determine the absorbances, A_T and A_S, of the solutions, respectively, at the absorbance maximum wavelength of about 380 nm.

$$\text{Amount (mg) of hydroxyprogesterone caproate}(C_{27}H_{40}O_4) = \text{Amount (mg) of hydroxyprogesterone caproate RS} \times \frac{A_T}{A_S} \times 5$$

Isoniazid solution—Dissolve 0.375 g of isoniazid and 0.47 mL of hydrochloric acid in 500 mL of methanol.

Packaging and storage Preserve in hermetic containers.

Hydroxyzine Hydrochloride
히드록시진염산염



and enantiomer

$C_{21}H_{27}ClN_2O_2 \cdot 2HCl$: 447.83

2-[2-[4-[(4-Chlorophenyl)-phenylmethyl]piperazin-1-yl]ethoxy]ethanoldihydrochloride [*2192-20-3*]

Hydroxyzine Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of hydroxyzine hydrochloride ($C_{21}H_{27}ClN_2O_2 \cdot 2HCl$).

Description Hydroxyzine Hydrochloride occurs as a white crystalline powder, which is odorless and has a bitter taste.
It is very soluble in water, freely soluble in ethanol(95), methanol or acetic acid(100), very slightly soluble in acetic anhydride, and practically insoluble in ether.

Melting point—About 200 °C (with decomposition).

Identification (1) To 5 mL of an aqueous solution of Hydroxyzine Hydrochloride (1 in 100), add 2 to 3 drops of ammonium thiocyanate-cobalt nitrate TS; a blue precipitate is produced.

(2) Determine the absorption spectra of a solution of Hydroxyzine Hydrochloride in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) An aqueous solution of Hydroxyzine Hydrochloride (1 in 10) responds to the Qualitative Analysis for chloride.

pH Dissolve 1.0 g of Hydroxyzine Hydrochloride in 20 mL of water; the pH of this solution is between 1.3 and 2.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Hydroxyzine Hydrochloride in 10 mL of water; the solution is colorless and clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Hydroxyzine Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve 0.20 g of Hydroxyzine Hydrochloride in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL of the test solution and the standard solution onto a plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, ethanol(95) and ammonia water(28) (150 : 95 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Allow the plate to stand in iodine steam; the spots other than the principal spot from the test solution are not more intense than those from the standard solution.

Loss on drying NMT 3.0% (1 g, 105 ℃, 2 hours).

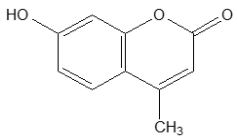
Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.1 g of Hydroxyzine Hydrochloride, previously dried, dissolve in 60 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 22.392 mg of $C_{21}H_{27}ClN_2O_2 \cdot 2HCl$

Packaging and storage Preserve in tight containers.

Hymecromone
히메크로몬



Hymecromone $C_{10}H_8O_3$: 176.17

7-Hydroxy-4-methyl-2*H*-chromen-2-one [*90-33-5*]

Hymecromone, when dried, contains NLT 98.0% and NMT 101.0% of hymecromone ($C_{10}H_8O_3$).

Description Hymecromone occurs as white crystals or a crystalline powder, which is odorless and tasteless.
It is freely soluble in *N*,*N*-dimethylformamide, sparingly soluble in ethanol(99) or ethanol(99.5) or acetone, slightly soluble in ether and practically insoluble in water.

Identification (1) Dissolve about 2 mg of Hymecromone in 5 mL of ammonia-ammonium chloride buffer solution, pH 11; the solution exhibits an intense bluish purple fluorescence.

(2) Dissolve 25 mg of Hymecromone in 5 mL of diluted ethanol (1 in 2), and add 1 drop of iron(III) chloride TS; the solution initially exhibits dark brown and turns yellowish brown after standing for a while.

(3) Determine the absorption spectra of solutions of Hymecromone and hymecromone RS in ethanol(99.5) (1 in 250000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of ab-

sorption at the same wavelengths.

(4) Determine the infrared spectra of Hymecromone and hymecromone RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 187 and 191 ºC.

Purity (1) ***Chloride***—Dissolve 0.8 g of Hymecromone in 40 mL of a mixture of acetone and water (2 : 1), and add 6 mL of dilute nitric acid and a mixture of acetone and water (2 : 1) to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 6 mL of dilute nitric acid and a mixture of acetone and water (2 : 1) to 0.25 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.011%).

(2) ***Sulfate metals***—Dissolve 0.8 g of Hymecromone in 40 mL of a mixture of acetone and water (2 : 1), and add 1 mL of dilute hydrochloric acid and a mixture of acetone and water (2 : 1) to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 1 mL of dilute hydrochloric acid to 0.40 mL of 0.005 mol/L sulfuric acid, and add a mixture of acetone and water (2 : 1) to make 50 mL (NMT 0.024%).

(3) ***Heavy metals***—Proceed with 2.0 g of Hymecromone according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Prepare the test solution with 1.0 g of Hymecromone according to Method 3, and perform the test (NMT 2 ppm).

(5) ***Related substances***—Dissolve 80.0 mg of Hymecromone in 10 mL of ethanol(95) and use this solution as the test solution. Pipet 1 mL of this solution and add ethanol(95) to make exactly 50 mL. Pipet 1 mL of this solution, add ethanol(95) to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform and ethanol(95) (10 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Allow the plate to stand in iodine vapor for 5 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.25 g of Hymecromone, previously dried, dissolve in 90 mL of *N*,*N*-Dimethylformamide, and titrate with 0.1 mol/L tetramethylammonium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test with a solution prepared by adding 14 mL of water to 90 mL of *N*,*N*-dimethylformamide and make any necessary correction.

Each mL of 0.1 mol/L tetramethylammonium hydroxide VS
= 17.617 mg of $C_{10}H_8O_3$

Packaging and storage Preserve in tight containers.

Hypromellose and Dextran 70 Ophthalmic Solution
히프로멜로오스·덱스트란70 점안액

Hypromellose and Dextran 70 Ophthalmic Solution contains NLT 90.0% and NMT 110.0% of the labeled amount of hypromellose 2910 and dextran 70.

Method of preparation Prepare as directed under Ophthalmic Solutions, with Hypromellose 2910 and Dextran 70.

Identification (1) ***Hypromellose 2910***—(i) Add gradually 1 mL of anthrone TS to 2 mL of Hypromellose and Dextran 70 Ophthalmic Solution; the boundary layer exhibits a blue to green color.

(ii) A white precipitation is formed when heating this solution on a steam bath; the white precipitation disappears when cooling the solution.

(2) ***Dextran 70***—Add gradually 2 mL of anthrone TS to 1 mL of Hypromellose and Dextran 70 Ophthalmic Solution; the resulting solution exhibits a bluish green color which gradually changes to a dark bluish green color. To this solution, add 1 mL of diluted sulfuric acid (1 in 2) or 1 mL of acetic acid(100); the resulting solution does not change in color.

pH Between 6.5 and 8.5.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Particulate matter in ophthalmic solutions Meets requirements.

Assay Pipet 5 mL of Hypromellose and Dextran 70 Ophthalmic Solution, add water to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 150 mg of hypromellose 2910 RS and about 50 mg of dextran 70 RS, place them in a 500-mL volumetric flask, and add slowly 350 mL of hot water, stirring continuously until the mixture reaches room temperature. Allow to stand overnight, then completely dissolve, and use this solution as the standard solution.

Take 2.0 mL each of the test solution and the standard solution, put in a test tube, add 2.0 mL each of water,

and use this solution as the test solution and the standard solution for total carbohydrates assay.

Separately, take 2.0 mL each of the test solution and the standard solution, put in a centrifuge tube, add 2.0 mL of saturated sodium sulfate solution, centrifuge, and use the clear supernatant as the test solution and the standard solution for dextran 70 assay.

Take 1.0 mL each of the test solution and the standard solution for total carbohydrates assay and those for dextran 70 assay, add 5.0 mL of diphenylamine TS, react for 30 minutes in an oil bath maintained at a constant temperature of 105 to 110 ℃, and then cool in iced water for 10 minutes to bring to room temperature. Determine the absorption spectra of these solutions, A_{CT}, A_{CS}, A_{DT}, and A_{DS}, as directed under the Ultraviolet-visible Spectroscopy at the 635 nm wavelength.

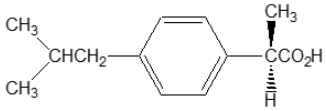
Amount (mg/mL) of total carbohydrate
= Concentration (mg/mL) of the standard solution for total carbohydrate assay $\times \frac{A_{CT}}{A_{CS}}$

Amount (mg/mL) of dextran 70
= Amount (concentration) (mg/mL) of dextran 70 $\times \frac{A_{DT}}{A_{DS}}$

Amount (mg/mL) of hypromellose 2910
= Amount (mg/mL) of total carbohydrate - Concentration (mg/mL) of dextran 70

Packaging and storage Preserve in tight containers.

Ibuprofen
이부프로펜



and enantiomer

$C_{13}H_{18}O_2$: 206.28

2-[4-(2-Methylpropyl)phenyl]propanoic acid [*15687-27-1*]

Ibuprofen, when dried, contains NLT 98.5% and NMT 101.0% of ibuprofen ($C_{13}H_{18}O_2$).

Description Ibuprofen occurs as a white crystalline powder.
It is freely soluble in ethanol(95) or acetone and practically insoluble in water.
It is soluble in dilute sodium hydroxide TS.

Identification (1) Determine the absorption spectra of Ibuprofen and ibuprofen TS in dilute sodium hydroxide solution (15 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelength.

(2) Determine the infrared spectrum of Ibuprofen and ibuprofen RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

Melting point Between 75 and 77 ºC.

Purity (1) ***Heavy metals***—Proceed with 3.0 g of Ibuprofen as directed under Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Ibuprofen as directed under Method 3 and perform the test (NMT 2 ppm).

(3) ***Related substances***—Weigh 0.50 g of Ibuprofen, dissolve in exactly 5 mL of acetone, and use this solution as the test solution. Pipet 1 mL of this solution, add acetone to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Next, develop the plate with a mixture of hexane, ethyl acetate and acetic acid(100) (15 : 5 : 1) as the developing solvent to a distance of about 10 cm and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 0.5% (1 g, NMT 0.67 kPa, phosphorus pentoxide, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Ibuprofen, previously dried, dissolve in 50 mL of ethanol(95), and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of phenolphthalein TS). Perform a blank test in the same manner and make any necessary correction.

1 mL of 0.1 mol/L sodium hydroxide VS
= 20.63 mg of $C_{13}H_{18}O_2$

Packaging and storage Preserve in well-closed containers.

Ibuprofen Capsules
이부프로펜 캡슐

Ibuprofen Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of ibuprofen ($C_{13}H_{18}O_2$: 206.28).

Method of preparation Prepared as directed under Cap-

sules, with Ibuprofen.

Identification (1) Weigh an amount of Ibuprofen Capsules, equivalent to 0.2 g of ibuprofen according to the labeled amount, add 20 mL of methanol, shake well to mix, centrifuge, and use the clear supernatant as the test solution. Separately, weigh 0.1 g of ibuprofen RS, add methanol to make 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of 1-butanol, 20% ammonia water and water (12 : 1 : 1), and air-dry the plate. Spray evenly bromocresol green TS on the plate; the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

(2) The retention times of the major peaks obtained from the test solution and the standard solution under Assay are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Related substances Weigh accurately the mass of the content of NLT 20 capsules of Ibuprofen Capsules. Weigh accurately an amount of the content, equivalent to about 0.2 g of ibuprofen ($C_{13}H_{18}O_2$), add 30 mL of methanol, shake to dissolve for 30 minutes, then add 30 mL of methanol and water to make exactly 100 mL, filter, and use the filtrate as the test solution. Pipet 2 mL of this solution, add the mobile phase to make 200 mL, and use this solution as the standard solution (1). Separately, take about 50 mg of ibuprofen RS, add 2.5 mL of 0.006% methanolic 2-(4-butylphenyl)-propionic acid RS and methanol to make 25 mL, and use this solution as the standard solution (2). Perform the test with 20 μL each of the test solution, the standard solutions (1) and (2) as directed under the Liquid Chromatography according to the following operating conditions. Determine the peak area of each solution as directed in the automatic integration method, and measure the amount of each related substance; the peak area of 2-(4-butylphenyl)-propionic acid obtained from the test solution is not larger than that of 2-(4-butylphenyl)-propionic acid obtained from the standard solution (2) (NMT 0.3%), and peak areas other than ibuprofen are not greater than 0.3 times the major peak area obtained from standard solution (1) (NMT 0.3%), and the sum of each peak area is not greater than 0.7 times the major peak area obtained from standard solution (1) (NMT 0.7%). However, ignore the peaks attributed to the solvent on chromatogram from the test solution and the peaks less than 0.1 times of major peak area from standard solution (1) (NMT 0.1%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Add 0.5 mL of phosphoric acid, 340 mL of acetonitrile and 600 mL of water, then add water to make 1000 mL.

Flow rate: 2.0 mL/min

Time span of measurement: About 1.5 times the retention time of ibuprofen

System suitability

System performance: Determine the peak height (a) of 2-(4-butylphenyl)-propionic acid and the lowest height (b) of the ibuprofen peaks from the standard solution (2). The value of (a) is NLT 1.5 times that of (b).

Assay Take NLT 20 capsules of Ibuprofen Capsules, weigh an amount of the content, equivalent to 0.12 g of ibuprofen ($C_{13}H_{18}O_2$), add 10.0 mL of the internal standard solution, add the mobile phase to make exactly 100 mL, filter, and use this solution as the test solution. Separately, weigh accurately about 0.12 g of ibuprofen RS, add 10.0 mL of the internal standard solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, of ibuprofen to the internal standard.

$$\text{Amount (mg) of ibuprofen } (C_{13}H_{18}O_2) = \text{Amount (mg) of ibuprofen RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh 35 mg of valerophenone, and add the mobile phase to make 0.35 mg/mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: Dissolve 4.0 g of chloroacetic acid in 400 mL of water, adjust the pH to 3.0 with ammonia water, add 600 mL of acetonitrile, and filter.

Flow rate: 2 mL/min

System suitability

System performance: Weigh accurately 4-isobutylacetophenone, dissolve in acetonitrile to make 0.6 mg/mL, and take 2.0 mL of the resulting solution. Add the internal standard solution to make 100 mL, and use this solution as the 4-isobutylacetophenone standard solution. Proceed with 20 μL of this solution according to the above conditions; valerophenone and 4-isobutylacetophenone are eluted in this order with the

resolution being NLT 2.5.

System repeatability: Repeat the test 6 times with 20 μL of the 4-isobutylacetophenone standard solution according to the above conditions; the relative standard deviation is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Ibuprofen Syrup
이부프로펜 시럽

Ibuprofen Syrup contains NLT 90.0% and NMT 110.0% of the labeled amount of ibuprofen ($C_{13}H_{18}O_2$: 206.28).

Method of preparation Prepare as directed under Syrups, with Ibuprofen.

Identification The retention time of major peak of the test solution and the standard solution for Assay is the same.

pH Between 3.0 and 5.0.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Weigh accurately an amount of Ibuprofen Syrup, equivalent to 0.12 g of ibuprofen ($C_{13}H_{18}O_2$) according to the labeled amount, add 10.0 mL of the internal standard solution, and add the mobile phase to make exactly 100 mL. Filter and use the filtrate as the test solution. Separately, weigh accurately about 0.12 g of ibuprofen RS, add 10.0 mL of the internal standard solution, add the mobile phase to make exactly 100 mL, and use the solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, of ibuprofen to the internal standard.

$$\text{Amount (mg) of ibuprofen } (C_{13}H_{18}O_2) = \text{Amount (mg) of ibuprofen RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh 35 mg of valerophenone, and add the mobile phase to make 0.35 mg/mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: Dissolve 4.0 g of chloroacetic acid in 400 mL of water, adjust the pH to 3.0 with ammonia water, add 600 mL of acetonitrile, and filter.

Flow rate: 2 mL/min

System suitability

System performance: Weigh accurately 4-isobutylacetophenone, dissolve in acetonitrile to make 0.6 mg/mL, and take 2.0 mL of the resulting solution. Add the internal standard solution to make 100 mL, and use this solution as the 4-isobutylacetophenone standard solution. Proceed with 20 μL of this solution according to the above operating conditions and perform the test; valerophenone and 4-isobutylacetophenone are eluted in this order, with the resolution between these peaks being NLT 2.5.

System repeatability: Repeat the test 6 times with 20 μL of the 4-isobutylacetophenone standard solution according to the above conditions; the relative standard deviation is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Ichthammol
이크타몰

[*8029-68-3*]

Ichthammol contains NLT 2.5% of ammonia (NH_3 : 17.03), NMT 8.0% of ammonium sulfate [$(NH_4)_2SO_4$: 132.14] and NLT 10.0% of total sulfur (S : 32.07), calculated on the dried basis.

Description Ichthammol occurs as a reddish brown to blackish brown, viscous liquid and has a characteristic odor.
It is miscible with water.
It is sparingly soluble in ethanol(95) or ether.

Identification (1) To 4 mL of an aqueous solution of Ichthammol (3 in 10), add 8 mL of hydrochloric acid; a yellowish brown to blackish brown, oily or resinous precipitate is formed. Cool the precipitate with ice to solidify the precipitate, and discard the water layer by decantation. Wash the residual precipitate with ether; a part of the precipitate dissolves but it does not dissolve completely until the last washing is almost colorless. Perform the following test with this residue.

(i) To 0.1 g of the residue, add 1 mL of a mixture of ether and ethanol(95) (1 : 1); it dissolves.

(ii) To 0.1 g of the residue, add 2 mL of water; it dissolves. To 1 mL of this solution, add 0.4 mL of hydrochloric acid; a yellowish brown to blackish brown oily or resinous precipitate is formed.

(iii) To 1 mL of the solution obtained in (B), add 0.3 g of sodium chloride; a yellowish brown or blackish brown oily or resinous precipitate is formed.

(2) Boil 2 mL of an aqueous solution of Ichthammol (1 in 10) with 2 mL of sodium hydroxide TS; the gas evolved changes the color of the moistened red litmus

paper to blue.

Loss on drying NMT 50% (0.5 g, 105 °C, 6 hours).

Residue on ignition NMT 0.5% (1 g).

Assay (1) ***Ammonia***—Weigh accurately about 5 g of Ichthammol, put into a Kjeldahl flask, and add 60 mL of water, 1 mL of 1-octanol and 4.5 mL of a solution of sodium hydroxide (2 in 5). Connect the flask to a distilling tube and a condenser with a spray trap. To a receiver, add exactly 30 mL of 0.25 mol/L sulfuric acid, and immerse the lower outlet end of the condenser. Distill slowly, collect about 50 mL of the distillate and titrate the excess sulfuric acid with 0.5 mol/L sodium hydroxide VS (indicator: 3 drops of methyl red TS). Perform a blank test in the same manner.

Each mL of 0.25 mol/L sulfuric acid VS
= 8.515 mg of NH_3

(2) ***Ammonium sulfate***—Weigh accurately about 1 g of Ichthammol, add 25 mL of ethanol(95), stir thoroughly to mix, and filter. Wash with a mixture of ethanol(95) and ether (1 : 1) until the washings are clear and colorless. Air-dry the residue and the filter paper. Dissolve the residue in 200 mL of warm water acidified slightly with hydrochloric acid, and filter. Boil the filtrate, add 30 mL of barium chloride TS slowly, heat for 30 minutes on a steam bath, and filter. Wash the precipitate with water, dry, and ignite to constant weight. Weigh the residue as the amount (mg) of barium sulfate ($BaSO_4$: 233.39).

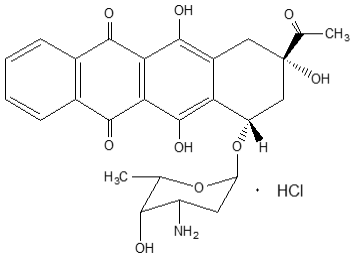
Amount (mg) of ammonium sulfate [$(NH_4)_2SO_4$]
= Amount (mg) of barium sulfate ($BaSO_4$) × 0.5662

(3) ***Total sulfur***—Weigh accurately about 0.6 g of Ichthammol, put into a 200-mL Kjeldahl flask, add 30 mL of water and 5 g of potassium chlorate, then add slowly 30 mL of nitric acid, and evaporate the solution by heating to about 5 mL. Put into a 300-mL beaker washing with 25 mL of hydrochloric acid, and evaporate by heating to 5 mL. Add 100 mL of water to this solution, boil, filter and wash with water. Heat the combined filtrate and washings to boil, add gradually 30 mL of barium chloride TS, heat on a steam bath for 30 minutes. Wash the precipitate with water, dry, and ignite to constant weight. Weigh the residue as the amount (mg) of barium sulfate ($BaSO_4$).

Amount (mg) of total sulfur (S)
= Amount (mg) of barium sulfate ($BaSO_4$) × 0.13739

Packaging and storage Preserve in tight containers.

Idarubicin Hydrochloride
이다루비신염산염



$C_{26}H_{27}NO_9 \cdot HCl$: 533.95

(7*S*,9*S*)-9-Acetyl-7-[(2*R*,4*S*,5*S*,6*S*)-4-amino-5-hydroxy-6-methyloxan-2-yl]oxy-6,9,11-trihydroxy-8,10-dihydro-7*H*-tetracene-5,12-dione hydrochloride [*57852-57-0*]

Idarubicin Hydrochloride contains NLT 960 μg and NMT 1030 μg (potency) of idarubicin hydrochloride ($C_{26}H_{27}NO_9 \cdot HCl$: 533.95) per mg, calculated on the anhydrous basis.

Description Idarubicin Hydrochloride occurs as a yellowish red powder.
It is sparingly soluble in methanol, slightly soluble in water or ethanol(95), and practically insoluble in acetonitrile or ether.

Identification (1) Determine the absorption spectra of solutions of Idarubicin Hydrochloride and idarubicin hydrochloride RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Idarubicin Hydrochloride and idarubicin hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) Dissolve 2 mg of Idarubicin Hydrochloride in 3 mL of water, and add 1 mL of dilute nitric acid and 3 drops of silver nitrate TS; the solution becomes turbid in white.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between 191° and +197° (20 mg, calculated on the anhydrous basis, methanol, 20 mL, 100 mm).

pH Dissolve 0.1 g of Idarubicin Hydrochloride in 20 mL of water; the pH of this solution is between 5.0 and 6.5.

Absorbance $E_{1cm}^{1\%}$ (482 nm): Between 204 and 210 (20 mg calculated on the anhydrous basis, methanol, 1000 mL).

Purity ***Related substances***—Perform the test as directed

under the Assay to determine the peak area ratios for each related substance to the total peak area of the test solution excluding the solvent peak; total related substances is NMT 3.0% and each related substance is respectively NMT 1.0% with respect to the total amount.

Water NMT 5.0% (0.1 g, coulometric titration).

Sterility It meets the requirements when used in the manufacturing of sterile preparations.

Bacterial endotoxins It is less than 8.9 EU per mg (potency) of idarubicin hydrochloride when used in the manufacturing of sterile preparations.

Assay Weigh accurately about 10 mg (potency) each of Idarubicin Hydrochloride and idarubicin hydrochloride RS, dissolve in the mobile phase without sodium lauryl sulfate to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of idarubicin, A_T and A_S, in each solution.

$$\text{Potency (μg) of idarubicin hydrochloride } (C_{26}H_{27}NO_9 \cdot HCl) = \text{Idarubicin hydrochloride RS (μg)} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (4 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: Dissolve 10.2 g of potassium dihydrogen phosphate in water, add 1 mL of phosphoric acid and water to make 750 mL, and add 250 mL of tetrahydrofuran. To 500 mL of this solution, add 0.72 g of sodium lauryl sulfate and 0.5 mL of *N*,*N*-dimethyl-*n*-octylamine, and adjust the pH to 4 with sodium hydroxide TS.

Flow rate: Adjust the flow rate so that the retention time of idarubicin is about 15 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution under the above conditions; the number of theoretical plates of the peak of idarubicin is NLT 3000.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above operating conditions; the relative standard deviation of the peak area of idarubicin is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Idarubicin Hydrochloride for Injection
주사용 이다루비신염산염

Idarubicin Hydrochloride for Injection is a preparation for injection, which is dissolved before use, and contains NLT 90.0% and NMT 110.0% of the labeled amount of idarubicin hydrochloride ($C_{26}H_{27}NO_9 \cdot HCl$: 533.95).

Method of preparation Prepare as directed under Injections, with Idarubicin Hydrochloride.

Description Idarubicin Hydrochloride for Injection occurs as a yellowish red mass.

Identification (1) Weigh an amount of Idarubicin Hydrochloride for Injection, equivalent to 2 mg (potency) of idarubicin hydrochloride, according to the labeled amount, and dissolve in 5 mL of sodium hydroxide TS; the solution exhibits bluish purple.

(2) Weigh an amount of Idarubicin Hydrochloride for Injection, equivalent to 1 mg (potency) of idarubicin hydrochloride, according to the labeled amount, dissolve in 1 mL of water and add methanol to make 100 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 250 nm to 254 nm, 285 nm to 289 nm, 480 nm to 484 nm and 510 nm to 520 nm.

pH Dissolve an amount of Idarubicin Hydrochloride for Injection, equivalent to 5 mg (potency) of idarubicin hydrochloride, in 5 mL of water; the pH of this solution is 5.0 to 7.0.

Purity ***Clarity and color of solution***—Weigh an amount of Idarubicin Hydrochloride for Injection, equivalent to 5 mg (potency) of idarubicin hydrochloride, according to the labeled amount, and dissolve in 5 mL of water; the solution is clear and the color is yellowish red.

Water NMT 4.0% (0.3 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 8.9 EU per mg (potency) of idarubicin hydrochloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Perform the Content uni-

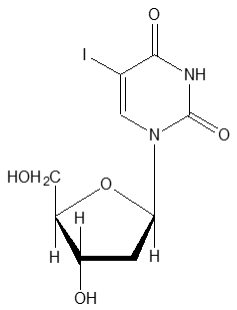
formity test according to the following procedure; it meets the requirements. Weigh 1 container of Idarubicin Hydrochloride for Injection, add the mobile phase containing no sodium lauryl sulfate to obtain V mL of a solution containing 0.2 mg (potency) of idarubicin hydrochloride ($C_{26}H_{27}NO_9 \cdot HCl$) per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately an amount of idarubicin hydrochloride RS, equivalent to about 10 mg (potency), add the mobile phase containing no sodium lauryl sulfate to make exactly 50 mL, and use this solution as the standard solution. Perform the test as directed under the Assay of Idarubicin Hydrochloride.

$$\text{Potency (mg) of idarubicin hydrochloride } (C_{26}H_{27}NO_9 \cdot HCl) = \text{Potency (mg) of idarubicin hydrochloride RS} \times \frac{A_T}{A_S} \times \frac{V}{50}$$

Assay Perform the test as directed under the Assay of Idarubicin Hydrochloride. However, weigh accurately a volume of Idarubicin Hydrochloride for Injection, equivalent to about 5 mg (potency) according to the labeled potency, dissolve in the mobile phase containing no sodium lauryl sulfate to make exactly 25 mL, and use this solution as the test solution.

Packaging and storage Preserve in hermetic containers.

Idoxuridine
이독수리딘



$C_9H_{11}IN_2O_5$: 354.10

1-[(2*R*,4*S*,5*R*)-4-Hydroxy-5-(hydroxymethyl) oxolan-2-yl]-5-iodo-1,2,3,4-tetrahydropyrimidine-2,4-dione [*54-42-2*]

Idoxuridine, when dried, contains NLT 98.0% and NMT 101.0% of idoxuridine ($C_9H_{11}IN_2O_5$).

Description Idoxuridine occurs as colorless crystals or a white crystalline powder and is odorless.

It is freely soluble in *N*,*N*-Dimethylformamide, slightly soluble in water, very slightly soluble in ethanol(95), and practically insoluble in ether.

It is soluble in sodium hydroxide TS.

Melting point—About 176 °C (with decomposition).

Identification (1) Add 5 mL of water to 0.01 g of Idoxuridine, dissolve by warming, add 5 mL of diphenylamine-acetic acid(100) TS, and heat for 5 minutes; the solution exhibits a blue color.

(2) Heat 0.1 g of Idoxuridine; a purple gas is generated.

(3) Dissolve 2 mg of Idoxuridine and idoxuridine RS in 50 mL of 0.01 mol/L sodium hydroxide TS, and with these solutions, determine the absorption spectra as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Optical rotation $[\alpha]_D^{20}$: Between +28° and +31° (0.20 g after drying, sodium hydroxide TS, 20 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 0.20 g of Idoxuridine in 5 mL of sodium hydroxide solution (1 in 200); the solution is colorless and clear.

(2) ***Iodine and iodide***—Dissolve 0.10 g of Idoxuridine in 20 mL of water and 5 mL of sodium hydroxide TS, add 5 mL of dilute sulfuric acid while immediately chilling with ice, mix with an occasional shaking, allow to stand for 10 minutes, and filter. Transfer the filtrate to a Nessler tube, add 10 mL of chloroform and 3 drops of a solution of potassium iodide (1 in 100), shake to mix for 30 seconds, and allow to stand; the chloroform layer is not more intense than the following control solution.

Control solution—Weigh accurately 0.111 g of potassium iodide and dissolve in water to make 1000 mL. Pipet 1 mL of this solution, add 19 mL of water, 5 mL of sodium hydroxide TS and 5 mL of dilute sulfuric acid, shake to mix, transfer the filtrate to a Nessler tube, and proceed in the same manner as the above.

(3) ***Heavy metals***—Proceed with 2.0 g of Idoxuridine according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Related substances***—Weigh 0.10 g of Idoxuridine, dissolve in 10 mL of a mixture of dilute ethanol and ammonia water(28) (99 : 1), and use this solution as the test solution. Perform the test with this solution as directed under the Thin Layer Chromatography. Spot 50 μL of the test solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate and diluted 2-propanol (2 in 3) (4 : 1) as the developing solvent to about 10 cm, and air-dry the plate. Again, change the developing direction to the perpendicular direction, proceed in the same manner to develop a second time, and air-dry the plate. Examine the plate under ultraviolet light (principal wavelength 254 nm); any spot other than the principal spot does not appear.

Loss on drying NMT 0.5% (2 g, in vacuum, 60 °C, 3

hours).

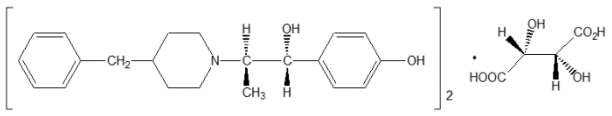
Residue on ignition NMT 0.3% (1 g).

Assay Weigh accurately about 0.7 g of Idoxuridine, previously dried, dissolve in 80 mL of *N*,*N*-dimethylformamide, and titrate the solution with 0.1 mol/L tetramethyl ammonium hydroxide VS (indicator: 5 drops of thymol blue-dimethyl formamide TS). The endpoint of the titration is when the yellow color of this solution turns to yellowish green and then finally to blue. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L tetramethylammonium hydroxide VS
= 35.410 mg of $C_9H_{11}IN_2O_5$

Packaging and storage Preserve in light-resistant, tight containers.

Ifenprodil Tartrate
이펜프로딜타르타르산염



$(C_{21}H_{27}NO_2)_2 \cdot C_4H_6O_6$: 800.98
4-[2-(4-Benzylpiperidin-1-yl)-1-hydroxypropyl]phenol; 2,3-dihydroxybutanedioic acid [*23210-58-4*]

Ifenprodil Tartrate contains NLT 98.5% and NMT 101.0% of ifenprodil tartrate [$(C_{21}H_{27}NO_2)_2 \cdot C_4H_6O_6$], calculated on the anhydrous basis.

Description Ifenprodil Tartrate occurs as a white crystalline powder and is odorless.
It is freely soluble in acetic acid(100), soluble in ethanol(95), slightly soluble in water or methanol, and practically insoluble in ether.

Optical rotation $[\alpha]_D^{20}$: Between + 11° and + 15° (1.0 g calculated on the anhydrous basis, ethanol(95), 20 mL, 100 mm).

Melting point About 148 °C (with decomposition).

Identification (1) Determine the absorption spectra of solutions of Ifenprodil Tartrate and Ifenprodil Tartrate RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Ifenprodil Tartrate and Ifenprodil Tartrate RS as directed in the potassium bromide disc method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers

(3) Dissolve 0.4 g of Ifenprodil Tartrate in 40 mL of water by warming. After cooling, add 0.5 mL of ammonia TS to this solution, extract twice with 40 mL each of chloroform, and collect the water layer separately. Take 30 mL of the water layer, and evaporate on a steam bath to dryness. After cooling, dissolve the residue in 6 mL of water; the resulting solution responds to the Qualitative Analysis for tartrate.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Ifenprodil Tartrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Dissolve 0.30 g of Ifenprodil Tartrate in 10 mL of diluted ethanol (3 in 4), and use this solution as the test solution. Pipet 1.0 mL of the test solution, add diluted ethanol (3 in 4) to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Then, develop the plate with a mixture of ethyl acetate, hexane, 1-butanol and ammonia water(28) (140 : 40 : 20 : 1) to a distance of about 10 cm, and air-dry the plate. Spray hexachloroplatinic(IV) acid-potassium iodide TS evenly on the plate; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Water NMT 4.0% (0.5 g, volume titration, direct titration).

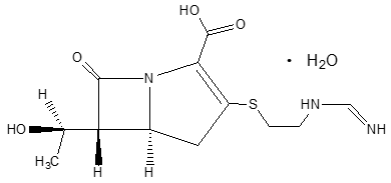
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Ifenprodil Tartrate, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 40.05 mg of $(C_{21}H_{27}NO_2)_2 \cdot C_4H_6O_6$

Packaging and storage Preserve in light-resistant, well-closed containers.

Imipenem Hydrate
이미페넴수화물



$C_{12}H_{17}N_3O_4S \cdot H_2O$: 317.36

(5*R*,6*S*)-3-({2-[(*E*)-(aminomethylidene)amino]ethyl}sulfanyl)-6-[(1*R*)-1-hydroxyethyl]-7-oxo-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylic acid [*54-42-2*]

Imipenem Hydrate contains NLT 980 μg and NMT 1010 μg (potency) of imipenem ($C_{12}H_{17}N_3O_4$: 299.35) per mg, calculated on the anhydrous basis.

Description Imipenem Hydrate occurs as a white to sulfur yellow crystalline powder.
It is sparingly soluble in water and practically insoluble in ethanol(99.5).

Identification (1) Determine the absorption spectra of solutions of Imipenem Hydrate and imipenem RS 0.1 mol/L 3-(*N*-morpholino) propanesulfonate buffer solution (pH 7.0) (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Imipenem Hydrate and imipenem RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between +89° and +94° (50 mg, calculated on the anhydrous basis, 3-(*N*-morpholino)propanesulfonate buffer solution (pH 7.0), 10 mL, 100 mm).

pH Dissolve 1.0 g of Imipenem Hydrate in 200 mL of water; the pH of this solution is between 4.5 and 7.0.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Imipenem and perform the test according to Method 2. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Weigh 2.0 g of Imipenem Hydrate in a crucible, add 5 mL of nitric acid and 1 mL of sulfuric acid, and heat carefully until white fumes are produced. Cool, add 2 mL of nitric acid, heat, and repeat this step one more time. Next, add 2 mL of hydrogen peroxide, heat, and repeat until the solution becomes colorless to pale yellow. After cooling, heat again until white fumes are produced. After cooling, perform the test with a solution prepared by adding water to make 5 mL (NMT 1 ppm).

(3) ***Related substances***—Weigh accurately about 50 mg of Imipenem Hydrate, dissolve in 0.1 mol/L 3-(*N*-morpholino)propanesulfonate buffer solution (pH 7.0) to make exactly 50 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add 0.1 mol/L 3-(*N*-morpholino) propanesulfonate buffer solution (pH 7.0) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak area of each solution as directed in the automatic integration method; the peak area of thienamycin from the test solution is not greater than 1.4 times the peak area of imipenem from the standard solution, and each of the peak areas other than those of imipenem and thienamycin from the test solution is not greater than 1/3 of the peak area of imipenem from the standard solution. Also, the sum of the peak areas other than those of imipenem and thienamycin from the test solution is not greater than the peak area of imipenem from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed under the operating conditions in the Assay.

System suitability

System performance: Proceed as directed under the system suitability under the Assay.

Test for required detectability: Pipet 5 mL of the standard solution and add 0.1 mol/L 3-(*N*-morpholino)propanesulfonate buffer solution (pH 7.0) to make exactly 50 mL. Confirm that the peak area of imipenem obtained from 10 μL of this solution is within the range between 7% and 13% of the peak area of imipenem from the standard solution.

System repeatability: Repeat the test 6 times according to the above conditions with 10 μL each of the standard solutions; the relative standard deviation of the peak area of imipenem is NMT 2.0%.

Relative retention time: The relative retention time of thienamycin with respect to imipenem is about 0.8.

Time span of measurement: About 2 times the retention time of imipenem.

Water Between 5.0% and 8.0% (20 mg, coulometric titration, moisture evaporation temperature 140 ℃).

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins Less than 0.17 EU per mg (potency) of imipenem when used in the manufacturing of sterile preparations.

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 50 mg (potency) of

imipenem hydrate and imipenem RS, dissolve in 0.1 mol/L 3-(*N*-morpholino) propanesulfonate buffer solution (pH 7.0) to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas A_T and A_S of imipenem. However, perform the test within 30 minutes after preparing the test solution and the standard solution.

$$\text{Potency (μg) of imipenem } (C_{12}H_{17}N_3O_4S) = \text{Potency (μg) of imipenem RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of 0.1 mol/L 3-(*N*-morpholino)propanesulfonate buffer solution (pH 7.0) and acetonitrile (100 : 1).

Flow rate: Adjust the flow rate so that the retention time of imipenem is about 6 minutes.

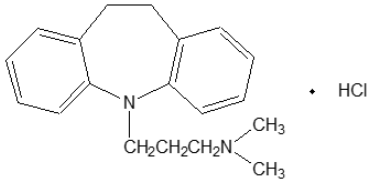
System suitability

System performance: Weigh accurately about 50 mg of Imipenem Hydrate and about 75 mg of resorcinol and dissolve in 50 mL of 0.1 mol/L 3-(*N*-morpholino) propanesulfonate buffer solution (pH 7.0). Proceed with 10 μL of this solution under the above conditions; imipenem and resorcinol are eluted in this order with the resolution being NLT 4.

System repeatability: Repeat the test 5 times according to the above conditions with 10 μL each of the standard solutions; the relative standard deviation of the peak area of imipenem is NMT 0.80%.

Packaging and storage Preserve in hermetic containers.

Imipramine Hydrochloride
이미프라민염산염



$C_{19}H_{24}N_2 \cdot HCl$: 316.87

3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-*N*,*N*-dimethylpropan-1-amine Hydrochloride [*113-52-0*]

Imipramine Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of imipramine hydrochloride ($C_{19}H_{24}N_2 \cdot HCl$).

Description Imipramine Hydrochloride occurs as a white to pale yellowish white crystalline powder and is odorless.

It is freely soluble in water or ethanol(95) and practically insoluble in ether.

Dissolve 1.0 g of Imipramine Hydrochloride in 10 mL of water; the pH of this solution is between 4.2 and 5.2.

It is gradually colored by light.

Identification (1) Dissolve 5 mg of Imipramine Hydrochloride in 2 mL of nitric acid; the resulting solution exhibits a deep blue color.

(2) Determine the absorption spectra of solutions prepared by dissolving 5 mg each of Imipramine Hydrochloride and imipramine hydrochloride RS in 250 mL of 0.01 mol/L hydrochloric acid TS as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Dissolve 50 mg of Imipramine Hydrochloride in 5 mL of water, add 1 mL of ammonia TS, allow to stand for 5 minutes, and filter. Acidify the filtrate with dilute nitric acid; the solution responds to the Qualitative Analysis (2) for chloride.

Melting point Between 170 and 174 ℃ (with decomposition).

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Imipramine Hydrochloride in 10 mL of water; the solution is clear and the color is not more intense than the following control solution.

Control solution—Pipet accurately 1.0 mL of cobaltous(II) chloride hexahydrate colorimetric stock solution, 2.4 mL of iron(III) chloride hexahydrate colorimetric stock solution, 0.4 mL of copper(II) Sulfate pentahydrate colorimetric stock solution and 6.2 mL of diluted hydrochloric acid (1 in 40) to mix, pipet 0.5 mL of the resulting solution, and add exactly 9.5 mL of water to mix.

(2) ***Heavy metals*—**Proceed with 1.0 g of Imipramine Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Iminodibenzyl*—**Weigh 50 mg of Imipramine Hydrochloride, transfer to a 25-mL brown volumetric flask, dissolve in 10 mL of a mixture of hydrochloric acid and ethanol(95) (1 : 1), add 5 mL of ethanol(95) solution of furfural (1 in 250) and 5 mL of hydrochloric acid while cooling with iced water, and allow to stand at 25 ℃ for 3 hours. Next, add a mixture of hydrochloric acid and ethanol(95) (1 : 1) to make 25 mL. Determine the absorption spectra of the solution according to the Ultraviolet-visible Spectroscopy; absorbance at wavelength of 565

nm is NMT 0.16.

(4) ***Related substances***—Dissolve 0.20 g of Imipramine Hydrochloride in 10 mL of ethanol(95) and use this solution as the test solution. Pipet 1 mL of this solution and add ethanol(95) to make exactly 50 mL. Pipet 5 mL of this solution, add ethanol(95) to make exactly 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, acetic acid(100), hydrochloric acid and water (11 : 7 : 1 : 1) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Spray potassium dichromate-hydrochloric acid TS evenly onto the plate; spots other than the principal spot from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Imipramine Hydrochloride, previously dried, dissolve in 20 mL of water, and add 5 mL of sodium hydroxide TS. Extract 3 times with 20 mL of chloroform. Each time, filter the chloroform extract with a funnel with anhydrous sodium sulfate on cotton wool. Combine all of the chloroform extracts and titrate with 0.1 mol/L perchloric acid VS (indicator: 10 drops of metanil yellow). However, the endpoint of titration is when the yellow color of the solution turns purple. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 31.687 mg of $C_{19}H_{24}N_2 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Imipramine Hydrochloride Tablets
이미프라민염산염 정

Imipramine Hydrochloride Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of imipramine hydrochloride ($C_{19}H_{24}N_2 \cdot HCl$: 316.87).

Method of preparation Prepare as directed under Tablets, with Imipramine Hydrochloride.

Identification (1) Weigh an amount of Imipramine Hydrochloride Tablets, previously powdered, equivalent to 0.25 g of imipramine hydrochloride according to the labeled amount, add 25 mL of chloroform, shake well to mix, and then filter. Evaporate the filtrate to dryness on a steam bath, and perform the test with the residue as directed under the Identification (1) of Imipramine Hydrochloride.

(2) Take an amount of the residue from (1), equivalent to 5 mg of imipramine hydrochloride, and dissolve in 250 mL of 0.01 mol/L hydrochloric acid TS. Determine the absorption spectra of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 249 nm and 253 nm and a shoulder between 270 nm and 280 nm.

(3) Dry the residue from (1) at 105 ℃ for 2 hours; the melting point is between 170 and 174 ℃ (with decomposition).

Dissolution Perform the test with 1 tablet of Imipramine Hydrochloride Tablets at 75 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of diluted pH 6.8 phosphate buffer solution (1 in 2) as the dissolution medium. Take 20 mL or more of the dissolved solution 60 minutes after starting the test, and filter through a membrane filter with a pore size of NMT 0.8 μm. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add diluted pH 6.8 phosphate buffer solution (1 in 2) to make exactly *V* mL of a solution containing about 10 μg per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 25 mg of imipramine hydrochloride RS, previously dried at 105 ℃ for 2 hours, and dissolve in pH 6.8 phosphate buffer solution (1 in 2) to make exactly 100 mL. Pipet 4 mL of this solution, add diluted pH 6.8 phosphate buffer solution (1 in 2) to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances of the test solution and the standard solution, A_T and A_S, as directed under the Ultraviolet-visible Spectroscopy at the wavelength of 250 nm.

The acceptable dissolution criterion is that dissolution rate of Imipramine Hydrochloride Tablets in 60 minutes is NLT 75%.

Dissolution rate (%) of the labeled amount of imipramine hydrochloride ($C_{19}H_{24}N_2 \cdot HCl$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 36$$

W_s: Amount (mg) of the reference standard

C: Labeled amount (mg) of imipramine hydrochloride ($C_{19}H_{24}N_2 \cdot HCl$) in 1 tablet

Uniformity of dosage units Meets the requirements.

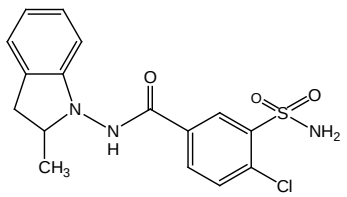
Assay Take 20 tablets of Imipramine Hydrochloride Tablets, add exactly 200 mL of 0.01 mol/L hydrochloric acid TS, and shake well to mix until the tablets completely disintegrate. After centrifuging this solution, pipet an amount of the clear supernatant equivalent to about 25 mg of imipramine hydrochloride ($C_{19}H_{24}N_2 \cdot HCl$), add 0.01 mol/L hydrochloric acid TS to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg of imipramine hydrochlo-

ride RS, previously dried at 105 ℃ for 2 hours, dissolve in 0.01 mol/L hydrochloric acid TS to make exactly 100 mL, and use this solution as the standard solution. Pipet 3 mL each of the test solution and the standard solution, transfer into two separatory funnels containing 15 mL of pH 5.6 potassium hydrogen phthalate, 8 mL of bromocresol green-sodium hydroxide TS and 30 mL of chloroform, respectively, and shake to mix. Filter the chloroform layer through a small amount of absorbent cotton placed on the funnel, and transfer into a 100-mL volumetric flask. Then repeat the same procedure 2 times with 30 mL each of chloroform, combine the chloroform layer into the volumetric flask above, and add chloroform to make 100 mL. Perform the test with these solutions as directed under the Ultraviolet-visible Spectroscopy, using a solution, prepared with 3 mL of 0.01 mol/L hydrochloric acid TS in the same manner, as a control solution, and determine the absorbances of each solution obtained from the test solution and the standard solution, A_T and A_S, at the wavelength of 416 nm, respectively.

Amount (mg) of imipramine hydrochloride ($C_{19}H_{24}N_2 \cdot HCl$)
= Amount (mg) of imipramine hydrochloride RS$\times \frac{A_T}{A_S}$

Packaging and storage Preserve in tight containers.

Indapamide
인다파미드



$C_{16}H_{16}ClN_3O_3S$: 365.84
4-Chloro-*N*-(2-methyl-2,3-dihydroindol-1-yl)-3-sulfamoylbenzamide [*26807-65-8*]

Indapamide contains NLT 98.0% and NMT 101.0% of indapamide ($C_{16}H_{16}ClN_3O_3S$), calculated on the dried basis

Description Indapamide occurs as a white crystalline powder.
It is freely soluble in ethanol(99.5) and practically insoluble in water.
A solution of Indapamide in ethanol(99.5) (1 in 10) shows no optical rotation.

Identification (1) Determine the absorption spectra of solutions of Indapamide and indapamide RS in methanol (1 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Indapamide and Indapamide RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Perform the test with Indapamide as directed under the Flame Coloration; it exhibits a green color.

Melting point Between 167 and 171 ℃.

Purity (1) ***Chloride***—Dissolve 1.5 g of Indapamide in 50 mL of water, shake to mix for 15 minutes, allow to stand in an ice water for 30 minutes, and filter. To 30 mL of the filtrate, add 6 mL of dilute acetic acid and water to make 50 mL, and perform the test using this solution as the test solution. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid (NMT 0.01%).

(2) ***Heavy metals***—Proceed with 2.0 g of Indapamide according to Method 2 under the Heavy Metals, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Perform the test while protected from light. Dissolve 0.3 g of Indapamide in methanol to make exactly 10 mL, and use this solution as the test solution. Separately, dissolve 30 mg of Indapamide RS in methanol to make exactly 100 mL, and use this solution as the standard solution (1). Add methanol to 10 mL of the standard solution (1) to make exactly 20 mL, and use this solution as the standard solution (2). And, add methanol to 10 mL of the standard solution (2) to make exactly 20 mL, and use this solution as the standard solution (3). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution, the standard solution (1), the standard solution (2) and the standard solution (3) on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of toluene, ethyl acetate and acetic acid(100) (70 : 30 : 1) to a distance of about 15 cm, and air-dry the plate. Examine under ultraviolet light; the spots other than the principal spot obtained from the test solution are not larger or more intense than the spots from the standard solution (2) (0.5%), and the total intensity of the spots other than the principal spot obtained from the test solution is NMT 2.0%.

Loss on drying NMT 3.0% (0.5 g, NMT 0.67 kPa, phosphorus pentoxide, 110 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.1 g of Indapamide, dissolve in 5.0 mL of the internal standard solution, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately 20 mg of Indapamide RS, dissolve in 1.0 mL of the internal standard solution, add the mobile phase to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and

the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the ratios Q_T and Q_S, of the peak area of indapamide to the peak area of the internal standard substance from each solution.

$$\text{Amount (mg) of Indapamide } (C_{16}H_{16}ClN_3O_3S) = \text{Amount (mg) of indapamide RS} \times \frac{Q_T}{Q_S} \times 5$$

Internal standard solution—Weigh accurately 50 mg of *p*-chloroacetanilide, and dissolve in methanol to make exactly 10 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of water, acetonitrile, methanol and acetic acid(100) (650 : 175 : 175 : 1).

Flow rate: 2.0 mL/min

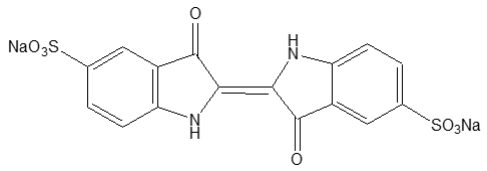
System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; the resolution between *the p*-chloroacetanilide peak and the indapamide peak is NLT 2.0, and the symmetry factor of Indapamide peak is NMT 2.0.

System repeatability: Repeat the test 5 times with 5 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of Indapamide is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Indigocarmine
인디고카르민



$C_{16}H_8N_2Na_2O_8S_2$: 466.35

Disodium (2*E*)-3-oxo-2-(3-oxo-5-sulfonato-1*H*-indol-2-ylidene)-1*H*-indole-5-sulfonate [*860-22-0*]

Indigocarmine, when dried, contains NLT 95.0% and NMT 101.0% of Indigocarmine ($C_{16}H_8N_2Na_2O_8S_2$).

Description Indigocarmine occurs as a blue to dark blue powder or grain, and is odorless.

It is sparingly soluble in water and practically insoluble in ethanol(95) or ether.

It is hygroscopic.

When compressed, it exhibits a color and luster similar to those of copper.

Identification (1) An aqueous solution of Indigocarmine (1 in 100) exhibits a dark blue color. Perform the test as below using this solution as the test solution; the dark blue color of each solution disappears.

(i) Add 1 mL of nitric acid to 2 mL of the test solution.

(ii) Add 1 mL of bromine TS to 2 mL of the test solution.

(iii) Add 1 mL of chlorine TS to 2 mL of the test solution.

(iv) Add 2 mL of sodium hydroxide TS and 0.2 g of zinc powder to 2 mL of the test solution, and warm the solution.

(2) Dissolve 0.1g of Indigocarmine and Indigocarmine RS in 100 mL of ammonium acetate (1 in 650). Add ammonium acetate (1 in 650) to 1 mL each of these solutions to make 100 mL and determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Ignite 1 g of Indigocarmine to carbonize After cooling, add 20 mL of water to the residue, shake to mix and filter; the filtrate responds to the Qualitative Analysis (1) for sodium salt and sulfate.

pH Dissolve 0.10 g of Indigocarmine in 20 mL of water; the pH of this solution is between 5.0 and 6.0.

Purity (1) ***Water insoluble matter***—Add 200 mL of water to 1.0 g of Indigocarmine and shake to mix, filter it through a tared glass filter, wash with water until the last washings exhibit no blue color, and dry at 105 ℃ for 4 hours; the mass of the residue is NMT 5.0 mg.

(2) ***Lead***—Put 4.0 g of Indigocarmine in a Kjeldahl flask, moisten it with water, and then add 10 mL of sulfuric acid and 5 mL of nitric acid. As soon as the initial violent reaction subsides, heat until the most of the brown fumes disappears. Add 1 to 3 mL of nitric acid repeatedly while heating until Indigocarmine is almost decomposed and most of the organic matter becomes a solution. Then, carefully add 5 mL of perchloric acid little by little. When the initial violent reaction subsides, keep adding nitric acid little by little while heating until it becomes colorless. Add perchloric acid and allow to stand for 10 to 20 minutes. If the solution does not become clear, add 1 to 3 mL of perchloric acid and add nitric acid until the solution becomes colorless. Boil this solution for 10 to 15 minutes, then cool, and neutralize with 1 mol/L sodium hydroxide. Transfer this solution into a 100-mL volumetric flask, add water to make 100 mL, and use this solution as the test solution. Put 5 mL of the test solution into a separatory funnel, wash the flask with 10 mL of water and combine the washings into it. Add 3 mL of diammonium hydrogen citrate, 0.5 mL of hydroxylamine hydrochloride TS and 2 drops of phenol red TS, and then add

ammonia water(28) until the solution becomes alkaline. Cool the solution, if necessary, add 1 mL of potassium cyanide solution, then extract with 5 mL of extracting dithizone solution until the extract turns green, and combine the extract into another separatory funnel. Add 20 mL of diluted nitric acid (1 in 100) to the combined extracts, shake to mix for 30 seconds, and discard the chloroform layer. Add 5.0 mL of standard dithizone solution and 4 mL of ammonia-cyanide TS to the nitric acid layer, and shake for 30 seconds to mix. The purple color of the chloroform layer is not more intense than that of the solution prepared in the same manner as the test solution with 10 mL of diluted lead standard solution (NMT 10 ppm).

Diluted lead standard solution—Pipet 5 mL of the lead standard solution, and add diluted nitric acid (1 in 100) to make 50 mL.

(3) ***Arsenic***—Put 0.8 g of Indigocarmine into a Kjeldahl flask, add 5 mL each of sulfuric acid and nitric acid, and heat gently. Add 2 to 3 mL of nitric acid from time to time, and continue heating until the liquid becomes colorless to pale yellow. After cooling, add 15 mL of saturated ammonium oxalate, then heat to concentrate until thick white fumes appear, and make 2 to 3 mL. After cooling, add water to make 10 mL, and perform the test with 5 mL of this solution as the test solution (NMT 5 ppm).

Loss on drying NMT 10.0% (1 g, 105 ℃, 2 hours).

Residue on ignition Between 28.0% and 38.0% (1 g after drying).

Assay Weigh accurately about 0.5 g of Indigocarmine, previously dried, dissolve it in 15 g of sodium hydrogen tartrate monohydrate and 200 mL of water, boil while passing through carbon dioxide, and titrate with 0.1 mol/L titanium(III) chloride VS while hot. The endpoint of the titration is when the blue color of this solution turns yellow to orange.

Each mL of 0.1 mol/L titanium(III) chloride VS
= 23.318 mg of $C_{16}H_8N_2Na_2O_8S_2$

Packaging and storage Preserve in light-resistant, tight containers.

Indigocarmine Injection
인디고카르민 주사액

Indigocarmine Injection is an aqueous solution for injection. Indigocarmine Injection contains NLT95.0% and NMT 105.0% of the labeled amount of indigocarmine ($C_{16}H_8N_2Na_2O_8S_2$: 466.35).

Method of preparation Prepare as directed under Injections, with Indigocarmine.

Description Indigocarmine Injection occurs as a dark blue liquid.

pH—Between 3.0 and 5.0.

Identification (1) Take an amount of Indigocarmine Injection, equivalent to 20 mg of Indigocarmine, according to the labeled amount, add 1 mL of nitric acid; the dark blue color of the solution disappears and a yellowish brown color develops.

(2) Take an amount of Indigocarmine Injection, equivalent to 20 mg of Indigocarmine, according to the labeled amount, add 1 mL of bromine TS; the dark blue color disappears and a yellowish brown color develops.

(3) Take an amount of Indigocarmine Injection, equivalent to 20 mg of Indigocarmine, according to the labeled amount, add 1 mL of chlorine TS; the dark blue color disappears and a yellowish brown color develops.

(4) Take an amount of Indigocarmine Injection, equivalent to 10 mg of Indigocarmine, according to the labeled amount, add ammonium acetate solution (1 in 650) to make 1000 mL and determine the absorption spectrum of the solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at 610 nm to 614 nm.

Sterility Meets the requirements.

Bacterial endotoxins Less than 7.5 EU per mg of indigocarmine.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

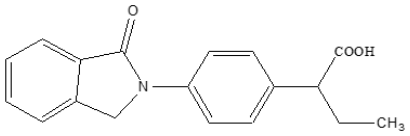
Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Indigocarmine Injection equivalent to about 0.2 g of indigocarmine ($C_{16}H_8N_2Na_2O_8S_2$), dissolve in 6 g of sodium hydrogen tartrate monohydrate and water to make 200 mL, boil under a carbon dioxide stream, and perform the test as directed in the Assay of Indigocarmine.

Each mL of 0.1 mol/L titanium(III) chloride VS
= 23.318 mg of $C_{16}H_8N_2Na_2O_8S_2$

Packaging and storage Preserve in light-resistant, hermetic containers.

Indobufen
인도부펜



$C_{18}H_{17}NO_3$: 295.33

(±)-4-(1,3-Dihydro-1-oxo-2*H*-isoindol-2-yl)-α-ethylbenzeneacetic acid, [*63610-08-2*]

Indobufen contains NLT 97.0% and NMT 101.0% of indobufen ($C_{18}H_{17}$ NO $_3$), calculated on the anhydrous basis.

Description Indobufen occurs as a white creamy powder.
It is freely soluble in dimethylformamide and slightly soluble in methanol and practically insoluble in water.

Identification Determine the infrared spectra of Indobufen and indobufen RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

Absorbance $E_{1cm}^{1\%}$ (282 nm): Between 460 and 510 (calculated on the anhydrous basis, 1 mg, methanol, 100 mL).

Melting point Between 180 ℃ and185 ˚C.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Indobufen in 40 mL of 0.1 mol/L sodium hydroxide; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Indobufen according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Zinc***—Dissolve 1.0 g of Indobufen in 50 mL of water and 5 mL of 30% ammonia water, add water to make 100 mL, and use this solution as the test solution. Separately, take 2.0 mL of standard zinc solution, add 5 mL of 30% ammonia water, add water to make 100 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Atomic Absorption Spectroscopy according to the following conditions; the absorbance of the test solution is not greater than that of the standard solution (NMT 50 ppm).

Gas: Air–acetylene
Lamp: Zinc hollow cathode lamp
Wavelength: 213.9 nm

(4) ***Related substances***—Weigh accurately 0.1 g of Indobufen, add methanol to make 50 mL, and use this solution as the test solution. Perform the test with the test solution as directed under the Liquid Chromatography according to the conditions under the Assay. Determine the peak area of each solution as directed in the automatic integration method, and calculate the amount of each related substance; the area of the peaks other than indobufen is NMT 2.0% of the total peak areas.

Water NMT 1.0% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.1 g each of Indobufen and indobufen RS and dissolve in methanol to make 50 mL. Pipet 2.0 mL of the resulting solution, add methanol to make 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of indobufen, A_T and A_S, in each solution.

$$\text{Amount (g) of Indobufen } (C_{18}H_{17}NO_3) = \text{Amount (g) of indobufen RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 256 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 to 10 μm in particle diameter).

Mobile phase: A mixture of acetic acid buffer solution (pH 4.5) and methanol (55 : 45).

Flow rate: 2.0 mL/min

Packaging and storage Preserve in tight containers.

Indobufen Tablets
인도부펜 정

Indobufen Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of indobufen ($C_{18}H_{17}NO_3$: 295.33).

Method of preparation Prepare as directed under Tablets, with Indobufen.

Identification The retention times of major peaks of the test solution and the standard solution for Assay is the same.

Dissolution Perform the test with 1 tablet of Indobufen Tablets at 150 revolutions per minute according to Method 1, using 900 mL of phosphate buffer solution, pH 6.8, as the dissolution medium. Filter the medium 20 minutes after starting the dissolution test, take 10.0 mL of the filtrate, add phosphate buffer solution, pH 6.8, to make 250 mL, and use this solution as the test solution. Sepa-

rately, weigh accurately about 50 mg of indobufen RS, add phosphate buffer solution, pH 6.8, dissolve on a steam bath by warming gently to make a solution having 8 μg/mL of indobufen concentration, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance at the wavelength of 279 nm. The dissolution rate in 20 minutes is NLT 70%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Indobufen Tablets, and powder. Weigh accurately an amount, equivalent to about 0.1 g of indobufen ($C_{18}H_{17}NO_3$), add 40 mL of methanol, shake for about 1 hour to mix, and add methanol to make 50 mL. After filtering this solution, take 2.0 mL of the filtrate, add methanol to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of indobufen RS, and add methanol to make 50 mL. Take 2.0 mL of this solution, add methanol to make 100 mL, and use it as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of indobufen in each solution.

$$\text{Amount (mg) of indobufen } (C_{18}H_{17}NO_3) = \text{Amount (mg) of indobufen RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 256 nm).

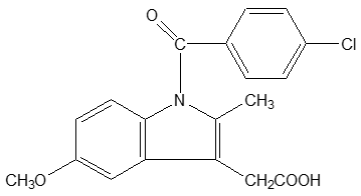
Column: A stainless steel column about 4.6 mm in internal diameter and 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of pH 4.5 acetic acid buffer solution and methanol (55 : 45).

Flow rate: 2.0 mL/min

Packaging and storage Preserve in well-closed containers.

Indometacin
인도메타신



$C_{19}H_{16}ClNO_4$: 357.79

2-{1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid [*53-86-1*]

Indometacin, when dried, contains NLT 98.0% and NMT 101.0% of indometacin ($C_{19}H_{16}ClNO_4$).

Description Indometacin occurs as a fine white to pale yellow crystalline powder.
It is sparingly soluble in methanol, ethanol(95) or ether and is practically insoluble in water.
It dissolves in sodium hydroxide TS.
It is colored by light.

Melting point—Between 155 and 162 °C.

Identification (1) Prepare 100 mL of a solution made by dissolving 2 mg of Indometacin in 100 mL of methanol, and determine the absorption spectrum of the solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 317 nm and 321 nm.

(2) Determine the infrared spectra of Indometacin and Indometacin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers. If any difference appears between the spectra, recrystallize each from ether, take the crystals, previously dried, and perform the test.

(3) Perform the test with Indometacin as directed under the Flame Coloration (2); a green color is observed.

Purity (1) ***Acid***—Add 50 mL of water to 1.0 g of Indometacin, shake well to mix for 5 minutes, and filter it. To the filtrate, add 0.20 mL of 0.1 mol/L sodium hydroxide TS and 1 drop of phenolphthalein TS; the solution exhibits a red color.

(2) ***Heavy metals***—Proceed with 1.0 g of Indometacin according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Indometacin according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.10 g of Indometacin in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution and add methanol to make exactly 50 mL. Pipet 5 mL of this solution, add methanol to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 25 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Then, develop the plate with a mixture of anhydrous ether and acetic acid(100) (100: 3) to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 °C, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.7 g of Indometacin, previously dried, dissolve in 60 mL of methanol, add 30 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of phenolphthalein TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 35.779 mg of $C_{19}H_{16}ClNO_4$

Packaging and storage Preserve in light-resistant, tight containers.

Indometacin Capsules
인도메타신 캡슐

Indometacin Capsules contain NLT 90.0% and NMT 110.0% of indometacin ($C_{19}H_{16}ClNO_4$: 357.79).

Method of preparation Prepare as directed under Capsules, with Indometacin.

Identification Take out the content of Indometacin Capsules, powder, and use it as a sample. Weigh an amount of powder, equivalent to 0.1 g of indometacin according to the labeled amount, add 20 mL of chloroform, and shake well to mix. Then centrifuge, and filter the clear supernatant. Evaporate the filtrate to dryness, cool, and dissolve in 20 mL of methanol. Add methanol to 10 mL of this solution to make 50 mL. Add methanol to 2 mL of this solution to make 100 mL, and use this solution as the test solution. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at 317 nm to 321 nm.

Purity ***Related substances***—Take out the content of Indometacin Capsules and power. Take a portion of the powder, equivalent to 0.10 g of Indometacin according to the labeled amount, add exactly 10 mL of methanol, shake well, filter and use the filtrate as the test solution. Separately, weigh 25 mg of indometacin RS and dissolve in methanol to make exactly 50 mL. Pipet 1 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the standard solution. Perform the test as directed under the Purity (4) of Indometacin.

Dissolution Perform the test with 1 capsule of Indometacin Capsules at 100 revolutions per minute as directed under the Method 1 under the Dissolution, using 900 mL of a mixture of water and phosphate buffer solution, pH 7.2, (4 : 1) as the dissolution medium. Take NLT 20 mL of the dissolved solution after 20 minutes from starting the dissolution test, and filter through a membrane filter with a pore size of NMT 0.8 μm. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 30 mg of indometacin RS, previously dried at 105 ℃ for 4 hours, dissolve in a mixture of water and phosphate buffer solution, pH 7.2, (4 : 1) to make exactly 1000 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 320 nm as directed under the Ultraviolet-visible Spectroscopy.

It meets the requirements if the dissolution rate of Indometacin Capsules in 20 minutes is NLT 75%.

Dissolution rate (%) of the labeled amount of indometacin ($C_{19}H_{16}ClNO_4$) $= W_S \times \frac{A_T}{A_S} \times \frac{90}{C}$

W_s: Amount (mg) of the reference standard
C: Labeled amount (mg) of indometacin ($C_{19}H_{16}ClNO_4$) per capsule

Uniformity of dosage units Meets the requirements.

Assay With NLT 20 capsules of Indometacin Capsules, open the capsule, carefully take out the content, weigh accurately the mass, and powder. Weigh accurately an amount the powder, equivalent to about 50 mg of indometacin ($C_{19}H_{16}ClNO_4$), dissolve with 40 mL of methanol, and add methanol again to make exactly 50 mL. Filter this solution, discarding the first 10 mL of the filtrate. Pipet the subsequent 5.0 mL of the filtrate, add exactly 3 mL of the internal standard solution, add the mobile phase to make 100 mL and use this solution as the test solution. Separately, weigh accurately about 50 mg of indometacin RS, previously dried at 105 °C for 4 hours, and dissolve in methanol to make exactly 50 mL. Pipet 5 mL of this solution, add exactly 3 mL of the internal standard solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under Liquid Chromatography according to the following conditions and calculate the ratios, QT and QS, of the peak area of Indometacin to that of the internal standard, for the test solution and the standard solution, respectively.

Amount (mg) of indometacin ($C_{19}H_{16}ClNO_4$)
= Amount (mg) of indometacin RS $\times \frac{Q_T}{Q_S}$

Internal standard solution—A solution of butyl p-hydroxybenzoate in methanol (1 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (7 μm in particle diameter).

Column temperature: A constant temperature of

about 25 °C.

Mobile phase: A mixture of methanol and diluted phosphoric acid (1 in 1000) (7 : 3).

Flow rate: Adjust the flow rate so that the retention time of indometacin is about 8 minutes.

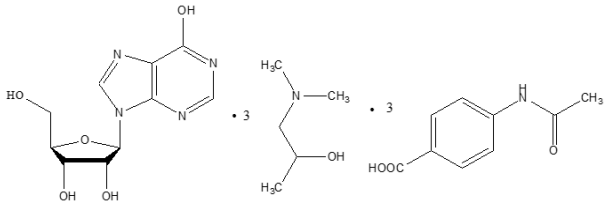
System suitability

System performance: Dissolve 50 mg of 4-chlorobenzoate, 30 mg of butyl p-hydroxybenzoate, and 50 mg of indometacin in 50 mL of methanol. To 5 mL of this solution, add the mobile phase to make 100 mL. Proceed with 20 μL of this solution under the above operating conditions; 4-chlorobenzoate, butyl p-hydroxybenzoate and indometacin are eluted in this order. The resolution between 4-chlorobenzoate and butyl p-hydroxybenzoate is NLT 2.0, and the resolution between butyl p-hydroxybenzoate and indometacin is NLT 5.0

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution under the above operating conditions; the relative standard deviation of the ratios of the peak areas of indometacin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Inosiplex
이노시플렉스



$C_{52}H_{78}N_{10}O_{17}$: 1115.23

Inosine 1-(dimethylamino)-2-propanol 4-(acetylamino)benzoate (1:3:3), *[36703-88-5]*

Inosiplex contains *N*,*N*-dimethylaminoisopropanol, para-acetaminobenzoic acid and inosine at a molecular ratio of 3 : 3 : 1. Inosiplex, when dried, contains NLT 26.4% and NMT 29.1% of *N*,*N*-dimethylaminoisopropanol ($C_5H_{13}NO$: 103.16), NLT 45.8% and NMT 50.6% of para-acetaminobenzoic acid ($C_9H_9NO_3$: 179.17), and NLT 22.9% and NMT 25.3% of inosine ($C_{10}H_{12}N_4O_5$: 268.23).

Description Inosiplex occurs as a white to milky white crystalline powder.
It is freely soluble in water, and practically insoluble in acetone, chloroform or toluene.
It has a slightly bitter taste.

Identification (1) Determine the absorption spectra of an aqueous solution (1 in 100000) of Inosiplex as directed under Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelength of 260 nm.

(2) Perform the test with Inosiplex according to the Assay (2); the retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Purity (1) ***Clarity and color of solution*—**An aqueous solution of Inosiplex (1 in 10) is colorless and clear.

(2) ***Chloride*—**Dissolve 0.70 g of Inosiplex in 30 mL of water and add 6 mL of dilute nitric acid to mix. Filter the precipitate that forms using a glass filter (G_4) under vacuum, wash with 15 mL of water, collect the washed filtrate and washings, and add water to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution with 0.2 mL of 0.01 mol/L hydrochloric acid (NMT 0.01%).

(3) ***Sulfate*—**Weigh 1.0 g of Inosiplex, dissolve in 30 mL of water, add 1 mL of dilute hydrochloric acid, and shake to mix. Filter the precipitate that forms using a glass filter (G_4) under vacuum, wash with a small amount of water, collect the washed filtrate and washings and add water to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution with 0.4 mL of 0.005 mol/L sulfuric acid (NMT 0.002%).

(4) ***Heavy metals***—Proceed with 2.0 g of Inosiplex according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

Loss on drying NMT 1.0% (1 g, 60℃, 30 minutes, in vacuum).

Assay (1) ***N,N-dimethylaminoisopropanol***—Weigh accurately about 0.1 g of Inosiplex, previously dried, and dissolve in 10 mL of 1 mol/L sodium hydroxide VS and 10 mL of water in a distillation flask. Add 20 mL of 0.1 mol/L hydrochloric acid VS to the receptacle and distill under weak vacuum. Stop distillation when the solution in the distillation flask becomes about 5 mL, cool, add 10 mL of water, and continue distilling until the solution in the distillation flask becomes about 5 mL. Titrate the distillate collected in the receptacle with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of bromocresol green-methyl red TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L hydrochloric acid VS
= 10.316 mg of $C_5H_{13}NO$

(2) ***Para-acetaminobenzoic acid and inosine***—Weigh accurately about 0.1 g of Inosiplex, previously dried, and add the mobile phase to make 100 mL. Pipet 5.0 mL of this solution, add 5.0 mL of the internal standard solution, add the mobile phase to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of para-acetaminobenzoic acid RS and about 25 mg of inosine RS, and add the mobile phase to make 100 mL. Pipet 5.0 mL of this solution, add 5.0 mL of the internal standard solution, add the mobile

phase to make 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak area ratios of para-acetaminobenzoic acid and inosine, Q_{T1}, Q_{T2}, Q_{S1} and Q_{S2}, with respect to the peak area of the internal standard.

Amount (mg) of para-acetaminobenzoic acid ($C_9H_9NO_3$)
= Amount (mg) of para-acetaminobenzoic acid RS× $\frac{Q_{T1}}{Q_{S1}}$

Amount (mg) of inosine ($C_{10}H_{12}N_4O_5$)
= Amount (mg) of inosine RS× $\frac{Q_{T2}}{Q_{S2}}$

Internal standard solution—Weigh about 50 mg of methyl chlorothiazide RS and add the mobile phase to make 50 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 - 10 μm in particle diameter).

Mobile phase: A mixture of water and acetonitrile (65 : 35), adjusted the pH to 2.2 with 0.2% trifluoroacetic acid.

Flow rate: 1.5 mL/min

Packaging and storage Preserve in tight containers.

Inosiplex Syrup
이노시플렉스 시럽

Inosiplex Syrup contains NLT 26.4% and NMT 29.1% of *N*,*N*-dimethylaminoisopropanol ($C_5H_{13}NO$: 103.16), NLT 45.8% and NMT 50.6% of *p*-acetaminobenzoic acid ($C_9H_9NO_3$: 179.17) and NLT 22.9% and NMT 25.3% of inosine ($C_{10}H_{12}N_4O_5$: 268.23), according to the labeled amount of inosiplex.

Method of preparation Prepare as directed under Syrups, with Inosiplex

Identification Perform the test as directed under the Assay (2); the retention times of the major peaks obtained from the test solution and the standard solution are the same.

pH Between 5.2 and 7.2.

Uniformity of dosage units (distribution) Meets the requirements.

Assay (1) ***N,N-Dimethylaminoisopropanol***—Weigh accurately an amount of Inosiplex Syrup, equivalent to 0.25 g of inosiplex, transfer to a distillation flask filled with 10 mL of water, add 10 mL of 1 mol/L sodium hydroxide solution, and distill in vacuum until the volume of the solution is reduced to about 5 mL. Add 20 mL of 0.1 mol/L hydrochloric acid to the receiver. Titrate the solution collected into the receiver with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of bromocresol green-methyl red TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L hydrochloric acid VS
= 10.316 mg of $C_5H_{13}NO$

(2) ***p-Acetaminobenzoic acid and inosine***—Weigh accurately an amount of Inosiplex Syrup, equivalent to 0.1 g of inosiplex, add the mobile phase to make 100 mL, and filter with a Millipore filter paper. Take 5.0 mL of the filtrate, add 5.0 mL of the internal standard solution, add the mobile phase to make 50 mL, and use the solution as the test solution. Separately, weigh accurately about 50 mg of para-acetaminobenzoic acid RS and about 25 mg of inosine RS, and add the mobile phase to make 100 mL. Pipet 5.0 mL of this solution, add 5.0 mL of the internal standard solution, add the mobile phase to make 50 mL, and use the solution as the standard solution. Perform the test with each 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak area ratios, Q_{T1} and Q_{T2}, Q_{S1} and Q_{S2}, of *p*-acetaminobenzoic acid and inosine to the internal standard, respectively, from each solution.

Amount (mg) of p-acetaminobenzoic acid ($C_9H_9NO_3$)
= Amount (mg) of *p*-acetaminobenzoic acid RS× $\frac{Q_{T1}}{Q_{S1}}$

Amount (mg) of inosine ($C_{10}H_{12}N_4O_5$)
= Amount (mg) of inosine RS× $\frac{Q_{T2}}{Q_{S2}}$

Internal standard solution—Weigh about 50 mg of methylclothiazide RS and add the mobile phase to make 50 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of water and acetonitrile (65 : 35), adjusted to pH 2.2 with 0.2% trifluoroacetic acid.

Flow rate: 1.5 mL/min

Packaging and storage Preserve in tight containers.

Inosiplex Tablets
이노시플렉스 정

Inosiplex Tablets contain NMT 26.4% and NLT 29.1% of *N,N*-dimethylaminoisopropanol ($C_5H_{13}NO$: 103.16), NMT 45.8% and NLT 50.6% of para-acetaminobenzoic acid ($C_9H_9NO_3$: 179.17), and NLT 22.9% and NMT 25.3% of inosine ($C_{10}H_{12}N_4O_5$: 268.23).

Method of preparation Prepare as directed under Tablets, with Inosiplex.

Identification (1) Filter an aqueous solution of Inosiplex Tablets (1 in 100000), and determine the absorption spectra of this filtrate as directed under Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelength of 260 nm.

(2) Perform the test according to the Assay (2); the retention times of the major peaks obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 tablet of Inosiplex Tablet at 100 revolutions per minute according to Method 2, using 900 mL of 0.05 mol/L of sodium acetate buffer solution, pH 4.0, as the dissolution medium. Take the dissolved solution 45 minutes after starting the test, and filter. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add the dissolution medium to make *V'* mL of a solution containing about 10 μg of inosine per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 24 mg of inosine RS, add the dissolution medium to make 200 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of inosine in each solution. The acceptable dissolution criterion of Inosiplex Tablets is NLT 75% of inosine dissolved in 45 minutes.

Dissolution rate (%) of inosine ($C_{10}H_{12}N_4O_5$) in labeled amount of inosiplex

$$= W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times \frac{1115.23}{268.23}$$

Ws: Amount of inosine RS (mg)

C: Labeled amount (mg) of Inosiplex ($C_{52}H_{78}N_{10}O_{17}$) in 1 tablet

1115.23: Molecular weight of inosiplex ($C_{52}H_{78}N_{10}O_{17}$)

268.23: Molecular weight of inosine ($C_{10}H_{12}N_4O_5$)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: To a mixture of water and acetonitrile (65 : 35), add 0.2% trifluoroacetic acid to adjust the pH to 2.2.

Flow rate: 1.5 mL/min

Uniformity of dosage units Meets the requirements.

Assay (1) ***N,N-dimethylaminoisopropanol***—Weigh accurately the mass of NLT 20 Inosiplex Tablets, and powder. Weigh accurately an amount equivalent to about 0.25 g of inosiplex ($C_{52}H_{78}N_{10}O_{17}$), and transfer into a distillation flask containing 10 mL of 1 mol/L sodium hydroxide TS and 10 mL of water to dissolve. To the collector, add 20 mL of 0.1 mol/L hydrochloric acid, then distill under a weak vacuum. Stop distillation when the solution in the distillation flask becomes about 5 mL, then cool, add 10 mL of water, and continue distilling until the solution in the distillation flask becomes about 5 mL. Titrate the distillate received in the collector with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of bromocresol green-methyl red TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L hydrochloric acid VS
= 10.316 mg of $C_5H_{13}NO$

(2) ***Para-acetaminobenzoic acid***—Weigh accurately the mass of NLT 20 Inosiplex Tablets, and powder. Weigh accurately an amount equivalent to 0.1 g of inosiplex, add 100 mL of the mobile phase, shake to mix, and then filter. Take 5.0 mL of this filtrate, add 5.0 mL of the internal standard solution, add the mobile phase to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of para-acetaminobenzoic acid RS and about 25 mg of inosine RS, and add the mobile phase to make 100 mL. Pipet 5.0 mL of this solution, add 5.0 mL of the internal standard solution, add the mobile phase to make 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak area ratios, Q_{T1}, Q_{T2}, Q_{S1} and Q_{S2}, of para-acetaminobenzoic acid and inosine to the peak area of the internal standard, respectively.

Amount (mg) of para-acetaminobenzoic acid ($C_9H_9NO_3$)
= Amount (mg) of para-acetaminobenzoic acid RS $\times \frac{Q_{T1}}{Q_{S1}}$

Amount (mg) of inosine ($C_{10}H_{12}N_4O_5$)
= Amount (mg) of inosine RS $\times \frac{Q_{T2}}{Q_{S2}}$

Internal standard solution—Weigh 50 mg of methyl chlorothiazide RS, and add the mobile phase to make 50 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

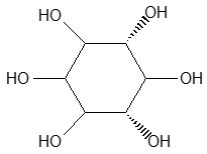
Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of water and acetonitrile (65 : 35), adjusted the pH to 2.2 with 0.2% trifluoroacetic acid.

Flow rate: 1.5 mL/min

Packaging and storage Preserve in tight containers.

Inositol
이노시톨



Inosit $C_6H_{12}O_6$: 180.16

Cyclohexane-1,2,3,4,5,6-hexol [*87-89-8*]

Inositol, when dried, contains NLT 97.0% and NMT 101.0% of inositol ($C_6H_{12}O_6$).

Description Inositol occurs as white crystals or a crystalline powder, is odorless and has a sweet taste.
It is freely soluble in water and practically insoluble in ethanol(95), chloroform or ether.
It has no optical rotation.
An aqueous solution of Inositol is neutral.

Identification (1) Add 6 mL nitric acid to 1 mL of an aqueous solution of Inositol (1 in 50) and evaporate to dryness on a steam bath; add 0.5 mL of strontium nitrate solution (1 in 10) to the residue and evaporate to dryness on a steam bath again; the residue exhibits a purple color.

(2) Add 1 mL of lead subacetate TS to 4 mL of an aqueous solution of Inositol (1 in 100) and shake to mix and heat on a steam bath for 5 minutes; the solution turns into a translucent gel.

(3) Weigh accurately about 0.2 g of Inositol, previously dried, transfer to a 250-mL beaker, add 5 mL of a mixture of 1 mL of dilute hydrochloric acid and 50 mL of acetic anhydride, cover the beaker with a watch glass, heat on a steam bath for 20 minutes, and cool with ice. Next, add 100 mL of water, boil for 20 minutes and cool, put the contents of the beaker into a 250 mL separatory funnel, wash with a small amount of water again, and transfer the washings. Extract with 30 mL, 25 mL, 20 mL, 15 mL, 10 mL and 10 mL of chloroform, combine all of the chloroform extracts, and wash with 10 mL of water. Filter the chloroform layer with cotton wool, wash the water layer and cotton wool with 10 mL of chloroform, combine the filtrate and washings, evaporate to dryness on a steam bath, and dry for 2 hours at 105 ℃. Cool to obtain hexacetylinositol with a melting point of between 212 and 216 ℃.

Melting point Between 223 and 227 ℃.

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Inositol in water; the solution is colorless and clear.

(2) ***Chloride*—**Perform the test with 2.0 g of Inositol. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.005%).

(3) ***Sulfate***—Perform the test with 4.0 g of Inositol. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid (NMT 0.006%).

(4) ***Lead***—Weigh 20.0 g of Inositol and dissolve in dilute acetic acid to make 100 mL. Add 2 mL of saturated ammonium pyrrolidinedithiocarbamate solution and 10 mL of 4-methyl-2-pentanone to this solution, shake for 30 seconds, and allow to stand until the layers separate while protected from light. Then, take the 4-methyl-2-pentanone layer, and use this solution as the test solution. Separately, weigh 20.0 g each of Inositol, add 0.5 mL, 1.0 mL and 1.5 mL of lead standard solution, respectively, and proceed in the same manner as the test solution. and use these solutions as the standard solutions. Add 2 mL of saturated ammonium pyrrolidinedithiocarbamate solution and 10 mL of 4-methyl-2-pentanone, shake for 30 seconds, and allow to stand until the layers separate while protected from light. Then, take the 4-methyl-2-pentanone layer, and use this solution as the blank test solution. Perform the test with the test solution, the standard solution and the blank test solution as directed under the calibration curve under the Atomic Absorption Spectroscopy according to the following conditions, and determine the concentration of lead in the test solution; it is NMT 0.5 ppm.

Gas: Air–acetylene
Lamp: Lead hollow-cathode lamp
Wavelength: 283.3 nm

(5) ***Barium***—Weigh 10.0 g of Inositol, dissolve in water to make 100 mL, pipet 10 mL of this solution, add 1 mL of dilute sulfuric acid, and allow to stand for 1 hour; the turbidity of the solution is not more intense than that of the control solution.

Control solution—Weigh 10.0 g of Inositol, dissolve in water to make 100 mL, pipet 10 mL of this solution, and add 1 mL of distilled water.

(6) ***Iron***—Dissolve 2.0 g of Inositol in 40 mL of water, and add 2 mL of hydrochloric acid, 40 mg of ammonium peroxysulfate and 2 mL of ammonium thiocyanate TS; the color of the solution is not more intense than that of the following control solution.

Control solution—Take 1.0 mL of iron standard solution instead of Inositol and proceed as above.

(7) ***Calcium***—Dissolve 1.0 g of Inositol in water, add 1 mL of ammonium oxalate TS, and allow to stand for 1 minute; the solution is clear.

(8) ***Fehling's TS reducing substances***—Dissolve 0.5 g of inositol in 10 mL water, add 5 mL of Fehling's TS, boil for 3 minutes, and allow to stand for 30 minutes; no orange to red precipitate is produced.

(9) ***Related substances***—Weigh accurately 0.5 g of Inositol, dissolve in water to make 10 mL, and use this solution as the test solution. Separately, weigh accurately 0.5 g of inositol RS, dissolve in water to make 10 mL, and use this solution as the standard stock solution. Pipet 2.0 mL of this solution, dissolve in water to make 100 mL of a solution containing 1 mg of Inositol per mL, and use this solution as the standard solution. Perform the test according to the Liquid Chromatography with 20 μL each of the test solution and the standard solution under the following conditions and determine the amount of related substances; the amount of each related substance is NMT 0.3% and the total amount of related substances is NMT 1.0%. However, exclude any related substances with the amount less than 0.05%.

$$\text{Content (\%) of related substances} = 100 \times \frac{C_S}{C_T} \times \frac{A_i}{A_S}$$

C_S: Concentration (mg/mL) of Inositol in the standard solution

C_T: Concentration (mg/mL) of Inositol in the test solution

A_i: Peak area of each related substance obtained from the test solution

A_S: Peak area of Inositol obtained from the standard solution

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed under the operating conditions in the Assay.

System suitability

System performance: Weigh accurately appropriate amounts of inositol RS and D-mannitol, dissolve in water to make a solution containing 0.05 mg of each per mL, and use this solution as the system suitability solution. Proceed with 20 μL of this solution under the above operating conditions; the relative retention time of D-mannitol with respect to the retention time of Inositol is about 1.3, and the resolution between the two peaks is NLT 4.0.

System repeatability: Repeat the test 5 times according to the above conditions with 20 μL of the standard stock solution each time; the relative standard deviation of the peak areas is NMT 2.0%.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g each of Inositol and inositol RS, dissolve each in water to make exactly 10 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas A_T and A_S of inositol.

$$\text{Amount (mg) of inositol } (C_6H_{12}O_6) = \text{Amount (mg) of inositol RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: A differential refractometer (constant temperature of about 30 to 35 ℃).

Column: A stainless steel column about 7.8 mm in internal diameter and about 30 cm in length or equivalent, packed with strong acidic ion exchange resin for liquid chromatography (styrene-divinylbenzene copolymer sulfonic acid resin calcium type) (9 μm in particle diameter).

Column temperature: A constant temperature of about 85 °C.

Mobile phase: Water

Flow rate: 0.5 mL/min

System suitability

System performance: Weigh accurately appropriate amounts of inositol RS and D-mannitol, dissolve in water to make a solution containing 0.05 mg of each per mL, and use this solution as the system suitability solution. Proceed with 10 μL of this solution under the above operating conditions; the relative retention time of D-mannitol with respect to the retention time of inositol is about 1.3, and the resolution between the two peaks is NLT 4.0.

System repeatability: Repeat the test 5 times according to the above conditions with 10 μL of the standard solution each time; the relative standard deviation of the peak area is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Insulin
인슐린

Insulin is obtained from the pancreas of healthy bovine or porcine, and lowers blood sugar. It contains NLT 26 insulin units per mg, calculated on the dried basis.

Insulin is labeled to indicate the animal species from which it is derived.

Description Insulin occurs as a white, crystalline pow-

der and is odorless.
It is practically insoluble in water, ethanol(95) or ether.
It is soluble in diluted hydrochloric acid (1 in 360) or dilute sodium hydroxide TS.
It is hygroscopic.

Identification Dissolve 10 mg of Insulin in 10 mL of 0.1 mol/L hydrochloric acid TS, and use this solution as the test solution. Perform the test with the test solution as directed under the Identification for Insulin Injection

Purity (1) ***Clarity and color of solution*—**Dissolve 0.10 g of Insulin in 10 mL of diluted hydrochloric acid; the resulting solution is colorless to pale yellow.

(2) ***Related substances*—**Put 7.5 mg of Insulin in a vial with a suitable cap, and add 2.0 mL of 0.01 mol/L hydrochloric acid. Cap the vial and shake gently. Do not store this solution for more than 2 hours at room temperature or 12 hours in the refrigerator. Separately, weigh accurately 37.5 mg of Insulin RS, dissolve in 0.01 mol/L hydrochloric acid to make 10 mL, and use this solution as the standard solution (1). Pipet 1 mL of the standard solution (1), add 0.01 mol/L hydrochloric acid to make 10 mL, and use this solution as the standard solution (2). Pipet 1 mL of the standard solution (2), add 0.01 mol/L hydrochloric acid to make 10 mL, and use this solution as the standard solution (3). The standard solution can be stored at room temperature for 12 hours or refrigerated for up to 48 hours. Take 20 μL of the test solution and perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the peak area A_I of insulin, the peak area A_D of A-21 desamido insulin, and the sum of all peak areas A_S according to the automatic integration method and determine each amount as directed under the percentage peak area method; A-21 desamido insulin is NMT 10.0%, and the sum of other related substances excluding Insulin and A-21 desamido insulin is NMT 5.0%. However, in the case of insulin derived from a single species, the amount of cross contamination is NMT 1.0% when the peak corresponding to the bovine or porcine insulin is measured.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows. Adjust the composition of the mobile phase so that the retention time of insulin is about 31 minutes, and the A-21 desamido insulin elutes at the beginning of the gradient elution.

Mobile phase A: A mixture of a solution prepared by dissolving 28.4 mg of anhydrous sodium sulfate in 1000 mL of water, then adding 2.7 mL of phosphoric acid and, if necessary, and adding 2-Aminoethanol to adjust the pH to 2.3; resulting solution and acetonitrile (82 : 18).

Mobile phase B: A mixture of a solution prepared by dissolving 28.4 mg of anhydrous sodium sulfate in 1000 mL of water, then adding 2.7 mL of phosphoric acid and, if necessary, and adding 2-Aminoethanol to adjust the pH to 2.3 and acetonitrile (50 : 50).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0	81	19
0 - 60	81	19
60 - 85	81 → 36	19 → 64
85 - 91	36	64
91 - 92	36 → 81	64 → 19

Flow rate: 1 mL/min

System suitability

Test for required detectability: Proceed with 20 μL of standard solutions (1), (2) and (3) under the above conditions to obtain the peak area A_A of the standard solution (1), the peak area A_B of the standard solution (2), and the peak area A_C of the standard solution (3). Calculate according to the following equations (1) and (2), and confirm that the values are 0.91 to 1.09 and 0.7 to 1.3, respectively.

$$(1)\ 10 \times \frac{A_B}{A_A}$$

$$(2)\ 10 \times \frac{A_C}{A_A}$$

System performance: Weigh about 1.5 mg of Insulin, and dissolve in 1.0 mL of 0.01 mol/L hydrochloric acid Allow this solution to stand at room temperature for NMT 3 days to obtain a solution containing NLT 5% of A-21 desamido insulin, and use the solution as the system suitability solution. Proceed with 20 μL of this solution under the above operating conditions; the resolution between Insulin and A-21 desamido insulin is NLT 2.0 with the symmetry factor of the insulin peak being NMT 1.8.

Loss on drying NMT 10.0% (0.2 g, 105 °C, 16 hours).

Residue on ignition Weigh accurately 20 to 40 mg of Insulin in a tared platinum dish, previously measured the mass, add 2 drops of nitric acid, and heat it gently at first, and then heat strongly to incinerate. Put it back into the furnace and heat it at 600 °C for 15 minutes, then cool it in a desiccator (silica gel) and weigh its mass; the residue is NMT 2.5%.

Bacterial endotoxins Less than 10 EU in each mg of Insulin.

Microbiological examination of non-sterile products When tested, the total aerobic microbial count is NMT 300 CFU per each gram of Insulin, and the total combined yeasts/molds count is NMT 100 CFU. Also, *Escherichia coli*, *Salmonella*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* are not detected.

Zinc Content Weigh accurately about 10 mg of Insulin, dissolve in 5 mL of 0.1 mol/L hydrochloric acid TS and water to make exactly 50 mL, if necessary, add water again to dilute the solution so that each mL contains 0.4 to1.0 μg of zinc (Zn: 65.41, and use this solution as the test solution. Separately, take an appropriate amount of standard zinc solution for atomic absorption spectrophotometry, add water to dilute the solution so that each mL contains 0.3 to 1.2 μg of zinc, and use this solution as the standard solution. Perform the test using the test solution and the standard solution according to the Atomic Absorption Spectroscopy under the following conditions. Obtain the content of zinc in the solution using a calibration curve made from the absorbance of the standard solution; the content is NLT 0.27% and NMT 1.08%, calculated on the dried basis.

Gas: Air–acetylene
Lamp: Zinc hollow-cathode lamp
Wavelength: 213.9 nm

Nitrogen content Weigh accurately about 20 mg of Insulin, dissolve in 10 mL of 0.1 mol/L hydrochloric acid TS, and perform the test as directed under the Nitrogen Determination; the content of nitrogen (N: 14.01) is NLT 14.5% and NMT 16.5%, calculated on the dried basis.

Assay (1) ***Test animals*—**Raise healthy rabbits weighing NLT 1.8 kg in the laboratory by feeding with an appropriate and regular diet and water for at least 1 week before testing.

(2) ***Solvent for insulin*—**Dissolve 1.0 to 2.5 g of phenol or *m*-cresol in 500 mL of 0.01 mol/L hydrochloric acid, and add 14 to 18 g of glycerin and 0.01 mol/L hydrochloric acid to make 1000 mL.

(3) ***Standard stock solution*—**Weigh accurately about 20 mg of Insulin RS, dissolve in the solvent for insulin to make a solution containing 20.0 units of Insulin per mL. Store this solution at 1 to 15 ℃ and use it within 6 months after preparation.

(4) ***Standard solutions*—**Dilute the standard stock solution using the solvent for Insulin to make solutions containing 2.0 units and 1.0 unit of Insulin per mL, respectively. Use these solutions as the high-capacity standard solution S_H and the low-capacity standard solution S_L, respectively.

(5) ***Test solutions*—**Weigh accurately about 20 mg of Insulin, dissolve in the solvent for insulin to make solutions containing 2.0 units and 1.0 unit of Insulin per mL, respectively. Use these solutions as the high-capacity test solution T_H and the low-capacity test solution T_L, respectively.

(6) ***Injection amount*—**It is determined by preliminary testing or experience, but is usually 0.3 to 0.5 mL. Use the same amount throughout each test.

(7) ***Procedure*—**Select test animals of similar weight and divide them into 4 groups, with each group having the same number of animals (NLT 6). Do not feed each test animal for more than 14 hours before injection. During the test, do not give water until the last blood draw is completed. Also, during the test, handle the test animal with care to avoid causing strong irritation.
For the first injection, inject the standard solution and the test solution subcutaneously into each test animal as follows.

Group 1	S_H	Group 2	S_L
Group 3	T_H	Group 4	T_L

Make a second injection the next day or within one week using the standard and test solutions as follows.

Group 1	T_L	Group 2	T_H
Group 3	S_L	Group 4	S_H

At 1 hour and 2.5 hours after injection, collect sufficient blood from the veins around the ears of each test animal, and quantify the blood sugar level according to (8).

Conversion Table for Blood Sugar Levels (%)

mL*	0	1	2	3	4	5	6	7	8	9
0.0	0.385	0.382	0.379	0.376	0.373	0.370	0.367	0.364	0.361	0.358
0.1	0.355	0.352	0.350	0.348	0.345	0.343	0.341	0.338	0.336	0.333
0.2	0.331	0.329	0.327	0.325	0.323	0.321	0.318	0.316	0.314	0.312
0.3	0.310	0.308	0.306	0.304	0.302	0.300	0.298	0.296	0.294	0.292
0.4	0.290	0.288	0.286	0.284	0.282	0.280	0.278	0.276	0.274	0.272
0.5	0.270	0.268	0.266	0.264	0.262	0.260	0.259	0.257	0.255	0.253
0.6	0.251	0.249	0.247	0.245	0.243	0.241	0.240	0.238	0.236	0.234
0.7	0.232	0.230	0.228	0.226	0.224	0.222	0.221	0.219	0.217	0.215
0.8	0.213	0.211	0.209	0.208	0.206	0.204	0.202	0.200	0.199	0.197
0.9	0.195	0.193	0.191	0.190	0.188	0.186	0.184	0.182	0.181	0.179
1.0	0.177	0.175	0.173	0.172	0.170	0.168	0.166	0.164	0.163	0.161

1.1	0.159	0.157	0.155	0.154	0.152	0.150	0.148	0.146	0.145	0.143
1.2	0.141	0.139	0.138	0.136	0.134	0.132	0.131	0.129	0.127	0.125
1.3	0.124	0.122	0.120	0.119	0.117	0.115	0.113	0.111	0.110	0.108
1.4	0.106	0.104	0.102	0.101	0.099	0.097	0.095	0.093	0.092	0.090
1.5	0.088	0.086	0.084	0.083	0.081	0.079	0.077	0.075	0.074	0.072
1.6	0.070	0.068	0.066	0.065	0.063	0.061	0.059	0.057	0.056	0.054
1.7	0.052	0.050	0.048	0.047	0.045	0.043	0.041	0.039	0.038	0.036
1.8	0.034	0.032	0.031	0.029	0.027	0.025	0.024	0.022	0.020	0.019
1.9	0.017	0.015	0.014	0.012	0.010	0.008	0.007	0.005	0.003	0.002

* Indicate the consumption of 0.005 mol/L sodium thiosulfate. For example, according to the table above, the blood sugar level for 1.28 mL is 0.127%.

(8) ***Guantification of blood sugar*—**Put 5.0 mL of zinc sulfate (9 in 2000) in a test tube with an outer diameter of 18 mm and a length of 165 mm, add 1.0 mL of sodium hydroxide (1 in 250), and then gently transfer 0.10 mL of blood using a blood sugar pipette. To combine the blood remaining on the inner wall of the pipette into the test tube, repeatedly suck up the clear liquid from the surface of the test tube, and add the washings to the test tube (repeat it until the pipette is completely washed). Shake the content of the test tube well to mix, then heat on a steam bath for 3 minutes. Cover this solution with a small amount of cotton wool, and filter it into a test tube with an inside diameter of 30 mm and a length of 90 mm using a funnel with a diameter of 30 to 40 mm (prepared by washing it twice with 3 mL of warm water each). Wash the previous test tube and funnel twice with 3 mL of water each and add the washings to the filtrate. Add 2.0 mL of alkaline potassium hexacyanoferrate(III) acid TS to this solution, heat on a steam bath for 15 minutes, and then cool immediately. After adding 3.0 mL of Potassium iodide-zinc sulfate TS and 2.0 mL of diluted acetic acid(100) (3 in 100), titrate the free iodine with 0.005 mol/L sodium thiosulfate VS (indicator: 2-4 drops of starch-sodium chloride TS). Perform a blank test in the same manner and make any necessary correction. Obtain the blood sugar level (%) from the consumption amount (mL) of 0.005 mol/L sodium thiosulfate according to the Conversion Table of Blood Sugar Levels (%).

(9) ***Calculation method*—**After injection for each test animal, add up the two quantitative values of blood sugar for each test animal. Obtain the difference between the blood sugar values obtained in the first injection test and those values obtained in the second injection test of the test animals in groups 1 and 3, and name them y_1 and y_3, respectively. Obtain the difference between the blood sugar values obtained in the second injection test and those values obtained in the first injection test of the test animals in groups 2 and 4, and name them y_2 and y_4, respectively. Sum up NLT 6 of y_1, y_2, y_3 and y_4, respectively, and name them Y_1, Y_2, Y_3 and Y_4, respectively.

$$\text{Number of units in each mg of Insulin} = \text{anti log } M \times (\text{Number of units in Each mL of the high-capacity standard solution}) \times \frac{b}{a}$$

$$M = 0.301 \times \frac{Y_a}{Y_b}$$
$$Y_a = -Y_1 + Y_2 + Y_3 - Y_4$$
$$Y_b = Y_1 + Y_2 + Y_3 + Y_4$$

a: Weight (mg) of sample taken

b: Total volume (mL) when diluted with an insulin solvent to create a high-capacity test solution from the weight (mL) of sample taken

However, when calculating L ($p = 0.95$) using the following equation, L is NMT 0.1212.

If this value is exceeded, increase the number of test animals until it falls below this value, or adjust the experimental conditions, and then repeat the test.

$$L = 2\sqrt{(C-1)(CM^2 + 0.09062}$$
$$C = \frac{Y_b^2}{Y_b^2 - 4fa^2t^2}$$
$$s^2 = \frac{\sum y^2 - \frac{Y}{f}}{n}$$
$$Y = Y_1^2 + Y_2^2 + Y_3^2 + Y_4^2$$
$$n = 4(f\text{-}1)$$

f: Number of test animals in each group

Σy_2: The sum of the squares of y_1, y_2, y_3 and y_4 in each group.

t^2: The values in the following table for *n* when s^2 was calculated.

n	$t^2 = F$	*n*	$t^2 = F$	*n*	$t^2 = F$
1	161.45	13	4.667	25	4.242
2	18.51	14	4.600	26	4.225
3	10.129	15	4.543	27	4.210
4	7.709	16	4.494	28	4.196
5	6.608	17	4.451	29	4.183
6	5.987	18	4.414	30	4.171
7	5.591	19	4.381	40	4.085
8	5.318	20	4.351	60	4.001
9	5.117	21	4.325	120	3.920
10	4.965	22	4.301	∞	3.841
11	4.844	23	4.279		
12	4.747	24	4.260		

Packaging and storage Preserve in tight containers and store at below 8 ℃.

Insulin Injection
인슐린 주사액

Insulin Injection is an aqueous solution for injection. Insulin Injection contains NLT 95.0% and NMT 105.0% of the labeled Insulin units.

Method of preparation Suspend Insulin in water for injection, dissolve by adding hydrochloric acid and prepare as directed under Injections. Insulin Injection contains 0.10 to 0.25 g of phenol or cresol and 1.4 to 1.8 g of concentrated glycerin for each 100 mL of Insulin Injection. It contains no sodium chloride.

Description Insulin Injection occurs as a clear, colorless to pale yellow liquid.

Identification Adjust the pH of Insulin Injection to 5.1 to 5.3 with a solution of sodium hydroxide (1 in 100); a precipitate is formed. Adjust the pH of the solution to 2.5 to 3.5 by adding dilute hydrochloric acid; the precipitate dissolves.

pH Between 2.5 and 3.5.

Residue on ignition Pipet an amount of Insulin Injection, containing 500 to 1000 units according to the labeled units, in a tared platinum dish and evaporate slowly on a steam bath to dryness. Add 2 drops of nitric acid to the residue and heat at first gently, then strongly to incinerate. Place in a muffle furnace and heat at 600 ºC for 15 minutes, cool in a desiccator (silica gel) and weigh: the weight of the residue is NMT 1.0 mg for each labeled 1000 units.

Sterility Meets the requirements.

Bacterial endotoxins Less than 80 EU per 100 insulin units of Insulin Injection.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Nitrogen content Perform the test as directed under the Nitrogen Determination; the amount of nitrogen (N: 14.01) for the labeled 100 units is NLT 0.50 mg and NMT 0.64 mg.

Assay Perform the test as directed under the Assay under Insulin. However, (5) Test solution and (9) Calculation are as follows.

(5) ***Test solution***—According to the labeled units, dilute Insulin Injection with the diluent for Insulin to make two different test solutions, one to contain exactly 2.0 units in each mL which is designated as the high-dose test solution, T_H and the other to contain exactly 1.0 unit in each mL which is designated as the low-dose test solution, T_L.

(9) ***Calculation***—Proceed as directed under the Assay under Insulin, using the following equation.

Number of units in each mg of Insulin Injection "= anti log M×(number of units in each mL of the high-dose standard solution)× $\frac{b}{a}$

a: Mass (mg) of the sample taken" is changed to

Number of units in each mg of Insulin Injection "= anti log M×(number of units in each mL of the high-dose standard solution) × $\frac{b}{a}$

a: Volume (mL) of the sample taken".

Packaging and storage Preserve in hermetic containers in a cold place, avoiding freezing.

Expiration date 24 months after preparation.

Isophane Insulin Injection (Aqueous Suspension)
이소판인슐린 수성현탁주사액

Isophane Insulin Injection (Aqueous Suspension) is an aqueous suspension for injection. Isophane Insulin Injection (Aqueous Suspension) contains NLT 90.0% and NMT 110.0% of the labeled Insulin units It also contains NLT 10 μg and NMT 40 μg of zinc (Zn: 65.41) for each labeled 100 units. When sodium chloride is used in the method of preparation for Isophane Insulin Injection (Aqueous Suspension), this should be indicated on the label.

Method of preparation Prepare as directed under Injections, with Insulin and Protamine Sulfate. To each 100 mL of Isophane Insulin Injection (Aqueous Suspension), add either 0.38 g to 0.63 g of dibasic sodium phosphate, 1.4 g to 1.8 g of concentrated glycerin, 0.15 g to 0.17 g of cresol and 0.06 g to 0.07 g of phenol, or 0.38 g to 0.63 g of dibasic sodium phosphate, 0.42 g to 0.45 g of sodium chloride, 0.7 g to 0.9g of concentrated glycerin and 0.18 g to 0.22 g of cresol.

Description Isophane Insulin Injection (Aqueous Suspension) occurs as a white aqueous suspension. When allowed to stand, it separates into a white precipitate and colorless, clear supernatant and the precipitate easily re-

turns to the form of suspension by gentle shaking.
When examined microscopically, the precipitate mostly consists of fine, oblong crystals of 5 μm to 30 μm and does not contain amorphous substances or large aggregates.

Identification Adjust the pH of Isophane Insulin Injection (Aqueous Suspension) to 2.5 to 3.5 with dilute hydrochloric acid; the precipitate dissolves and the solution is clear and colorless.

pH Between 7.0 and 7.4.

Purity (1) ***Protein***—Perform the test as directed under the Nitrogen Determination; the amount of nitrogen (N: 14.01) for the labeled 100 units is NMT 0.85 mg.

(2) ***Isophane ratio***—(i) Buffer solution A: Dissolve 2.0 g of anhydrous sodium dihydrogen phosphate, 16 g of glycerin, 1.6 g of *m*-cresol and 0.65 g of phenol in water to make exactly 200 mL.

(ii) Buffer solution B: Dissolve 2.0 g of anhydrous sodium dihydrogen phosphate, 4.35 g of sodium chloride, 8.0 g of glycerin and 2.0 g of *m*-cresol in water to make exactly 200 mL.

(iii) Insulin solution: Weigh accurately 1000 units of Insulin RS, dissolve in 1.5 mL of diluted hydrochloric acid (1 in 360) and add 5.0 mL of buffer solution A and water to make 20 mL. Adjust the pH to 7.2 with dilute hydrochloric acid or sodium hydroxide TS. The solution is clear. Dilute with water to make exactly 25 mL, The solution is clear and the pH is 7.1 to 7.4. When it is stated on the label that sodium chloride is used in the preparation, use 5.0 mL of buffer solution B instead of buffer solution A in the above procedure. To this solution, add dilute hydrochloric acid or sodium hydroxide TS to adjust the pH to 7.2. The solution is clear. Then, add water to make exactly 25 mL. The solution is clear and the pH is 7.1 to 7.4. When it is stated on the label that Sodium Chloride is used in the preparation, use 5.0 mL of buffer solution B instead of buffer solution A in the above procedure.

(iv) Protamine solution: Weigh accurately 50 mg of protamine sulfate RS, and add 2 mL of buffer solution A and water to make 8 mL. To this solution, add dilute hydrochloric acid or sodium hydroxide TS to adjust the pH to 7.2, and add water to make exactly 10 mL. The solution is clear and the pH is 7.1 to 7.4. When it is stated on the label that Sodium Chloride is used in the preparation, use 2 mL of buffer solution B instead of buffer solution A in the above procedure.

(v) Procedure: When Isophane Insulin Injection (Aqueous Suspension) contains 40 units per ml, centrifuge a portion of the suspension, measure exactly two 10 mL volumes of the supernatant in two tubes A and B, respectively, add exactly 1 mL of the Insulin solution to tube, A and 1 mL of the protamine solution to tube B, mix the contents of each tube, allow to stand for 10 minutes and determine the turbidity of each mixture by using a photometer or a nephelometer: the turbidity of the mixture in tube B is not greater than that in tube A. When Isophane Insulin Injection (Aqueous Suspension) contains 80 units per ml, measure exactly 5 mL of the supernatant and proceed in the same manner.

Sterility Meets the requirements.

Bacterial endotoxins Less than 80 EU per 100 insulin units.

Extractable volume of injections Meets the requirements.

Assay (1) ***Insulin***—To Isophane Insulin Injection (Aqueous Suspension), add diluted hydrochloric acid (1 in 100) to adjust the pH to about 2.5 and perform the test with the resulting clear solution as directed under the Assay under Insulin Injection.

(2) ***Zinc***—Pipet a volume of Isophane Insulin Injection (Aqueous Suspension), equivalent to about 400 units according to the labeled units, add 1 mL of 0.1 mol/L hydrochloric acid TS and water to make exactly 100 mL, dilute, if necessary, with water to contain 0.6 to 1.0 μg of zinc pet mL and use this solution as the test solution. Separately, pipet a volume of standard zinc solution for the Atomic Absorption Spectrophotometry, dilute with water to contain 0.4 to 1.2 μg of zinc per mL and use this solution as the standard solution. Perform the test with the test solution and the standard solution according to the Atomic Absorption Spectrophotometry under the following conditions and determine the amount of zinc in the test solution using the analytical curve obtained from the absorbance of the standard solution.

Gas: Air–acetylene
Lamp: Zinc hollow-cathode lamp
Wavelength: 213.9 nm

Packaging and storage Preserve in hermetic containers and store in a cold place.

Expiration date 24 months after preparation.

Insulin Zinc Injection (Aqueous Suspension)
인슐린아연 수성현탁주사액

Insulin Zinc Injection (Aqueous Suspension), is an aqueous suspension for injection, which contains NLT 90.0% and NMT 110.0% of the labeled insulin units. and NLT 0.12 mg and NMT 0.30 mg of zinc (Zn: 65.41) for each labeled 100 units.

Method of preparation Prepare as directed under Injections, with Insulin and Zinc Chloride. Insulin Zinc Injection (Aqueous Suspension) contains 0.15 g to 0.17 g of sodium acetate trihydrate, 0.65 g to 0.75 g of sodium chloride and 90 mg to 110 mg of methyl *p*-hydroxybenzoate per 100 mL.

Description Insulin Zinc Injection (Aqueous Suspension) occurs as a white suspension. When allowed to stand, it separates into a white precipitate and colorless, clear supernatant and the precipitate easily returns to the suspension state by gentle shaking.
When it is examined microscopically, most part of the particles in the suspension are crystals, the dimension of which is mostly 10 μm to 40 μm. Others are amorphous with less than 2 μm.

Identification Adjust the pH of Insulin Zinc Injection (Aqueous Suspension) to 2.5 to 3.5 with dilute hydrochloric acid; the precipitate dissolves and the solution is clear and colorless.

pH Between 7.1 and 7.5.

Purity ***Dissolved insulin***—Perform the test according to the Purity (2) of Insulin Zinc Protamine Injection (Aqueous Suspension).

Sterility Meets the requirements.

Bacterial endotoxins Less than 80 EU per 100 insulin units.

Extractable volume of injections Meets the requirements.

Nitrogen content Perform the test as directed under the Nitrogen Determination; the amount of nitrogen (N: 14.01) for the labeled 100 units is NLT 0.50 mg and NMT 0.64 mg.

Assay (1) ***Insulin***—To Insulin Zinc Injection (Aqueous Suspension), add diluted hydrochloric acid (1 in 100) to adjust the pH to about 2.5 and proceed with the clear liquid according to the Assay under Insulin Injection.

(2) ***Zinc***—Perform the test according to the Assay (2) of Insulin Zinc Protamine Injection (Aqueous Suspension).

(3) ***Crystalline insulin***—Pipet an amount of Insulin Zinc Injection (Aqueous Suspension), equivalent to about 600 units according to the labeled units, centrifuge, discard the clear supernatant, and suspend the residue in 5 mL of water. Add 10 mL of sodium acetate-acetone TS, shake for 3 minutes to mix and centrifuge. Discard the clear supernatant and repeat the procedure in the same manner. Wash down the residue into a Kjeldahl flask with 15 mL of sulfuric acid and perform the test as directed under the Nitrogen Determination; the amount of nitrogen (N: 14.01) is NLT 55.0% and NMT 70.0% of the total nitrogen amount. Calculate the total nitrogen content for insulin units of a sample from the values of nitrogen obtained in the nitrogen content.

Packaging and storage Preserve in hermetic containers and store in a cold place.

Expiration date 24 months after preparation.

Iodine
요오드

I : 126.90

Iodine contains NLT 99.5% and NMT 101.0% of iodine (I).

Description Iodine occurs as grayish black plate crystals or heavy granular crystals having a metallic luster and a characteristic odor.
It is freely soluble in ether, soluble in ethanol(95), sparingly soluble in chloroform, and very slightly soluble in water.
It is soluble in potassium iodide TS.
It volatilizes at ordinary temperature.

Identification (1) A solution of iodine in ethanol(95) (1 in 50) exhibits a reddish brown color.

(2) A solution of Iodine in chloroform (1 in 1000) exhibits a purple to violet color.

(3) Add 0.5 mL of starch TS to 10 mL of saturated solution of Iodine; the solution exhibits a dark blue color. When boiled, the color of the solution disappears, and the color reappears when cooled.

Purity (1) ***Sublimation residue***—Heat and sublime 2.0 g of iodine on a steam bath, and dry the residue for 1 hour at 105 ℃; the amount of residue is NMT 1.0 mg.

(2) ***Chloride or bromide***—Add 1.0 g of Iodine, previously powdered, to 20 mL of water, shake well to mix, and filter. Add diluted sulfurous acid solution (1 in 5) dropwise to 10 mL of the filtrate until the yellow color disappears. Add 1 mL of ammonia TS to this solution and add 1 mL of silver nitrate TS in small amounts. Add water to make 20 mL, shake well to mix, and filter. Discard the first 2 mL of filtrate and take the subsequent 10 mL of filtrate, then add 2.0 mL of nitric acid and water to make 20 mL; the turbidity of the resulting solution is not more intense than that of the following control solution.

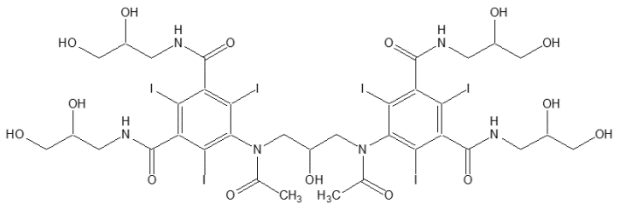
Control solution—To 0.20 mL of 0.01 mol/L hydrochloric acid, add 5 mL of water, 2.5 mL of ammonia TS, 1 mL of silver nitrate TS, 2.0 mL of nitric acid, and then water to make 20 mL.

Assay Weigh accurately 1 g of potassium iodide and 1 mL of water in a stoppered flask, add about 0.3 g of Iodine to this solution, weigh accurately and shake gently to mix and dissolve. Add 20 mL of water and 1 mL of dilute hydrochloric acid and titrate with 0.1 mol/L sodium thiosulfate VS (indicator: 1 mL of starch TS).

Each mL of 0.1 mol/L sodium thiosulfate VS
= 12.690 mg of I

Packaging and storage Preserve in tight containers.

Iodixanol
이오딕산올



$C_{35}H_{44}I_6N_6O_{15}$: 1550.18

5-{*N*-[3-(*N*-{3,5-*bis*[(2,3-Dihydroxypropyl) carbamoyl]-2,4,6-triiodophenyl}acetamido)-2-hydroxypropyl]acetamido}-1-*N*,3-*N*-*bis*(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide [*92339-11-2*]

Iodixanol contains NLT 98.6% and NMT 101.0% of Iodixanol ($C_{35}H_{44}I_6N_6O_{15}$), calculated on the anhydrous basis.

Description Iodixanol occurs as a white, amorphous powder and is odorless.
It is very soluble in water.
It is hygroscopic.

Identification (1) Determine the infrared spectra of Iodixanol and iodixanol RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption of absorption at the same wavenumbers.

(2) The retention times of the two major peaks obtained from the test solution in the Related substance (B) is same as the retention times of the two peaks obtained from the standard solution (2). A third isomer may appear as a minor peak.

(3) Take about 0.5 g of Iodixanol and heat in a crucible; purple gases are evolved.

Optical rotation $[\alpha]_D^{25}$: Between -0.5° and +0.5° (1 g, water, 20 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 1 g of Iodixanol according to Method 1 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Free iodine***—Weigh 2.0 g of Iodixanol, add 20 mL of water, 5 mL of toluene, and 5 mL of 1 mol/L sulfuric acid TS, shake vigorously, and allow to stand; the toluene layer does not exhibit a red or pink color.

(3) ***Free iodide***—Weigh 5.0 g of Iodixanol, dissolve in about 30 mL of water, and titrate with 0.001mol/L silver nitrate VS (potentiometric titration under the Titrimetry); NMT 10 μg per g of Iodixanol.

Each mL of 0.001 mol/L silver nitrate VS
= 126.9 μg of I

(4) ***Free aromatic amine***—Weigh accurately about 0.2 g of Iodixanol, dissolve in 15 mL of water, and use this solution as the test solution. Weigh accurately a suitable amount of iohexol related substance III RS, dissolve in water so that the solution contains 10 μg per mL. To 10 mL of this solution, add 5 mL of water and use this solution as the standard solution. Separately, use 15 mL of water as the blank test solution. Cool the test solution, the standard solution, and the blank test solution in an ice bath for 5 minutes, add 1.5 mL of 6 mol/L hydrochloric acid TS, stir to mix, add 1.0 mL each of sodium nitrite solution (2 in 100), mix, and allow to stand in the ice bath for 4 minutes. Remove the solutions from the ice bath, add 1.0 mL of 4% sulfamic acid, and stir gently until gas evolution ceases. Add 1.0 mL of a solution of *N*-(1-Naphthyl) ethylenediamine dihydrochloride in a mixture of propylene goycol and water (70 : 30) (3 in 10000), prepared before use, mix, add water to make exactly 25 mL, and allow to stand for 5 minutes. Compare the color with these solutions; the color obtained from the test solution is not more intense than the color obtained from the standard solution (0.05%). If the color obtained from the test solution is same as or more intense than the color from the standard solution, perform the test with the blank test solution, the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, determine the absorbance A_B, A_T and A_S, in 5 cm cells, at the absorbance maximum wavelength of about 495 nm, using water as the control solution(NMT 0.05%).

$$\text{Content (\%) of free aromatic amine} = \frac{C}{W} \times \frac{A_T - A_B}{A_S - A_B}$$

C: Concentration of iohexol related compound III RS in the standard solution (μg/mL)
W: Amount (mg) of Iodixanol taken

(5) ***Calcium***—Weigh accurately about 2.0 g of Iodixanol, dissolve in 10 mL of water, add 2 mL of the internal standard solution water to make exactly 20 mL, and use this solution as the test solution. Prepare a solution containing 10 μg of calcium per mL with the calcium standard solution. Pipet 0.5 mL, 2.5 mL, 5.0 mL and 10.0 mL each of this solution, add 5.0 mL of the Internal standard solution to each solution, add water to make exactly 50 mL, and use these solutions as the standard solution (1), (2), (3) and (4). Pipet 5.0 mL of the internal standard solution, add water to make 50 mL, and use this solution as the blank test solution. Perform the test with the test solution and the standard solutions (1), (2), (3) and (4) as directed under the Atomic Absorption Spectroscopy. Determine the absorbances of each standard solution and the test solution at 393.366 nm (calcium emission line) and 361.38 nm (scandium emission line) using the blank test solution, calculate the ratio of calcium absorbance to scandium absorbance, plot a calibration curve relative to calcium concentrations in the standard solutions. From the calibration curve, determine the calcium concentration, C (μg per mL), in the test so-

lution, and calculate the content of calcium (μg/g) (NMT 5 μg per g of Iodixanol).

$$\text{Amount (μg /g) of calcium (μg/g)} = 20 \times \frac{C}{W}$$

W: Amount (g) of Iodixanol taken to prepare the test solution

Internal standard solution—Weigh 3.067g of scandium oxide and dissolve in 1000 mL of water. To 10 mL of this solution and add water to make 100 mL.

(6) ***Ionic substances***—Wash all glass apparatus with water before use. Determine the conductivity of the aqueous solution of Iodixanol (2 in 100); the conductivity is not greater than the conductivity of sodium chloride solution (4 μg per mL) (NMT 0.02%).

(7) ***Methanol, 2-propanol and methoxyethanol***—Weigh accurately about 0.25 g of Iodixanol, transfer to a headspace vial, add 1.0 mL of the Internal standard solution, seal the vial with a cap, mix until dissolved, and use this solution as the test solution. Weigh accurately about 0.5 g of methanol, about 1.0 g of 2-propanol and 1.0 g of methoxyethanol, and add water to make exactly 500 mL. Add water to 5.0 mL to this solution to make exactly 100 mL. Pipet 10.0 mL of this solution and 1.0 mL of the internal standard solution and add water to make exactly 100 mL. Pipet 1.0 mL of this solution, seal, and use this solution as the standard solution. This solution contains about 0.005 mg of methanol, 0.01 mg of 2-propanol and 0.01 mg of methoxyethanol per mL. Perform the test with each 1 mL of the test solution and the standard solution as directed under the Gas Chromatography according to the following operating conditions, and determine the ratios Q_T and Q_S, of each peak area of methanol, 2-propanol and methoxyethanol to the peak area of the internal standard. Amounts of methanol, 2-propanol and methoxyethanol per g of Iodixanol are NMT 50 μg, respectively.

$$\text{Content (\%) of methanol, isopropanol and methoxyethanol} = 100 \times \frac{C}{W} \times \frac{Q_T}{Q_S}$$

C: Concentration (mg/mL) of each related substance
W: Amount (mg) of Iodixanol taken

Internal standard solution—Weigh about 0.5 g of 2-butanol and add water to make 500 mL. Pipet 1.0 mL of this solution and add water to make 100 mL.

Operating conditions

Detector: A flame ionization detector

Column: A capillary column about 0.54 mm in internal diameter and about 30 m in length, coated the inside with a 1 μm thick layer of polyethylene glycol with an average molecular weight of about 15000 (carbowax 20M).

Column temperature: Maintain at 40 ºC for 3 minutes, then increase linearly to 100 ºC at a rate of 8 ºC per minute, and maintain at 100 ºC for 1 minute.

Sample injection port temperature: 150 ºC

Detector temperature: 200 °C.

Carrier gas: Helium

Flow rate: 11 mL/min

System suitability

System performance: Perform the test with 1 mL of the standard solution according to the above operating conditions; methanol, 2-propanol, 2-butanol and methoxy ethanol are eluted in this order with the resolution between the methanol peak and the 2-propanol peak is NLT 1.0.

System repeatability: Repeat the test six time with 1mL of the standard solution according to the above operating conditions; the relative standard deviation of the ratios of the peak area for methanol and 2-propanol is NMT 0.5% and the relative standard deviation of the ratios of the peak area for methoxy ethanol is NMT 10%.

(8) ***Related substances***—(i) Weigh accurately an amount of Iodixanol, equivalent to 0.5 g of anhydrous Iodixanol, dissolve in water to make exactly 20 mL, and use this solution as the test solution (1). To 5.0 mL of the test solution (1), add water to make exactly 50 mL, and use this solution as the test solution (2). Separately, weigh accurately an appropriate amount of iodixanol RS and dissolve in water so that the solution contains 12.5 mg of anhydrous Iodixanol per mL, and use this solution as the standard stock solution (1). Weigh accurately an appropriate amount of iodixanol related substance I ((5-[acetyl[3-[[3,5-bis[[2,3-dihydroxypropyl)amino]carbonyl]-2,4,6-triiodophenyl]amino]-2-hydroxypropyl]amino]-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) RS, dissolve in water to obtain a solution containing about 0.25 mg of anhydrous iodixanol related substance I per mL, and use this solution as the standard stock solution (2). Weigh accurately an suitable amount of iodixanol related substance II (5-[acetyl(2-hydroxy-3-methoxypropyl)amino]-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenecarboxamide) RS, dissolve in water to obtain a solution containing about 0.025 mg of anhydrous iodixanol related substance II per mL, and use this solution as the standard stock solution (3). Pipet 2.0 mL of the standard stock solution (1), add water to make exactly 10 mL, and use this solution as the standard solution (1). Pipet 5.0 mL of the standard stock solution (1), 2.5 mL of the standard stock solution (2) and 2.5 mL of the standard stock solution (3), add water to make exactly 25 mL, use these solutions as the standard solution (2). Pipet 5.0 mL of the test solution (1) and 2.5 mL of the standard stock solution (2), add water to make exactly 50 mL, and use this solution as the control solution. Use water as the blank test solution. Perform the test with 10 μL each of the blank test solution, the test solution (1) and the test solution (2) as directed under the Liquid Chromatography according to the following operating conditions. With the test solution (1)

and the test solution (2), determine the content (%) of each related substance, when specified, according to the following formula.

$$\text{Content (\%) of related substances} = \frac{10X}{0.1Y + Z} \quad (1)$$

X: Peak area of the specified related substance obtained from the test solution (1)

Y: Total area of all the peaks eluted before and after iodixanol peak from test solution (1). However, disregard any peaks resulting from injection noise or solvent.

Z: Total area of the Iodixanol major peak and all related substances peaks obtained from the test solution (2)

① Iohexol—If Iohexol is present, two peaks appear at the relative retention time of about 0.37 and 0.39 to Iodixanol in the chromatogram obtained from the test solution (1). Draw a baseline at the height of the baseline obtained from the blank test solution. Determine the total area of the two peaks of Iohexol and calculate the amount of Iohexol according to the formular (1) (NMT 0.6%).

② Iodixanol related substance III—Related substance III (5-(acetylamino)-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenecarboxamide) is eluted as a single peak at the relative retention time of 0.34 to Iodixanol in the chromatogram obtained from the test solution (1). Determine the peak area of related substance III and calculate the amount of related substance III according to the equation (1) (NMT 0.2%).

③ Iodixanol related substance I—The first peak of related substance I appears at the relative retention time of 1.07, between the two major peaks of Iodixanol, and the second peak of related substances I co-elutes with iodixanol. The area of the first peak is about 80% of the total area of the peaks of related substance I. Determine the area of the first peak, X_2, and calculate the amount of related substance I using the following formular (NMT 0.4%).

$$\text{Content (\%) of Iodixanol related substances (\%)} = \frac{12.5X_2}{0.1Y + Z} \quad (2)$$

Y, *Z*: See formular (1)

④ Iodixanol related substance IV—Only the first peak of related substance IV {2-[[acetyl[3,5-bis[[2,3-dihydroxypropyl)amino]carbonyl]-2,4,6-triiodophenyl]methyl]-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,3-dihyro-5,7-diiodie-4H-1,4-benzoxazine-6,8-dicarboxamide} appears at the relative retention time of 0.8 to the Iodixanol in the chromatogram obtained from the test solution (1). The second peak co-elutes with iodixanol peak. The area of the first peak is about 25% of the total area of related substance IV. Determine the area of the first peak X_1, and calculate the amount of related substance IV using the following formula (NMT 0.2%).

$$\text{Content (\%) of Iodixanol related substance IV} = \frac{40X_1}{0.1Y + Z} \quad (3)$$

Y, *Z*: See formular (1)

⑤ Iodixanol related substance V—Only the second peak of related substance V {4-acetyl-2-[[acetyl[3,5-bis[[2,3-dihydroxypropyl)amino]carbonyl]-2,4,6-triiodophenyl]methyl]amino]-methyl]-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,3-dihyro-5,7-diiodide-4*H*-1.4-benzoxazine-6,8-dicarboxamide} appears at the relative retention time of 1.18 to Iodixanol in the chromatogram obtained from the test solution (1). The first peak co-elutes with iodixanol. The area of the second peak is about 85% of the total area of related substance V. Determine the area of the second peak, X3, and calculate the amount of related substance V using the following formular (NMT 0.2%).

$$\text{Content (\%) of Iodixanol related substance V} = \frac{10X_3}{0.85(0.1Y + Z)} \quad (4)$$

Y, *Z*: See formular (1)

⑥ Overalkylated related substances—Overalkylated related substances appear, after related substance V, with a retention time larger than the relative retention time of 1.18 to the last Iodixanol peak in the chromatogram of the test solution (1). Calculate the amount of overalkylated related substances by the formula (1) used to determine the amount of related substances (NMT 1.0%).

⑦ Unspecified related substance 1—Determine the area of each peak eluting before and after the major peak of Iodixanol, excluding the above mentioned peaks, in the chromatogram obtained from the test solution (1), and calculate the amount of unspecified related substance 1 according to the formula (1).

⑧ Unspecified related substance 2—Determine the area of each peak eluting between the major peaks of Iodixanol, excluding the above mentioned peaks, in the chromatogram obtained from the test solution (1), and calculate the amount of unspecified related substance 2. Amount of each related substance of ⑦ and ⑧ is NMT 2.0%, and amount of total unspecified related substances is NMT 0.5%.

⑨ Total related substances—Determine total area of all peaks eluting between the major peaks of Iodixanol in the chromatogram obtained from the test solution (1), and calculate the amount of total related substances (NMT 1.5%).

Content (%) of total related substances

$$= \frac{\left[100\left(Y - X_1 - X_3 + \frac{X_1}{0.25} + \frac{X_2}{0.8} + \frac{X_3}{0.85}\right)\right]}{10(0.1Y + Z)}$$

In which the variables are as defined above.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: A mixture of acetonitrile and water (1 : 1).

Mobile phase B: Water

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0	6	94
0 - 30	6 → 20	94 → 80
30 - 70	20 → 100	80 → 0
70 - 80	100	0
80 - 81	100 → 6	0 → 94
81 - 90	6	94

Flow rate: 1.0 mL/min

System suitability

Blank test solution: Inject in sequence of standard solution (1), the control solution and three replicates of the standard solution (2).

System performance: Proceed with 10 μL of the standard solution (1) according to the above operating conditions; the chromatogram obtained exhibits two or three unresolved major peaks. If the chromatogram exhibits two major peaks, their relative areas are 60% and 40%. If the chromatogram exhibits three major peaks, their relative areas are about 60%, 38% and 2%. Proceed with 10 μL of the standard solution (2) according to the above operating conditions; the chromatogram obtained exhibits two resolved peaks due to related substance II, which is eluted before Iodixanol, and one peak due to related substance I between the two principal Iodixanol peaks. The area of the two related substance II peaks is between 0.075% and 0.125% of the total peak area. However, disregard any peak due to the solvent front and any peak due to the blank test solution.

System repeatability: Repeat the test three times with each 10 μL of the standard solution (2) according to the above operating conditions; the relative standard deviation of total areas of two isomer peaks for related substance II is NMT 5%. Measure the height of the related substance I peak, and adjust the sensitivity to obtain a peak height between 80% and 100% of the full scale. Measure the height above the baseline, A, of the Iodixanol related substance I peak and the height above the baseline, B, of the lowest part of the curve where the peak of related substance I is separated from the first major peak of Iodixanol peak; A is NLT 1.3B. Perform the test with 10 μL of the control solution according to the above operating conditions; the peak of Iodixanol related substance I is measurable.

(ii) Weigh accurately an amount of Iodixanol, equivalent to about 0.125 g of anhydrous iodixanol, dissolve in water to make exactly 50 mL, and use this solution as the test solution. Weigh accurately an amount of iodixanol RS, equivalent to about 0.125 g of anhydrous iodixanol, dissolve in water to make exactly 10 mL, and use this solution as the standard stock solution (1). Weight accurately an amount of iodixanol related substance II RS, equivalent to about 0.125 g of anhydrous iodixanol, dissolve in water to make exactly 100 mL, and use this solution as the standard stock solution (2). Weigh accurately an amount of iodixanol related substance IV RS, equivalent to about 25 mg of anhydrous iodixanol, dissolve in water to make exactly 10 mL, and use this solution as the standard stock solution (3). Pipet 2.0 mL of the standard stock solution (1), add water to make exactly 10 mL, and use this solution as the standard solution (1). Pipet 5.0 mL of the standard stock solution (1) and 2.5 mL of the standard stock solution (2), add water to make exactly 25 mL, and use these solutions as the standard solution (2). Pipet 1.0 mL of the standard solution (1) and 1.0 mL of the standard stock solution (3), add water to make 3.0 mL, and use this solution as the standard solution (3). Use water as the blank test solution. Perform the test with 10 μL each of the test solution, the standard solution (1), the standard solution (2) and the standard solution (3) as directed under the Liquid Chromatography according to the following operating conditions. For the standard solution (2), inject three times. Compare the retention times of the peaks eluting from the test solution to those from the standard solution (3). Iodixanol related substance VI exhibits two partially overlapping peaks. Use only the area of the first and larger peak, which corresponds to about 60% of the total area of related substance V, and determine. the percent area of Iodixanol related substance VI {5-[[3-[[3-[[2,3-dihydroxypropyl)amino] carbonyl]-5-[[amino]carbonyl]-2,4,6-triiodophenyl] (acetylimino]-2-hydroxypropyl]-(acetylimino)]-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiod-1,3-benzenedicarboxide} by dividing this area obtained from the test solution by 0.6; it is NMT 0.3%. Calculate the percent area of the related substance VII peak appearing as a single peak, with a shoulder on the tail of the iodixanol peak, is NMT 0.6%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with a monomolecular layer of aminopropylsilyl silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Control the mixing ratio of mobile

phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: Acetonitrile
Mobile phase B: Water

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0	85	15
0 - 25	85 → 66	15 → 34

Flow rate: 2.5 mL/min
System suitability

System performance: Perform the test with 10 μL of the standard solution (1) according to the above operating conditions; three iodixanol peaks appear with the relative peak area of 62%, 35% and 3% and the retention time of the last peak is NMT 14 minutes. Perform the test with 10 μL of the standard solution (2) according to the above operating conditions; related substance II produces two partially overlapping peaks at the relative retention time of 0.33 and 0.39, respectively, and the peak area of each peak is between 0.075% and 0.125% of the total area. Perform the test with 10 μL of the standard solution (3) according to the above operating conditions; related substance VI produces two overlapping peaks at the relative retention time of 0.67 and 0.72, respectively. The resolution between the first peak of related substance VI and the first major peak of Iodixanol is NLT 5.0.

System repeatability: Repeat the test three times with each 10 μL of the standard solution (2) according to the above operating conditions; the relative standard deviation of total areas of two isomer peaks for related substance II is NMT 5%.

Water NMT 4.0% (0.5 g, volumetric titration, direct titration).

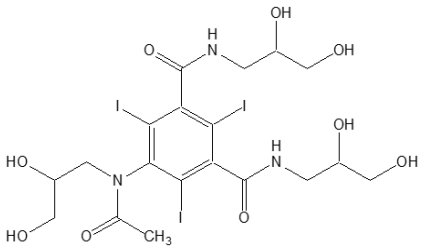
Microbiological examination of non-sterile products The total aerobic microbial count is NMT 100 CFU per g.

Assay Weigh accurately about 0.5 g of Iodixanol, add 25 mL of sodium hydroxide (1 in 20) and 0.5 g of zinc powder, connect the flask to a reflux condenser, and reflux for 1 hour. Cool the flask to room temperature, wash the condenser with 20 mL of water, combine the washings with the reaction mixture, and filter. Wash the flask and the filter with a small amount of water several times, filter, and combine the washings to the filtrate. Add 5 mL of acetic acid(100) and titrate with 0.1 mol/L silver nitrate VS (potentiometric titration under the Titrimetry).

Each mL of 0.1 mol/L silver nitrate VS
= 25.84 mg of $C_{35}H_{44}I_6N_6O_{15}$

Packaging and storage Preserve in light-resistant, well-closed containers.

Iohexol
이오헥솔



$C_{19}H_{26}I_3N_3O_9$: 821.14

1-*N*,3-*N*-*bis*(2,3-Dihydroxypropyl)-5-[*N*-(2,3-dihydroxypropyl)acetamido]-2,4,6-triiodobenzene-1,3-dicarboxamide [*66108-95-0*]

Iohexol contains NLT 98.0% and NMT 102.0% of iohexol ($C_{19}H_{26}I_3N_3O_9$), calculated on the anhydrous basis.

Description Iohexol occurs as a white or grayish white powder and is odorless.
It is very soluble in water or methanol, and practically insoluble in ether or chloroform.
It is hygroscopic.

Identification (1) Transfer about 0.5 g of Iohexol to a crucible, and heat; a purple gas is evolved.

(2) Determine the absorption spectra of aqueous solutions of Iohexol and Iohexol RS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit a maximum and a minimum of absorption at the same wavelengths.

(3) Determine the infrared spectra of Iohexol and Iohexol RS as directed in the potassium bromide disk method under the Mid-infrared absorption Spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) Weigh 0.1 g each of Iohexol and iohexol RS, dissolve in 10 mL of methanol, and use these solutions as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of 1-butanol, water and acetic acid(100) (50 : 25 : 11) to a distance of about 15 cm, and air-dry the plates. Examine under ultraviolet light (main wavelength: 254 nm); two principal spots corresponding to exo-isomer and endo-isomer appears from the test solution and the standard solution, and the R_f values of the spots obtained from the test solution and the standard solution are the same.

Optical rotation $[\alpha]_D^{20}$: Between -0.5° and +0.5° (0.5 g, water, 10 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Weigh 16.18 g

of Iohexol, dissolve in water to make exactly 25 mL, and filter through a membrane filter with a porosity of 0.22 μm. Determine the absorbances with this filtrate as directed under the Ultraviolet-visible Spectroscopy using water as the blank test solution at wavelengths of 400 nm, 420 nm and 450 nm; the absorbances are NMT 0.180, 0.030 and 0.015, respectively.

(2) ***Heavy metals***—To 5.0 g of Iohexol, add water to make 50 mL. Use 12 mL of this solution as the test solution. Separately, mix 10 mL of diluted lead standard solution with 2 mL of the test solution, and use this solution as the control solution. Separately, mix 10 mL of water with 2 mL of the test solution, and use this solution as the blank test solution. To 12 mL each of the test solution, the control solution and the blank test solution, add 2 mL of acetate buffer solution, pH 3.5, mix, add 1.2 mL of thioacetamide TS, and mix immediately. Allow to stand for 2 minutes; the color of the test solution is not more intense than that of the control solution (NMT 10 ppm).

Diluted lead standard solution—Immediately before use, pipet accurately 5 mL of lead standard solution, and add water to make 50 mL.

System suitability: The control solution exhibits a faint brown color compared to the blank test solution.

(3) ***Free aromatic amine***—Weigh accurately 0.2 g of Iohexol, transfer to a 50-mL volumetric flask, and dissolve with 15 mL of water. To a second 50-mL volumetric flask, transfer 5 mL of water and 10.0 mL of a solution prepared by dissolving Iohexol related substance I {5-(amino)-N,N,-bis(2,3-dihydroxypropyl)-2,4,6-triiod-1,3-benzenedicarboxyamide)} RS in water to make the concentration of 10 μg per mL. To a third 50-mL volumetric flask, add 15 mL of water. Place these solutions in an ice bath, and cool for 5 minutes. Add 3.0 mL each of 5 mol/L hydrochloric acid TS to each flask, stir to mix, add 2.0 mL of sodium nitrite solution (1 in 50), mix, and allow to stand for 4 minutes. Add 2.0 mL each of sulfamic acid solution (1 in 25), shake, and allow to stand for 1 minute. Remove these solutions from the ice bath, add 2 mL each of a solution of *N*-(1-naphthyl) ethylenediamine dihydrochloride dissolved in diluted propylene glycol (7 in 10) (1 in 1000), and mix. Add water to make 50 mL, allow to stand for 5 minutes, and use these solutions as the test solution, the standard solution and the blank test solution, respectively. With these solutions, perform the test as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbances of the test solution and the standard solution at 495 nm; the absorbance of the test solution is not larger than that of the standard solution (NMT 0.05%).

(4) ***Free iodine***—Weigh 2.1 g of Iohexol, transfer to a 50-mL centrifuge tube with a stopper, add 20 mL of water, and shake vigorously to dissolve. Add 5.0 mL of toluene and 5 mL of 1 mol/L sulfuric acid TS, shake, and centrifuge at high speed; the toluene layer exhibits no red or pink color.

(5) ***Free iodide***—Weigh 5.0 g of Iohexol, dissolve in about 20 mL of water, transfer to a centrifuge tube with a stopper. Add 20 mL of water, shake vigorously or heat gently to dissolve, and titrate with 0.001 mol/L silver nitrate VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction (0.001%).

Each mL of 0.001 mol/L $AgNO_3$
= 126.9 μg of I

(6) ***Ionic substances***—Rinse all glassware 5 times with distilled water. With an aqueous solution of Iohexol (1 in 50), determine the specific resistance (R_{SP}) at 20 ºC, and calculate the specific conductance, κ; the specific conductance is not larger than that of 0.0002% sodium chloride solution (NMT 0.01%).

$$\text{Specific conductance} = (1/R_{SP}) \times 106$$

(7) ***Methanol, 2propanol and methoxyethanol***—Weigh accurately 6.25 g of Iohexol, add 5 mL of internal standard solution, add water to make 25 mL, and use this solution as the test solution (1). Transfer 5.0 mL of the test solution (1) and 1 mL of water to a vial fitted with an elastomeric closure, and seal. Heat the sealed vial at 95 ºC for 15 minutes, and use this solution as the test solution (2). Transfer 5.0 mL of the test solution (1) and 1 mL of the standard solution (2) to a vial fitted with an elastomeric closure and seal. Heat the sealed vial at 95 ºC for 15 minutes, and use this solution as the test solution (3). Transfer 5.0 mL of the test solution (1) and 1.0 mL of the standard solution (3) to a vial fitted with an elastomeric closure and seal. Heat the sealed vial at 95 ºC for 15 minutes, and use this solution as the test solution (4). Transfer 5.0 mL of the test solution (1) and 1.0 mL of the standard solution (4) to a vial fitted with an elastomeric closure and seal. Heat the sealed vial at 95 ºC for 15 minutes, and use this solution as the test solution (5). Separately, weigh accurately about 0.6 g of methanol, add about 100 mL of water, mix, add about 0.6 g of 2-propanol, accurately weighed, add about 100 mL of water, and mix. To this solution, add about 0.6 g of methoxyethanol (95), accurately weighed, add 100 mL of water, mix, add water to make exactly 1000 mL, and use this solution as the standard solution (1). Pipet 10.0 mL of the standard solution (1), add water to make exactly 50 mL, pipet 10.0 mL of this solution, add water to make 100 mL, and use this solution as the standard solution (2). Pipet 5.0 mL of the standard solution (1), add water to make exactly 100 mL, and use this solution as the standard solution (3). To 10.0 mL of the standard solution (1), add water to make exactly 100 mL, and use this solution as the standard solution (4). To 10.0 mL of the standard solution (4) and 10.0 mL of internal standard solution, add water to make exactly 50 mL, transfer 6.0 mL of this solution to a vial fitted with an elastomeric closure, and seal. Heat the sealed vial at 95 ºC for 15 minutes, and use this solution as the standard solution (5). Perform the test with 2 mL each of the test

solution (2), the test solution (3), the test solution (4), the test solution (5) and the standard solution (5) as directed under the Gas Chromatography according to the following operating conditions using the injection port apparatus for the headspace, and calculate the area of the major peak from each chromatogram. Plot the peak area ratios of each component obtained from the test solutions against the amount of methanol RS, amount of 2-propanol RS and amount of methoxyethanol RS added per g of Iohexol. Extrapolate the line joining the points until the line intercepts the concentration axis. Determine the amounts (mg/g) of methanol, 2-propanol and methoxyethanol as the distance between the intercept and the point of intersection. Amounts (%) of methanol and 2-propanol are NMT 0.005%, respectively, and the content (%) of methoxyethanol is NMT 0.002%.

Internal standard solution—2-Prepare a solution by dissolving 2-butanol in water, containing about 0.05 mg per mL.

Operating conditions

Detector: A flame ionization detector

Column: A fused silica capillary column about 0.53 mm in internal diameter and 30 m in length, coated the inside with a 3 μm layer of 6% cyanopropylphenyl and 94% dimethylpolysiloxane.

Column temperature: Maintain at 40 ºC for 5 minutes, followed by an increase at a rate of 10 ºC per minute to 100 ºC, and maintain at 100 ºC for 1 minute.

Sample injection port temperature: 140 ºC

Detector temperature: 250 °C

Carrier gas: Helium

Flow rate: 14 mL/min

System suitability

System performance: Proceed with the standard solution (5) according to the above operating conditions; the relative retention times of methanol, 2-propanol, 2-butanol and methoxyethanol are about 0.3, 0.5, 1.0 and 1.3, respectively, with the resolution between methanol peak and 2-propanol peak being NLT 2.5.

System repeatability: Repeat the test 6 times with the standard solution (5) according to the above operating conditions, the relative standard deviation of each peak area is NMT 5%.

(8) ***3-chloro-1,2-propanediol***—Weigh accurately about 1 g of Iohexol, dissolve in 1.0 mL of water, extract 4 times with 2 mL of ethyl acetate, and combine the extracts. Dry the combined extracts with anhydrous sodium sulfate and filter. Wash the filter with a small amount of ethyl acetate, and combine the washings with the filtrate. Evaporate this solution to the volume of 2.0 mL on a warm water bath and under a stream of nitrogen, filter through a membrane filter, and use the filtrate as the test solution. Separately, dissolve 3-chloro-1,2-propanediol in ethyl acetate to prepare a solution containing 20 μg per mL, and use this solution as the standard solution. Perform the test with 2 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following operating conditions; 3-chloro-1,2-propanediol, a mixture of two isomers, exhibits two major peaks at 12 and 12.5 minutes, respectively. Measure the total of two peak areas of 3-chloro-1,2-propanediol, A_{ST} and A_{SA}, and calculate the amount of 3-chloro-1,2-propanediol (NMT 0.0025%).

$$\text{Amount (μg) of 3-chloro-1,2-propanediol} = 100 \times \frac{A_{ST}}{A_{SA}} \times \frac{2C_{ST}}{R}$$

C_{ST}: Concentration (μg/mL) of 3-chloro-1,2-propanediol in the standard solution

R: Recovery rate (%) measured in the system suitability test

Operating conditions

Detector: A flame ionization detector

Column: A fused silica capillary column about 0.32 mm in internal diameter and about 30 m in length, coated the inside with a 1-μm layer of 14% cyanopropylphenyl-86% methylpolysiloxane.

Column temperature: At first, maintain at 50 ºC for 2 minutes, followed by an increase at a rate of 10 ºC per minute to 200 ºC.

Sample injection port temperature: 230 ºC

Detector temperature: 250 °C

Carrier gas: Helium

System suitability

System performance: Proceed with the system suitability solution according to the above operating conditions; the recovery rate of 3-chloro-1,2-propanediol from Iohexol is between 60 and 90%.

$$\text{Recovery rate (\%) of 3-chloro-1,2-propanediol} = 100 \times \frac{A_{RC}}{A_{ST}} \times \frac{C_{ST}}{C_{RS}}$$

C_{RS}: Concentration (μg/mL) of 3-chloro-1,2-propanediol in the system suitability solution

C_{ST}: Concentration (μg/mL) of 3-chloro-1,2-propanediol in the standard solution

A_{RC}: Peak area of 3-chloro-1,2-propanediol obtained from the system suitability solution

A_{ST}: Peak area of 3-chloro-1,2-propanediol obtained from the standard solution

System repeatability: Repeat the test 6 times with the standard solution according to the above conditions; the relative standard deviation of peak area is NMT 10%.

System suitability solution—Add a solution of 1 g of Iohexol containing NMT 5 μg of 3-chloro-1,2-propanediol dissolved in 1 mL of water and 2.0 mL of a solution prepared by dissolving 3-chloro-1,2-propanediol in ethyl acetate, containing 25 μg per mL, and shake to mix. Separately store the ethyl acetate layer, and extract the aqueous layer three times with 2 mL each of ethyl acetate. Combine all the extracts, dry with anhydrous sodium sulfate, filter, and wash the filter with a

small amount of ethyl acetate. Combine the washings, concentrate to 2.0 mL under nitrogen stream, filter through a membrane filter, and use the filtrate as the system suitability solution.

(9) ***Related substances*—**Weigh accurately 75 mg of Iohexol, dissolve in water to make 50 mL, and use this solution as the test solution. Perform the test with 10 μL of this solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the amount of each related substance; the peaks other than the major peak are NMT 0.1%, respectively, the peaks of O-alkylated substances are NMT 0.6%, and the sum of all the related substances other than O-alkylated substances is NMT 0.3%.

$$\text{Content (\%) of the related substance} = 100 \times \frac{A_i}{A_S}$$

A_i: Each peak area other than the major peak
A_S: total area of all the peaks

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: Change the rate of acetonitrile and water to increase the percentage of acetonitrile from 1% to 13% at a rate of 0.2% per minute.

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 10 μL of the system suitability solution according to the above operating conditions; the relative retention time for the O-alkylated substances to 1.0 of the retention time for the exo-isomer of Iohexol is between 1.1 and 1.4, the resolution between the peaks of iohexol related substance II and Iohexol related substance III is NLT 20.0, and the peak area of iohexol related substance III is 0.5% ± 0.1% of the total area of all peaks in the chromatogram.

System suitability solution—Dissolve iohexol RS, Iohexol related substance II RS and Iohexol related substance I RS in water to prepare solutions containing 1.5 mg, 0.0075 mg and 0.0069 mg per mL, respectively, and use the solutions as the system suitability solutions.

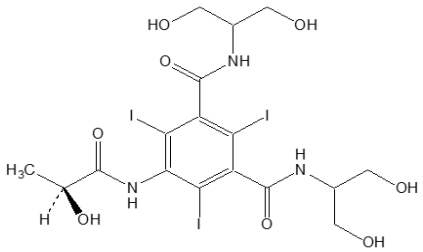
Water NMT 4.0% (0.3 g, volumetric titration, direct titration).

Assay Weigh accurately about 0.5 g of Iohexol, add 25 mL of 1.25 mol/L sodium hydroxide TS and 0.5 g of zinc powder, connect to a reflux condenser, and reflux the mixture for 1 hour. Cool to room temperature, rinse the condenser with 20 mL of water, add the washings in the reaction mixture, mix, and filter. Rinse the flask and the filter thoroughly with a small amount of water, and combine the washings to the filtrate. Add 5 mL of acetic acid(100), and titrate with 0.1 mol/L silver nitrate VS (potentiometric titration under the Titrimetry).

Each mL of 0.1 mol/L silver nitrate
= 27.37 mg of $C_{19}H_{26}I_3N_3O_9$

Packaging and storage Preserve in light-resistant, well-closed containers.

Iopamidol
이오파미돌



$C_{17}H_{22}I_3N_3O_8$: 777.09

1-*N*,3-*N*-*bis*(1,3-Dihydroxypropan-2-yl)-5-[[(2*S*)-2-hydroxypropanoyl]amino]-2,4,6-triiodo-benzene-1,3-dicarboxamide [*60208-45-9*]

Iopamidol, when dried, contains NLT 99.0% and not more the 101.0% of Iopamidol ($C_{17}H_{22}I_3N_3O_8$).

Description Iopamidol occurs as a white crystalline powder.
It is very soluble in water, sparingly soluble in methanol, and practically insoluble in ethanol(99.5).

Identification (1) To 0.05 g of Iopamidol, add 5 mL of hydrochloric acid, and heat on a steam bath for 10 minutes; the resulting solution responds to the Qualitative Analysis for primary aromatic amine.

(2) Heat 0.1 g of Iopamidol over a flame: a violet gas is evolved.

(3) Determine the infrared spectra of Iopamidol and Iopamidol RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared absorption Spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_{463nm}^{20}$: Between -4.6° and -5.2° (after drying, 4 g, water, warming, after cooling, 10 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Iopamidol in 10 mL of water; the solution is clear and colorless.

(2) ***Free acid or alkali***—Weigh accurately about 10.0 g of Iopamidol, dissolve in 100 mL of freshly boiled and cooled water, and titrate with 0.01 mol/L hydrochloric acid VS or 0.01 mol/L sodium hydroxide VS until the pH of the solution becomes 7.0; NMT 1.37 mL of 0.01 mol/L sodium hydroxide VS (NMT 0.005% as free acid)

or NMT 0.75 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.003% as free alkali) is consumed to adjust the pH of the test solution to 7.0.

(3) ***Primary aromatic amine***—Dissolve 0.60 g of Iopamidol in 8 mL of water, add 1 mL of sodium nitrite solution (1 in 50) and 12 mL of 2 mol /L hydrochloric acid TS, shake to mix, and allow to stand for 2 minutes. Add 1 mL of ammonium sulfamate solution (1 in 10), shake to mix, allow to stand for 1 minute, and add 1 mL of naphthylethylenediamine TS and water to make 50 mL. Determine the absorbance of this solution at the wavelength of 495 nm as directed under the Ultraviolet-visible Spectroscopy using a blank test solution prepared in the same manner as the control solution; the absorbance is NMT 0.12 (NMT 0.020%).

(4) ***Iodine***—Dissolve 2.0 g of Iopamidol in 25 mL of water, add 5 mL of 1 mol/L sulfuric acid TS and 5 mL of toluene, shake well to mix, and allow to stand; the toluene layer is colorless.

(5) ***Free iodine ion***—Weigh accurately about 5.0 g of Iopamidol, dissolve in 70 mL of water, and adjust the pH to about 4.5 with dilute acetic acid. To this solution, add 2 mL of 0.1 mol/L sodium chloride TS, and titrate with 0.001 mol/L silver nitrate VS (potentiometric titration under the Titrimetry). Determine the content (%) of iodine ion; it is NMT 0.001%.

Each mL of 0.001 mol/L silver nitrate VS
= 0.1269 mg of I

(6) ***Heavy metals***—Weigh 1.0 g of Iopamidol, moisten with a small quantity of sulfuric acid, and heat gently until almost incinerated at the lowest possible temperature. Allow to stand for cooling, moisten again with a small quantity of sulfuric acid, heat gently until a white fume is no longer evolved, and incinerate by ignition at 450 to 550 °C. Proceed according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(7) ***Related substances***—Weigh accurately 0.10 g of Iopamidol, dissolve in water to make exactly 10 mL, and use this solution as the test solution. Separately, weigh 10 mg of N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-hydroxyacetyl-amino–2,4,6-triiodoisophthalamide, and dissolve in water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; each area of the peaks other than iopamidol from the test solution is not larger than the peak area of N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-hydroxyacetyl-amino–2,4,6-triiodoisophthalamidearea from the standard solution. And the total area of these peaks is not larger than 2.5 times the peak area of N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-hydroxyacetyl-amino–2,4,6-triiodoisophthalamide from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: Water

Mobile phase B: A mixture of water and methanol (3 : 1).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 6	92	8
6 - 18	92 → 65	8 → 35
18 - 30	65 → 8	35 → 92
30 - 34	8	92

Flow rate: 1.5 mL/min

System suitability

System performance: Dissolve 1 mL of the test solution and 10 mg of N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-hydroxyacetylamino-2,4,6-triiodoisophthalamide in water to make 100 mL proceed with 20 μL of this solution according to the above operating conditions; N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-hydroxyacetylamino-2,4,6-triiodoisophthalamide and iopamidol are eluted in this order with the resolution being NLT 7.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-hydroxyacetylamino-2,4,6-triiodoisophthalamide is NMT 1.0%.

Time span of measurement: About 4.3 times the retention time of Iopamidol.

Loss on drying NMT 0.3% (1 g, 105 °C, 3 hours).

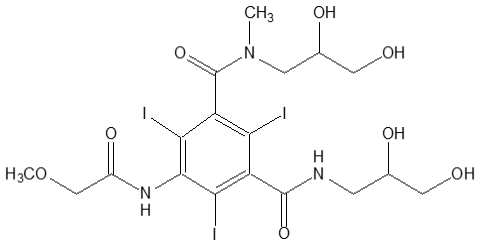
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Iopamidol, previously dried, transfer to a saponification flask, dissolve with 40 mL of sodium hydroxide TS, add 1 g of zinc powder, boil for 30 minutes under a reflux condenser, cool, and filter. Wash the flask and the filter paper with 50 mL of water, and combine the washings with the filtrate. Add 5 mL of acetic acid(100) to this solution, and titrate with 0.1 mol/L silver nitrate VS (potentiometric titration under the Titrimetry).

Each mL of 0.1 mol/L silver nitrate VS
= 25.90 mg of $C_{17}H_{22}I_3N_3O_8$

Packaging and storage Preserve in light-resistant, well-closed containers.

Iopromide
이오프로미드



$C_{18}H_{24}I_3N_3O_8$: 791.11

1-*N*,3-*N*-*bis*(2,3-Dihydroxypropyl)-2,4,6-triiodo-5-[(2-methoxyacetyl)amino]-3-*N*-methylbenzene-1,3-dicarboxamide [*73334-07-3*]

Iopromide contains NLT 97.0% and NMT 102.5% of Iopromide ($C_{18}H_{24}I_3N_3O_8$), calculated on the anhydrous and solvent-free basis.

Description Iopromide occurs as a white or pale yellow powder.
It is freely soluble in water and dimethylsulfoxide, and practically insoluble in acetone, ethanol(95) or ether.

Identification (1) Determine the infrared spectra of Iopromide and Iopromide RS, as directed in the potassium bromide disk method under the Mid-infrared absorption Spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Perform the test according to the other related substances under the Purity; the principal spots obtained from the test solution and the standard solution have the same R_f values.

Purity (1) ***Heavy metals***—Weigh 2.0 g of Iopromide, and add water to make 20 mL. Take 12 mL of this solution, and use this solution as the test solution. Separately, mix 10 mL of diluted lead standard solution with 2 mL of the test solution, and use this solution as the control solution. Separately, mix 10 mL of water with 2 mL of the test solution, and use this solution as the blank test solution. To 12 mL each of the test solution, the control solution and the blank test solution, add 2 mL of acetate buffer solution, pH 3.5, and mix. Add 1.2 mL of thioacetamide TS, and mix immediately. Allow to stand for 2 minutes; the color of the test solution is not more intense than that of the control solution (NMT 10 ppm).

Diluted lead standard solution—Immediately before use, pipet accurately 5 mL of lead standard solution, and add water to make 50 mL.

System suitability: The control solution exhibits a faint brown color compared to the blank test solution.

(2) ***Free iodine***—Weigh 2.0 g of Iopromide, dissolve in 20 mL of water, add 2 mL of toluene and 2 mL of diluted sulfuric acid, and shake vigorously to mix; the toluene layer does not exhibit a red color.

(3) ***Free iodide***—Weigh 10.0 g of Iopromide, dissolve in 70 mL of water, adjust pH to 3.5 ± 0.5 with 0.05 mol/L sulfuric acid TS, and titrate with 0.001 mol/L silver nitrate VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction (NMT 0.002%).

Each mL of 0.001 mol/L silver nitrate VS
= 126.9 μg of I

(4) ***Free aromatic amine***—Weigh accurately 0.5 g of Iopromide, transfer to a 25 mL volumetric flask, dissolve with 20 mL of water, and use this solution as the test solution. Separately, weigh accurately 25 mg of Iopromide related substance I [5-(acetylamino)-N,N'-bis(2,3-dihydroxypropyl-2,4,6-troiodo-N-methyl-1,3-benzene-dicarboxamide)] RS, and dissolve in water to make exactly 100 mL. Transfer 2.0 mL of this solution to a 25 mL volumetric flask, add 18.0 mL of water, mix, and use this solution as the standard solution Transfer 20 mL of water to a 25 mL volumetric flask, and use this solution as the blank test solution Place each flask in an ice bath while protected from light, add slowly 1.0 mL of 8 mol/L hydrochloric acid TS, mix, and allow to stand for 5 minutes. Add 1.0 mL of sodium nitrite solution (1 in 50), mix, and allow to stand for 5 minutes. Add 0.5 mL of freshly prepared sulfamic acid solution (8 in 100), shake vigorously for 5 minutes, venting off the gas that evolves. Then, to a mixture of propylene glycol and water (70 : 30), add 1.0 mL of freshly prepared solution of N-(1-naphthyl)ethylenediamine dihydrochloride (1 in 100), shake, remove the flasks from the ice bath, and allow to stand on a steam bath at 25 °C for 10 minutes. Add water in each flask to make exactly 25 mL, and degas by sonication for 1 minute.` With these solutions, determine the absorbances, A_T and A_S, from the test solution and the standard solution at the absorbance maximum wavelength at about 495 nm as directed under the Ultraviolet-visible Spectroscopy, using the blank test solution as the control solution, and calculate the content (%) of aromatic amine according to the following formula; it is NMT 0.10%. The absorbance of the standard solution is NLT 0.40.

$$\text{Content (\%) of aromatic amine} = 10 \times \frac{W_S}{W_U} \times \frac{A_T}{A_S}$$

W_S: Amount (mg) of Iopromide related substance I RS taken
W_U: Amount (mg) of sample taken

(5) ***Ethanol—***Weigh accurately 0.5 g of Iopromide, dissolve in *N*,*N*-dimethylformamide to make exactly 10 mL, and use this solution as the test solution. Separately,

weigh accurately a suitable amount of ethanol(95), add *N*,*N*-dimethylformamide and mix to prepare a solution containing about 0.050 mg of ethanol (C_2H_5OH) per mL, and use this solution as the standard solution. Use *N*,*N*-dimethylformamide as the blank test solution. Transfer 2.0 mL each of the test solution, the standard solution and the blank test solution to separate headspace vials, add 10 μL each of 1 mol/L hydrochloric acid TS, and then seal the vials tightly with stoppers. Perform the test as directed under the Gas Chromatography according to the following operating conditions, and determine the peak areas of ethanol, A_T and A_S (NMT 0.4%).

$$\text{Concentration (mg/mL) of ethanol} = \frac{C}{I} \times \frac{A_T}{A_S}$$

C: Concentration (mg/mL) of ethanol in the standard solution

I: Concentration (mg/mL) of Iopromide in the test solution

Operating conditions

Detector: A flame ionization detector

Column: A capillary column about 0.25 mm in internal diameter and about 30 cm in length, coated the inside with liquid 6% cyanopropylphenyl-94% dimethylpolysiloxane in a thickness of 1.4 μm.

Column temperature: Maintain at 40 ºC for 10 minutes, then increase at a rate of 5 ºC per minute to 70 ºC. Then, increase at a rate of 30 ºC per minute to 220 ºC.

Sample injection port temperature: 160 ºC

Headspace sampler temperature: 80 ºC

Detector temperature: Maintain at 250 ºC.

Carrier gas: Helium

Flow rate: 27 mm/second

System suitability

System performance: Proceed with 2.0 mL of the standard solution according to the above operating conditions; the retention time of ethanol is about 3 minutes.

System repeatability: Repeat the test 3 times with 2.0 mL each of the standard solution; the relative standard deviation of the peak area is NMT 4.0%. Proceed with the blank test solution according to the above operating conditions; there is no peak in the retention time range for ethanol.

(6) ***N-acetyl compound (iopromide related substance I)***—Calculate the content (%) of *N*-acetyl compound relative to the Iopromide from the chromatogram obtained in the Assay by the following formula; it is NMT 1.5%.

$$\text{Content (\%) of } N\text{-acetyl compound} = 20 \times \frac{W_B}{W_1} \times \left[\frac{(A_{Y1} + A_{Y2})}{(R_{Y1} + R_{Y2})}\right]$$

W_B: Amount (mg) of iopromide related substance I RS taken in preparing the related substance B standard solution

W_1: Amount (mg) of Iopromide taken in preparing the test solution

A_{Y1}, A_{Y2}: Peak areas of the Y1-isomer and Y2-isomer of Iopromide related substance I, respectively, obtained from the test solution

R_{Y1}, R_{Y2}: Peak areas of the Y1-isomer and Y2-isomer of Iopromide related substance I, respectively, obtained from the related substance I standard solution

(7) ***Other related substances***—Weigh accurately about 0.1 g of Iopromide, dissolve in a mixture of methanol and water (1 : 1) to make exactly 10 mL, and use this solution as test solution. Separately, weigh accurately a suitable amount of Iopromide RS, dissolve and dilute accordingly with a mixture of methanol and water (1 : 1) to make solutions containing 0.01 mg, 0.05 mg, 0.1 mg and 0.2 mg per mL, and use these solutions as the standard solutions. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 1 μL and 2 μL of the test solution and 1 μL each of the standard solutions on two separate thin-layer chromatographic plates of silica gel with fluorescent indicator for thin-layer chromatography. Immerse each plate in acidic developing solvent and basic developing solvent, respectively, develop the plates to a distance about 15 cm, and air-dry the plates. Examine the plates under ultraviolet light (main wavelength: 254 nm). Also, expose the plate developed in the acidic developing solvent to ammonia vapor for 10 to 30 minutes, and air-dry the plates. Expose both plates to ultraviolet light until the principal spots turn yellow, spray evenly coloring agent, examine the plate, and determine total concentration of spots other than principal spots, excluding free aromatic amines and *N*-acetyl compounds obtained from the test solution; it is NMT 3.0%.

Acidic developing solvent—A mixture of chloroform, methanol, water and formic acid (62 : 32 : 6 : 2).

Basic developing solvent—A mixture of 1,4-dioxane, water and ethanol(95) (85 : 15 : 4).

Coloring agent—Dissolve 2.7 g of iron(III) chloride hexahydrate in 100 mL of 2.4 mol/L hydrochloric acid TS, and use this solution as the solution A. Store this solution in a refrigerator. Dissolve 3.5 g of potassium hexacyanoferrate(III) in 100 mL of water, and use this solution as the solution B. Store this solution in a refrigerator. Dissolve 5.0 g of sodium arsenite in 30 mL of 1 mol/L sodium hydroxide TS, previously cooled to 0 ºC, add 65 mL of 2.4 mol/L hydrochloric acid TS, mix, and use this solution as the solution C. Store this solution at room temperature and use the clear supernatant. Mix 10 mL of the solution A, 10 mL of the solution B and 2.0 mL of the solution C, and use the resulting solution within 30 minutes after preparation.

(8) *Isomer*—Using the chromatogram obtained from

the test solution in the Assay, calculate the content (%) of each isomer of Iopromide according to the following formula; the amount of E_1-isomer and Z_1-isomer is between 40.0% and 51.0%, and the amount of E_2-isomer and Z_2-isomer is between 49.0% and 60.0%.

Content (%) of E1-isomer and Z1-isomer of Iopromide
$= 100(r_{E1} + r_{Z1})/(r_{E1} + r_{E2} + r_{Z1} + r_{Z2})$

Content (%) of E2-isomer and Z2-isomer of Iopromide
$= 100(r_{E2} + r_{Z2})/(r_{E1} + r_{E2} + r_{Z1} + r_{Z2})$

r_{E1}, r_{E2}, r_{Z1} and r_{Z2}: Peak areas of E_1, E_2, Z_1 and Z_2-isomers of Iopromide

Water NMT 1.5% (1 g, volumetric titration, direct titration)

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 38 mg of Iopromide, dissolve in a mixture of methanol and water (1 : 1) to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately about 38 mg of Iopromide RS (previously determine the water), dissolve in a mixture of methanol and water (1 : 1) to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak area of Iopromide from each solution. However, the peak of E-isomer is determined as follows. Transfer a suitable amount of the standard solution to a vial, seal, heat at 121 ºC for 15 minutes, and cool. Perform the test with the cooled solution according to the following operating conditions, and compare the peak with that of the standard solution unheated; identify the isomer with the retention time of the peak increasing after heating.

Amount (mg) of Iopromide ($C_{18}H_{24}I_3N_3O_8$)
$$= C \times \frac{A_T}{A_S}$$

C: Concentration (mg/mL) of Iopromide RS in the standard solution

A_T: Sum of peak areas of E_1, E_2, Z, and Z_2-Isomers obtained from the test solution

A_S: Sum of peak areas of E_1, E_2, Z, and Z_2-Isomers obtained from the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Mix 6 g of chloroform with 59 g of methanol, add 900 g of water, and gently mix. Do not shake or strongly extrude the mobile phase during use. Allow the mobile phase to flow for NLT 60 minutes after each injection.

Flow rate: About 1.2 mL/min

Column temperature: A constant temperature of about 20 °C.

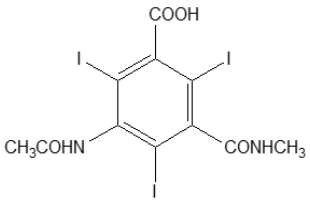
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; the relative retentiontimes of iopromide E_1-isomer, E_2-isomer, Z_1-isomer and Z_2-isomer are about 0.70, 0.75, 0.85, and 1.0, respectively with the resolution between peaks of iopromide Z_1 and Z_2 isomers being NLT 2.0. Separately, weigh accurately about 1.9 mg of Iopromide related substance I RS, and dissolve in a mixture of methanol and water (1 : 1) to make exactly 100 mL. Proceed with 10 μL of this solution according to the above operating conditions; the relative retention times of Y_1- and Y_2-isomers of the Iopromide related substance I are about 0.28 and 0.31, respectively, and the signal-to-noise ratio for Y_2-isomer peak is NLT 20.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the total peak areas of iopromide is NMT 2.0%.

Packaging and storage Preserve in light-resistant, well-closed containers.

Iotalamic Acid
이오탈람산



$C_{11}H_9I_3N_2O_4$: 613.91

3-Acetamido-2,4,6-triiodo-5-(methylcarbamoyl) benzoic acid [*2276-90-6*]

Iotalamic Acid, when dried, contains NLT 99.0% and NMT 101.0% of Iotalamic acid ($C_{11}H_9I_3N_2O_4$).

Description Iotalamic Acid occurs as a white powder and is odorless.
It is slightly soluble in ethanol(95), very slightly soluble in water, and practically insoluble in ether.
It dissolves in sodium hydroxide TS.
It is gradually colored by light.

Identification (1) Heat 0.1 g of Iotalamic Acid over a flame; a purple gas is evolved.

(2) Determine the infrared spectra of Iotalamic Acid and iotalamic acid RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the

same wavenumbers.

Purity (1) ***Clarity and color of solution***—Dissolve 2.0 g of Iotalamic Acid in 10 mL of sodium hydroxide TS; the resulting solution is clear and colorless.

(2) ***Primary aromatic amine***—To 0.50 g of Iotalamic Acid, add 15 mL of water and dissolve in1 mL of sodium hydroxide TS while ice0cooling, add 4 mL of sodium nitrite solution (1 in 100), immediately add 12 mL of 1 mol/L hydrochloric acid TS, and shake gently to mix. Allow to stand for exactly 2 minutes, add 8 mL of ammonium sulfamate TS, and shake occasionally to mix for 5 minutes. Add 3 drops of 1-naphthol in ethanol(95) (1 in 10), allow to stand for 1 minute, add 3.5 mL of ammonia-ammonium chloride buffer solution, pH 10.7, mix, and immediately add water to make 50 mL. Within 20 minutes, determine the absorbance of this solution at 485 nm as directed under the Ultraviolet-visible Spectroscopy, using a blank test solution prepared in the same manner as the control solution; the absorbance is NMT 0.25.

(3) ***Soluble halides***—Dissolve 0.5 g of Iotalamic Acid in 20 mL of diluted ammonia TS (1 in 40), add 6 mL of dilute nitric acid, and shake to mix. Allow to stand for 5 minutes, filter, and transfer the filtrate to a Nessler tube. Wash the residue with 20 mL of water, combine the filtrate and the washings, and add water to make 50 mL. Use the resulting solution as the test solution and proceed as directed under the Chloride. To 0.10 mL of 0.01 mol/L hydrochloric acid VS, add 20 mL of diluted ammonia TS (1 in 40), 6 mL of dilute nitric acid, and water to make 50 mL. Use this solution as the control solution.

(4) ***Iodine***—Dissolve 0.20 g of Iotalamic Acid in 2.0 mL of sodium hydroxide TS, add 2.5 mL of 0.5 mo1/L sulfuric acid TS, and allow to stand for 10 minutes with occasional shaking. Add 5 mL of chloroform, shake well to mix and allow to stand; the chloroform layer is colorless.

(5) ***Heavy metals***—Proceed with 1.0 g of Iotalamic Acid according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(6) ***Arsenic***—Weigh 0.6 g of Iotalamic Acid and proceed according to Method 3 and perform the test (NMT 3.3 ppm).

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

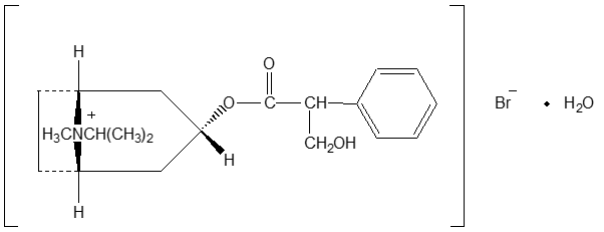
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Iotalamic Acid, previously dried, transfer to a flask, and dissolve in 40 mL of sodium hydroxide TS. Add 1 g of zinc powder, boil for 30 minutes under a reflux condenser, cool, and filter. Wash the flask and the filter paper with 50 mL of water and combine the washings and the filtrate. Add 5 mL of acetic acid(100) to this solution and titrate with 0.1 mol/L silver nitrate VS (indicator: 1 mL of tetrabromophenolphthalein ethyl ester TS). However, the endpoint of titration is when the color of the precipitate changes from yellow to green.

Each mL of 0.1 mol/L silver nitrate VS
= 20.464 mg of $C_{11}H_9I_3N_2O_4$

Packaging and storage Preserve in light-resistant, tight containers.

Ipratropium Bromide Hydrate
이프라트로퓸브롬화물수화물



Ipratropium Bromide $C_{20}H_{30}BrNO_3 \cdot H_2O$: 430.38
(1*R*,3*R*,5*S*,8*R*)-3-[(3-hydroxy-2-phenylpropanoyl)oxy]-8-methyl-8-(propan-2-yl)-8-azabicyclo[3.2.1] octan-8-ium bromide hydrate [*66985-17-9*]

Ipratropium Bromide, when dried, contains NLT 99.0% and NMT 101.0% of Ipratropium Bromide ($C_{20}H_{30}BrNO_3$: 412.36).

Description Ipratropium Bromide occurs as a white crystalline powder.
It is freely soluble in water, soluble in ethanol(99.5), slightly soluble in acetonitrile or acetic acid(100), and practically insoluble in ether.
The pH of a solution of 1.0 g of Ipratropium Bromide dissolved in 20 mL of water is between 5.0 and 7.5.

Melting point—About 223 ºC (with decomposition, after drying).

Identification (1) To 5 mg of Ipratropium Bromide, add 0.5 mL of fuming nitric acid, and evaporate on a steam bath to dryness. After cooling, dissolve the residue in 5 mL of acetone, and add 2 drops of potassium hydroxide-ethanol TS; the solution exhibits a purple color.

(2) Determine the absorption spectra of solutions of Ipratropium Bromide Hydrate and ipratropium bromide hydrate RS in 0.01 mol/L hydrochloric acid TS (3 in 2000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Ipratropium Bromide Hydrate and Ipratropium Bromide Hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) An aqueous solution of Ipratropium Bromide Hydrate (1 in 100) responds to the Qualitative Analysis for bromide.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Ipratropium Bromide Hydrate in 20 mL of water; the

solution is clear and colorless.

(2) ***Sulfate***—Perform the test with 1.0 g of Ipratropium Bromide Hydrate. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid (NMT 0.024%).

(3) ***Heavy metals***—Proceed with 2.0 g of Ipratropium Bromide Hydrate according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Proceed with 2.0 g of Ipratropium Bromide Hydrate according to Method 3 and perform the test. However, use a solution of magnesium nitrate in ethanol(95) (1 in 10) (NMT 1 ppm).

(5) ***Isopropylatropine bromide***—Dissolve 25 mg of Ipratropium Bromide Hydrate in the mobile phase to make exactly 100 mL, and use this solution as the test solution. With 25 μL of this solution, perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the peak area, A_a, of ipratropium and the peak area, A_b, having a ratio of the retention time to ipratropium about 1.3 by the automatic integration method; $A_b/(A_a+A_b)$ is NMT 0.01. No peak other than the peak of ipratropium and the peak having a ratio of the retention time to ipratropium about 1.3 appears within about 14 minutes of the retention time after the solvent peak.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4 mm in internal diameter and 10 cm to 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of diluted phosphoric acid (1 in 200), acetonitrile and methanesulfonic acid (1000 : 120 : 1)

Flow rate: Adjust the flow rate so that the retention time of ipratropium is about 7 minutes.

System suitability

Detection sensitivity: Adjust the detection sensitivity so that the peak height of ipratropium obtained from 25 μL of the test solution composes 50% to 80% of the full scale.

System performance: Heat a solution of Ipratropium Bromide Hydrate in 1 mol/L hydrochloric acid TS (1 in 100) at 100 ºC for 1 hour. After cooling, to 2.5 mL of this solution, add the mobile phase to make 100 mL. Proceed with 25 μL of this solution according to the above operating conditions; the resolution between the peak of ipratropium and the peak having a ratio of the retention time to ipratropium about 0.6 is NLT 3.

(6) ***Apo-compounds***—Weigh 0.14 g of Ipratropium Bromide Hydrate and dissolve in 0.01 mol/L hydrochloric acid TS to make 100 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy and determine the absorbances, A_1 and A_2, at 246 nm and 263 nm, respectively: A_1/A_2 is NMT 0.91.

Loss on drying Between 3.9% and 4.4% (1 g, 105 ºC, 4 hours).

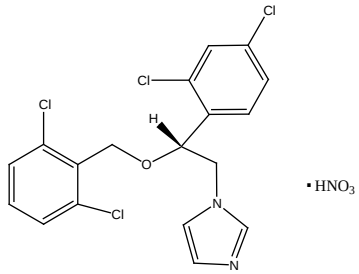
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Ipratropium Bromide Hydrate, previously dried, dissolve in 40 mL of acetic acid(100), add 40 mL of 1,4-dioxane and 2.5 mL of bismuth nitrate TS, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 41.24 mg of $C_{20}H_{30}BrNO_3$

Packaging and storage Preserve in tight containers.

Isoconazole Nitrate
이소코나졸질산염



and enantiomer

$C_{18}H_{14}Cl_4N_2O \cdot HNO_3$: 479.14

1-{2-[(2,6-Dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl}-1*H*-imidazole; nitric acid [*24168-96-5*]

Isoconazole Nitrate contains NLT 99.0% and NMT 101.0% of isoconazole nitrate ($C_{18}H_{14}Cl_4N_2O \cdot HNO_3$), calculated on the dried basis.

Description Isoconazole Nitrate occurs as a white powder.

It is soluble in methanol, slightly soluble in ethanol(95), and very slightly soluble in water.

Identification (1) Weigh the amount of Isoconazole Nitrate, equivalent to about 1 mg of nitric acid, add a mixture of 0.1 mL of nitrobenzene and 0.2 mL of sulfuric acid, and allow to stand for 5 minutes. After cooling in iced water, add 5 mL of water gently while stirring, add 5 mL of 10 mol/L sodium hydroxide TS and 5 mL of acetone, shake, and allow to stand; the upper layer of the resulting solution exhibits an intense purple color.

(2) Determine the infrared spectra of Isoconazole Nitrate and isoconazole nitrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 30 mg of Isoconazole Nitrate in 5 mL

of methanol, and use this solution as the test solution. Separately, dissolve 30 mg of isoconazole nitrate RS in 5 mL of methanol, and use this solution as the standard solution (1). Also, dissolve 30 mg of isoconazole nitrate RS and 30 mg of econazole nitrate RS in 5 mL of methanol, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution, the standard solution (1), and the standard solution (2) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of heptane, 2-propanol, and ammonium acetate TS (50 : 50 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate for about 15 minutes. Apply iodine vapor to the plate; the R_f values of the principal spots obtained from the test solution and the standard solution (1) are the same. This test is valid when the two spots obtained from the standard solution (2) separate clearly.

Optical rotation $[\alpha]_D^{20}$: Between -0.10° and +0.10° (0.2 g, methanol, 20 mL, 100 mm).

Melting point Between 178 and 182 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 0.2 g of Isoconazole Nitrate in methanol to make 20 mL; the resulting solution is clear.

(2) ***Related substances***—Weigh exactly about 0.10 g of Isoconazole Nitrate, dissolve in the mobile phase to make exactly 10 mL, and use this solution as the test solution. Separately, dissolve 2.5 mg of isoconazole nitrate RS and 2.5 g of econazole nitrate RS in the mobile phase to make exactly 100 mL, and use this solution as the standard solution (1). To 1.0 mL of the test solution, add the mobile phase to make exactly 100 mL. To 5.0 mL of this solution, add the mobile phase to make exactly 20 mL, and use this solution as the standard solution (2). Perform the test with 10 μL each of the test solution and the standard solution (2) as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak area of each solution by the automatic integration method; the peak area other than the major peak obtained from the test solution is not greater than the area of the major peak obtained from the standard solution (2)(0.25%). The sum of total peak areas other than the major peak obtained from the test solution is not greater than 2 times the area of the major peak of the standard solution (2)(0.5%). However, exclude any peaks having an area smaller than 0.2 times the area of the solvent, nitrate ion, and the major peak obtained from the standard solution (2).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 235 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Mobile phase: Dissolve 6 g of ammonium acetate in a mixture of water, methanol and acetonitrile (380 : 320 : 300).

Flow rate: 2.0 mL/min

System suitability

Detection sensitivity: Adjust the detection sensitivity so that the height of major peak obtained from 10 μL of the standard solution (2) is 50.0% of the full scale.

System performance: Proceed with 10 μL of the standard solution (1) under the above conditions; econazole and isoconazole are eluted in this order, the retention time is about 10 minutes and 14 minutes, respectively, and the resolution between the peak of econazole and the peak of isoconazole NLT 5.0.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.35 g of Isoconazole Nitrate, dissolve in 75 mL of a mixture of 2-butanone and acetic acid(100) (7 : 1), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 47.91 mg of $C_{18}H_{15}Cl_4N_3O_4$

Packaging and storage Preserve in light-resistant, well-closed containers.

Isoconazole Nitrate Cream
이소코나졸질산염 크림

Isoconazole Nitrate Cream contains NLT 90.0% and NMT 110.0% of the labeled amount of isoconazole nitrate ($C_{18}H_{14}Cl_4N_2O \cdot HNO_3$: 479.14).

Method of preparation Prepare as directed under Creams, with Isoconazole Nitrate.

Identification Weigh an amount of Isoconazole Nitrate Cream equivalent to 10 mg of isoconazole nitrate ($C_{18}H_{14}Cl_4N_2O \cdot HNO_3$), and extract 4 times with 10 mL of ethyl acetate each. For each extraction, add 8 g of anhydrous sodium sulfate and shake. Filter the clear supernatant with filter paper and evaporate to dryness on a steam bath. Dissolve the residue in 10 mL of ethyl acetate and use this solution as the test solution. Separately, dissolve isoconazole nitrate RS in ethyl acetate to make 1 mg/mL and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of n-hexane, ethyl acetate and

methanol (6 : 3 : 1) as the developing solvent and air-dry the plate. Spray evenly Dragendorff's TS on the plate; the R_f value and the color of the spots obtained from the test solution and the standard solution are the same.

Assay Weigh accurately an amount of Isoconazole Nitrate Cream equivalent to about 25 mg of isoconazole nitrate ($C_{18}H_{14}Cl_4N_2O \cdot HNO_3$), add 25.0 mL of the internal standard solution, and warm on a steam bath. After cooling, add chloroform to make 50 mL. Use this solution as the test solution. Separately, weigh accurately about 25 mg of isoconazole nitrate RS, dissolve in 25.0 mL of the internal standard solution, add chloroform to make 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and calculate the peak area ratios, Q_T and Q_S, of isoconazole nitrate to the peak area of the internal standard.

$$\text{Amount (mg) of isoconazole nitrate } (C_{18}H_{14}Cl_4N_2O \cdot HNO_3) = \text{Amount (mg) of isoconazole nitrate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh about 50 mg of diflucortolone valerate and add chloroform to make 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of methanol and 0.1 mol/L acetate buffer solution (pH 4.7) (8 : 2).

Flow rate: 2.0 mL/min

Packaging and storage Preserve in well-closed containers.

Isoconazole Nitrate and Diflucortolone Valerate Cream

이소코나졸질산염·

디플루코르톨론발레레이트 크림

Isoconazole Nitrate and Diflucortolone Valerate Cream contains NLT 90.0% and NMT 110.0% of isoconazole nitrate ($C_{18}H_{14}Cl_4N_2O \cdot HNO_3$: 479.15) and diflucortolone valerate ($C_{27}H_{36}F_2O_5$: 478.58) of the labeled amount.

Method of preparation Prepare as directed under Creams, with Isoconazole Nitrate and Diflucortolone Valerate.

Identification (1) ***Diflucortolone valerate***—Take 20 mL of the solution obtained from the Assay under Diflucortolone Valerate, evaporate to dryness on a steam bath, and dissolve the residue in 0.5 mL of chloroform. Use this solution as the test solution. Separately, dissolve diflucortolone valerate RS in chloroform to make 1 mg/mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Thin Layer Chromatography. Spot 10 mL of each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of ether and diethylamine (98 : 2) as the developing solvent and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

(2) ***Isoconazole nitrate***—Perform the test as directed under the Identification under Isoconazole nitrate cream.

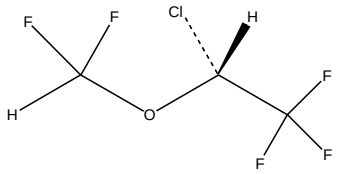
Assay (1) ***Diflucortolone valerate***—Weigh accurately an amount of Isoconazole Nitrate and Diflucortolone Valerate Cream equivalent to about 1 mg of diflucortolone valerate ($C_{27}H_{36}F_2O_5$), transfer to a 50-mL separatory funnel, add 30 mL of n-hexane and 10 mL of 90% methanol, and shake vigorously for 5 minutes until the cream completely becomes suspension. Next, extract 3 times using 10 ml of 90% methanol each time. If the extract is oily, add sodium chloride and remove. Collect the methanol extracts in a beaker, add a small amount of toluene, and evaporate to dryness on a steam bath. Add 10 mL of methanol to the evaporation residue and warm to dissolve. After cooling, filter into a 50-mL volumetric flask using a glass filter. Wash the filter with methanol, combine the washings, and fill with methanol to the gauge line. Use this solution as the test solution. Separately, weigh accurately about 10 mg of diflucortolone valerate RS and dissolve in methanol to a final concentration of 20 μg per mL. Pipet 1 mL each of the test solution, the standard solution and the blank test solution, place in a 20-mL volumetric flask and add 4.0 mL of 0.02 mol/L isoniazid solution to each volumetric flask. Fill with methanol to the gauge line and shake to mix. Warm each flask at 60 ℃ for 60 minutes, then cool to room temperature. With the test solution and the standard solution, using the blank test solution as a control solution, determine the absorbances A_T and A_S at the absorbance maximum wavelength near 401 nm.

$$\text{Amount (mg) of diflucortolone valerate } (C_{27}H_{36}F_2O_5) = \text{Amount (mg) of diflucortolone valerate RS} \times \frac{A_T}{A_S} \times \frac{1}{100}$$

(2) ***Isoconazole nitrate***—Perform the test as directed under the Assay under Isoconazole nitrate cream.

Packaging and storage Preserve in well-closed containers.

Isoflurane
이소플루란



and enantiomer

$C_3H_2ClF_5O$: 184.49

2-Chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane

[*26675-46-7*]

Isoflurane contains NLT 99.9% and NMT 101.0% of isoflurane ($C_3H_2ClF_5O$), calculated on the anhydrous basis.

It is a clear, colorless fluidal liquid.

It is slightly soluble in water.

It is miscible with ethanol(99.5), methanol or *o*-xylene.

It is volatile and has no inflammability.

It shows no optical rotation.

Refractive index n_D^{20}: About 1.30.

Boiling point: Between 47 and 50 ℃.

Identification (1) Determine the infrared spectra of Isoflurane and isoflurane RS as directed under the liquid film method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

(2) Prepare the test solution with 50 μL of Isoflurane using 40 mL of water as the absorbing liquid as directed under the Oxygen Flask Combustion; the test solution responds to the Qualitative Analysis for chloride and fluoride.

Specific gravity d_{20}^{20}: Between 1.500 and 1.520.

Purity (1) ***Acidity or alkalinity***—To 10 mL of Isoflurane, add 5 mL of freshly boiled and cooled water, and shake to mix for 1 minute; the separated water layer is neutral.

(2) ***Soluble chloride***—Weigh 60 g of Isoflurane, add 40 mL of water, shake well to mix, and separate the water layer. To 20 mL of the water layer, add 6 mL of dilute nitric acid and water to make 50 mL. Perform the test with this solution as the test solution as directed under the Chloride. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid (NMT 3 ppm).

(3) ***Soluble fluoride***—To 6 g of Isoflurane, add 12 mL of diluted 0.01 mol/L sodium hydroxide TS (1 in 20), and shake to mix for 10 minutes. Take 4.0 mL of the diluted 0.01 mol/L sodium hydroxide TS (1 in 20) layer, transfer into a Nessler tube, add 30 mL of a mixture of alizarin complexone TS, acetic acid-potassium acetate buffer solution, pH 4.3, and cerium(III) nitrate TS (1 : 1 : 1), and add water to make 50 mL. Allow to stand for 60 minutes and use this solution as the test solution. Separately, take 0.4 mL of the fluorine standard solution and 4.0 mL of diluted 0.01 mol/L sodium hydroxide TS (1 in 20), transfer to a Nessler tube, add 30 mL of a mixture of alizarin complexone TS, acetic acid-potassium acetate buffer solution, pH 4.3, and cerium(III) nitrate TS (1 : 1 : 1), then proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution at 600 nm as directed under the Ultraviolet-visible Spectroscopy, using a solution, obtained by proceeding with 4.0 mL of diluted 0.01 mol/L sodium hydroxide TS (1 in 20) in the same manner as above, as the control solution; the absorbance obtained from the test solution is NMT that of the standard solution (NMT 2 ppm).

Fluorine standard solution—Weigh accurately 2.21 g of sodium fluoride and dissolve in water to make exactly 1000 mL. Pipet 10 mL of this solution and add water to make exactly 1000 mL. 1 mL of the resulting solution contains 0.01 mg of fluorine (F).

(4) ***Related substances***—Use Isoflurane as the test solution. Pipet 1 mL of the test solution and add *o*-xylene to make exactly 100 mL. Pipet 1 mL of this solution, add *o*-xylene to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and determine each peak area by the automatic integration method; the area of the peak other than the Isoflurane obtained from the test solution is NMT the peak area of isoflurane from the standard solution. The total area of all peaks other than Isoflurane from the test solution is NMT 3 times the peak area of Isoflurane from the standard solution.

Operating conditions

Detector, column, column temperature, carrier gas and flow rate; proceed as directed in the operating conditions under the Assay.

System suitability

System performance and System repeatability; proceed as directed in System suitability under the Assay.

Test for required detectability: Pipet 1 mL of the standard solution and add *o*-xylene to make exactly 2 mL. Confirm that the peak area of Isoflurane obtained with 5 μL of this solution is between 35% and 65% of the peak area of Isoflurane obtained with 5 μL of the standard solution.

Time span of measurement: About 5 times of the Isoflurane retention time.

(5) ***Peroxide***—Transfer 10 mL of Isoflurane to a Nessler tube, add 1 mL of freshly prepared potassium iodide solution (1 in 10), shake vigorously to mix, and allow to stand in a dark place for 1 hour; the water layer does not exhibit a yellow color.

(6) ***Residue on evaporation***—Take exactly 65 mL of Isoflurane, evaporate on a steam bath, and dry the resi-

due at 105 ºC for 1 hour; the mass of residue is NMT 1 mg.

Water NMT 0.1% (2 g, coulometric titration).

Assay Pipet 5 mL each of Isoflurane and isoflurane RS (previously determine the water content in the same manner as Isoflurane), add exactly 3 mL of ethyl acetate as the internal standard, and add *o*-xylene to make exactly 50 mL. Pipet 5 mL each of these solutions and add *o*-xylene to make exactly 50 mL, and use these solutions as the test solution and the standard solution. Perform the test with 2 μL each of the test solution and standard solution as directed under the Gas Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of the peak area of Isoflurane to that of the internal standard.

$$\text{Amount (mg) of isoflurane } (C_3H_2ClF_5O) \text{ in 5 mL of Isoflurane} = V_s \times \frac{Q_T}{Q_S} \times 1000 \times 1.506$$

*V*s: Amount (mL) of Isoflurane RS taken, calculated on the anhydrous basis

1.506: Specific gravity (d_{20}^{20}) of Isoflurane

Operating conditions

Detector: A flame ionization detector

A stainless steel column about 3 mm in internal diameter and about 3.5 m in length, packed with diatomaceous earth for gas chromatography (125 μm - 149 μm in particle diameter), coated with nonylphenoxypoly(ethyleneoxy)-ethanol (10%) for gas chromatography and polyalkylene glycol (15%) for gas chromatography.

Column temperature: A constant temperature of about 80 °C.

Carrier gas: Nitrogen

Flow rate: Adjust the flow rate so that the retention time of isoflurane is about 7 minutes.

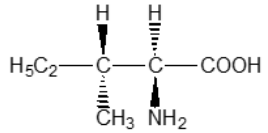
System suitability

System performance: Perform the test with 2 μL of the standard solution according to the above operating conditions; isoflurane and the internal standard are eluted in this order with the peak resolution is NLT 3.

System repeatability: Repeat the test six times with 2 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of the Isoflurane is NMT 1.0%.

Packaging and storage Preserve in tight containers at NMT 30 ℃.

L-Isoleucine
L-이소류신



Isoleucine $C_6H_{13}NO_2$: 131.17

(2*S*,3*S*)-2-Amino-3-methylpentanoic acid [*73-32-5*]

L-Isoleucine, when dried, contains NLT 98.5% and NMT 101.0% of L-isoleucine ($C_6H_{13}NO_2$).

Description L-Isoleucine occurs as white crystals or a crystalline powder. It is odorless or has a faint characteristic odor and a slightly bitter taste.
It is freely soluble in formic acid, sparingly soluble in water, and practically insoluble in ethanol(95) or ether.
It is soluble in dilute hydrochloric acid.

Identification Determine the infrared spectra of L-Isoleucine and L-isoleucine RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +39.5° and +41.5° (1 g, after drying, 6 mol/L hydrochloric acid TS, 25 mL, 100 mm).

pH Dissolve 1.0 g of L-Isoleucine in 100 mL of water; the pH of this solution is 5.5 to 6.5.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of L-Isoleucine in 10 mL of 1 mol/L hydrochloric acid TS; the resulting solution is clear and colorless.

(2) ***Chloride***—Perform the test with 0.5 g of L-Isoleucine. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.021%).

(3) ***Sulfate***—Perform the test with 0.6 g of L-Isoleucine. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid (NMT 0.028%).

(4) ***Ammonium***—Perform the test with 0.25 g of L-Isoleucine. Prepare the control solution with 5.0 mL of ammonium standard solution (NMT 0.02%).

(5) ***Heavy metals***—Dissolve 1.0 g of L-Isoleucine in 40 mL of water and 2 mL of dilute acetic acid by warming. After cooling, add water to make 50 mL, and use this solution as the test solution. Prepare the control solution by adding 2 mL of lead standard solution, 2 mL of dilute acetic acid, and water to make 50 mL (NMT 20 ppm).

(6) ***Iron***—Dissolve about 0.333 g of L-Isoleucine in water to make 45 mL, add 2 mL of hydrochloric acid, and use this solution as the test solution. Add water to 1.0 mL of iron standard solution to make 45 mL, add 2 mL of hydrochloric acid, and use this solution as the standard solution. Add 50 mg of ammonium peroxydisulfate, 3 mL of 30% ammonium thiocyanate in the test solution, and the standard solution, and mix; the color obtained from the test solution is not more intense than that from the standard solution (NMT 30 ppm).

(7) ***Arsenic***—Prepare the test solution with 1.0 g of

L-Isoleucine according to Method 2 and perform the test (NMT 2 ppm).

(8) ***Related substances***—Dissolve 0.10 g of L-Isoleucine in 25 mL of water and use this solution as the test solution. Pipet 1 mL of this solution and add water to make exactly 50 mL. Pipet 5 mL of this solution, add water to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, water, and acetic acid(100) (3 : 1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly a solution of ninhydrin in acetone (1 in 50) on the plate and heat at 80 ℃ for 5 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.3% (1 g, 105 ℃, 3 hours).

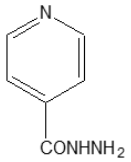
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.13 g of L-Isoleucine, previously dried, dissolve in 3 mL of formic acid, add 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 13.117 mg of $C_6H_{13}NO_2$

Packaging and storage Preserve in tight containers.

Isoniazid
이소니아지드



Isonicotinic Acid Hydrazide $C_6H_7N_3O$: 137.14
Pyridine-4-carbohydrazide [*54-85-3*]

Isoniazid, when dried, contains NLT 98.5% and NMT 101.0% of isoniazid ($C_6H_7N_3O$).

Description Isoniazid occurs as colorless crystals or white crystalline powder and is odorless.
It is freely soluble in water or acetic acid(100), sparingly soluble in ethanol(95), slightly soluble in acetic anhydride, and very slightly soluble in ether.

Identification (1) Dissolve 20 mg each of Isoniazid and isoniazid RS in water to make 200 mL. Take 5 mL of this solution and add 1 mL of 0.1 mol/L hydrochloric acid TS and water to make 50 mL. Determine the absorption spectra of both solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectrum of Isoniazid and isoniazid RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

Melting point Between 170 and 173 ºC.

pH Dissolve 1.0 g of Isoniazid in 10 mL of freshly boiled and cooled water; the pH of this solution is between 6.5 and 7.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Isoniazid in 20 mL of water; the solution is colorless and clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Isoniazid as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 0.40 g of Isoniazid as directed under Method 3 and perform the test. However, add 10 mL of ethanol(95) solution (1 in 50) of magnesium nitrate, add 1.5 mL of hydrogen peroxide water, and ignite and combust (NMT 5 ppm).

(4) ***Hydrazine***—Dissolve 0.10 g of Isoniazid in 5 mL of water, add 0.1 mL of an ethanol(95) solution (1 in 20) of salicylaldehyde, shake to mix immediately, and allow to stand for 5 minutes; the resulting solution is not turbid.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Isoniazid, previously dried, dissolve in 50 mL of acetic acid(100) and 10 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (indictor: 0.5 mL of 1-naphtholbenzein TS). However, the endpoint of the titration is when the color of the solution changes from yellow to green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 13.714 mg of $C_6H_7N_3O$

Packaging and storage Preserve in light-resistant, tight containers.

Isoniazid Tablets
이소니아지드 정

Isonicotinic Acid Hydrazide Tablets

Isoniazid Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of isoniazid ($C_6H_7N_3O$: 137.14).

Method of preparation Prepare as directed under Tablets, with Isoniazid.

Identification Weigh an amount of Isoniazid Tablets, previously powdered, equivalent to 20 mg of isoniazid according to the labeled amount, add 200 mL of water, shake to mix, and filter. To 5 mL of the filtrate, add 1 mL of 0.1 mol/L hydrochloric acid TS and water to make 50 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelengths 264 nm to 268 nm.

Dissolution Perform the test with 1 tablet of Isoniazid Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take NLT 20 mL of the dissolved solution 20 minutes after starting the dissolution test, and filter through a membrane filter with a pore size of NMT 0.45 μm. Discard the first 10 mL of the filtrate, then pipet 5 mL of the subsequent filtrate, add water to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 0.10 g of isoniazid RS, previously dried at 105 ℃ for 2 hours, dissolve in water to make exactly 100 mL, then pipet 5 mL of this solution, and add water to make 50 mL. Again, pipet 5 mL of this solution, add water to make exactly 50 mL, and use this solution as the standard solution. Determine the absorbances of the test solution and the standard solution, A_T and A_S, as directed under the Ultraviolet-visible Spectroscopy at a wavelength of 267 nm.
The dissolution rate of Isoniazid Tablets in 20 minutes is NLT 75%.

Rate of dissolution (%) of the labeled amount of isoniazid ($C_6H_7N_3O$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{90}{C}$$

W_S: Amount (mg) of the reference standard
C: Labeled amount (mg) of isoniazid ($C_6H_7N_3O$) in 1 tablet

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Isoniazid Tablets, and powder. Weigh accurately an amount, equivalent to about 0.10 g of isoniazid ($C_6H_7N_3O$), add 150 mL of water, shake for about 30 minutes to mix, add water to make exactly 200 mL, and filter. Discard the first 10 mL of the filtrate, pipet 5 mL of the subsequent filtrate, add the mobile phase to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of the isoniazid RS, previously dried at 105 °C for 2 hours, and dissolve in water to make exactly 100 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of isoniazid in each solution.

Amount (mg) of isoniazid ($C_6H_7N_3O$)

$$= \text{Amount (mg) of isoniazid RS} \times \frac{A_T}{A_S} \times 2$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 265 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 6.80 g of potassium dihydrogen phosphate in water to make 1000 mL. Separately, add water to 5.76 g of phosphoric acid to make 1000 mL. Mix these solutions to adjust the pH to 2.5. To 400 mL of this solution, add 600 mL of methanol, and then dissolve in 2.86 g of sodium tridecanesulfonate.

Flow rate: Adjust the flow rate so that the retention time of isoniazid is about 5 minutes.

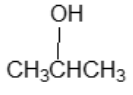
System suitability

System performance: Dissolve 5 mg each of Isoniazid Tablets and isonicotinic acid in 100 mL of the mobile phase. Proceed with 10 μL of this solution according to the above conditions; isonicotinic acid and isoniazid are eluted in this order with the resolution being NLT 1.5.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of isoniazid is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Isopropanol
이소프로판올



Isopropyl Alcohol C_3H_8O: 60.10
Propan-2-ol [*67-63-0*]

Description Isopropanol is a clear and colorless liquid. It has a characteristic odor.
It is miscible with water, methanol, ethanol(95), or ether.
It is volatile and easily flammable.

Identification (1) To 1 mL of Isopropanol, add 2 mL of iodine TS and 2 mL of sodium hydroxide TS, and shake

to mix; pale yellow precipitates are formed.

(2) To 5 mL of Isopropanol, add 20 mL of potassium dichromate TS and 5 mL of sulfuric acid carefully, and heat gently on a steam bath; the resulting gas has the smell of acetone and turns the filter paper moistened with a solution of salicylaldehyde in ethanol(95) (1 in 10) and sodium hydroxide solution (3 in 10) reddish brown.

Refractive index n_D^{20}: Between 1.376 and 1.378.

Specific gravity d_{20}^{20}: Between 0.785 and 0.788.

Purity (1) ***Clarity and color of solution***—To 2.0 mL of Isopropanol, add 8 mL of water, and shake mix: the resulting solution is clear.

(2) ***Acid***—To 15.0 mL of Isopropanol, add 50 mL of freshly boiled and cooled water, add 2 drops of phenolphthalein TS, and add 0.40 mL of 0.01 mol/L sodium hydroxide VS; the resulting solution exhibits a red color.

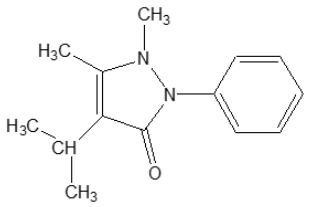
(3) ***Evaporation residue***—Evaporate 20.0 mL of Isopropanol on a steam bath, and dry the residue at 105 ℃ for 1 hour; the amount is NMT 1.0 mg.

Water NMT 0.75 w/v% (2 mL, volumetric titration, direct titration).

Distilling range Between 81 and 83 °C, NLT 94 vol%.

Packaging and storage Preserve in tight containers away from fire.

Isopropylantipyrine
이소프로필안티피린



Propyphenazone $C_{14}H_{18}N_2O$: 230.31
1,5-Dimethyl-2-phenyl-4-propan-2-ylpyrazol-3-one [*479-92-5*]

Isopropylantipyrine, when dried, contains NLT 98.0% and NMT 101.0% of isopropylantipyrine ($C_{14}H_{18}N_2O$).

Description Isopropylantipyrine occurs as white crystals or a crystalline powder. It is odorless and has a slightly bitter taste.
It is very soluble in acetic acid(100), freely soluble in ethanol(95) or acetone, soluble in ether and slightly soluble in water.

Identification (1) To 2 mL of an aqueous solution of Isopropylantipyrine (1 in 500), add 1 drop of iron(III) chloride TS; the resulting solution exhibits pale red color. To this solution, add 3 drops of sulfuric acid; the color turns pale yellow.

(2) To 5 mL of potassium hexacyanoferrate(III) TS, add 1 to 2 drops of iron(III) chloride TS, and add 5 mL of an aqueous solution of Isopropylantipyrine (1 in 500); the resulting solution slowly exhibits dark green color.

(3) To 2 mL of an aqueous solution of Isopropylantipyrine (1 in 500), add 2 to 3 drops of tannic acid TS; white precipitates are formed.

Melting point Between 103 and 105 ℃.

Purity (1) ***Chloride***—Dissolve 1.0 g of Isopropylantipyrine in 30 mL of dilute ethanol, and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 0.4 mL of 0.01 mol/L hydrochloric acid, 6 mL of dilute nitric acid, 30 mL of dilute ethanol, and water to make 50 mL (NMT 0.014%).

(2) ***Sulfate***—Dissolve 1.0 g of Isopropylantipyrine in 30 mL of dilute ethanol, and add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 0.40 mL of 0.005 mol/L sulfuric acid, 1 mL of dilute hydrochloric acid, 30 mL of dilute ethanol acid, and water to make 50 mL (NMT 0.019%).

(3) ***Heavy metals***—Proceed with about 1.0 g of Isopropylantipyrine, add 4 mL of a solution of magnesium sulfate heptahydrate in dilute sulfuric acid (1 in 4), mix, and evaporate to dryness by heating on a steam bath. Ignite the residue at NMT 800 °C to incinerate. After cooling, moisten the residue with a small amount of dilute sulfuric acid. Evaporate to dryness, and ignite within 2 hours to incinerate. After cooling, extract the residue twice each with 5 mL of 2 mol/L hydrochloric acid TS, add 0.1 mL of phenolphthalein TS, and add ammonia water(28) dropwise until the solution turns pale red. After cooling, add acetic acid(100) until the color disappears, and add another 0.5 mL. Filter, if necessary, and wash. Add water to make 20 mL, and use this solution as the test solution. Separately, add 1.0 mL of lead standard solution, instead of Isopropylantipyrine, and proceed in the same manner as the preparation of the test solution. To 10 mL of this solution, add 2 mL of the test solution, and use this solution as the control solution. Separately, to 10 mL of water, add 2 mL of the test solution, and use this solution as the blank test solution. To 12 mL each of the test solution, the control solution, and the blank test solution, add 2 mL of pH 3.5 acetate buffer solution, mix, add 1.2 mL of thioacetamide TS, and mix immediately. Allow to stand for 2 minutes; the color of the test solution is not more intense than that of the control solution (NMT 10 ppm).

System suitability: The control solution exhibits a faint brown color compared to the blank test solution. Also, add 5.0 mL of lead standard solution to the test solution. To 10 mL of this solution, add 2 mL of the test solution, and use this solution as the system suitability

solution. The system suitability solution is not less intense than the control solution.

(4) ***Arsenic***—Prepare the test solution with 1.0 g of Isopropylantipyrine according to Method 3, and perform the test (NMT 2 ppm).

(5) ***Antipyrine***—Dissolve 1.0 g of Isopropylantipyrine in 10 mL of dilute ethanol, and add 1 mL of sodium nitrite TS and 1 mL of dilute sulfuric acid; the resulting solution does not exhibit green color.

Loss on drying NMT 0.5% (1 g, in vacuum, silica gel, 5 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Isopropylantipyrine, previously dried, dissolve in 60 mL of a mixture of acetic acid(100) and acetic anhydride (2 : 1), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 23.031 mg of $C_{14}H_{18}N_2O$

Packaging and storage Preserve in tight containers.

Isopropylantipyrine, Acetaminophen and Caffeine Tablets
이소프로필안티피린·아세트아미노펜·카페인 정

Isopropylantipyrine, Acetaminophen and Caffeine Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of isopropylantipyrine ($C_{14}H_{18}N_2O$: 230.31), acetaminophen ($C_8H_9NO_2$: 151.16) and anhydrous caffeine ($C_8H_{10}N_4O_2$: 194.19).

Method of preparation Prepare as directed under Tablets, with Isopropylantipyrine, Acetaminophen and Anhydrous Caffeine.

Identification The retention time of major peaks of the test solution and the standard solution for Assay are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Isopropylantipyrine, Acetaminophen and Caffeine Tablets, and powder. Weigh accurately an amount, equivalent to about 150 mg of isopropylantipyrine ($C_{14}H_{18}N_2O$) [about 300 mg of acetaminophen ($C_8H_9NO_2$) and about 50 mg of anhydrous caffeine ($C_8H_{10}N_4O_2$)], and add water to make exactly 1000 mL. After sonicating for 20 minutes, filter, and use the filtrate as the test solution. Separately, weigh accurately about 30 mg of isopropylantipyrine RS, about 60 mg of acetaminophen RS and 10 mg of anhydrous caffeine RS, add water to exactly 200 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_{T1}, A_{T2}, A_{T3}, A_{S1}, A_{S2} and A_{S3}, of isopropylantipyrine, acetaminophen and anhydrous caffeine in each solution.

Amount (mg) of isopropylantipyrine ($C_{14}H_{18}N_2O$)
= Amount (mg) of isopropylantipyrine RS
× (A_{T1} / A_{S1}) × 5

Amount (mg) of acetaminophen ($C_8H_9NO_2$)
= Amount (mg) of acetaminophen RS × (A_{T2} / A_{S2}) × 5

= Amount (mg) of anhydrous caffeine ($C_8H_{10}N_4O_2$)
= Amount (mg) of anhydrous caffeine RS
× (A_{T3} / A_{S3}) × 5

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: A mixture of water and methanol (4 : 1).

Mobile phase B: A mixture of methanol and water (9 : 1).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 1	100	0
1 - 10	100 → 0	0 → 100
10 - 15	0	100
15 - 25	100	0

Flow rate: 1.0 mL/min

System suitability

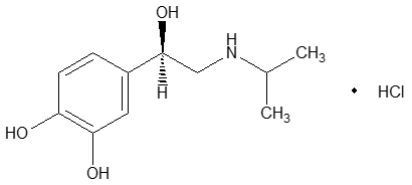
System performance: Proceed with 10 μL of the standard solution according to the above conditions; acetaminophen, anhydrous caffeine and isopropylantipyrine are eluted in this order with the resolution between the isopropylantipyrine peak and the anhydrous caffeine peak being NLT 28.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard devia-

tion of the peak areas of isopropylantipyrine, acetaminophen and anhydrous caffeine is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Isoproterenol Hydrochloride
이소프로테레놀염산염



and enantiomer

Isoprenaline Hydrochloride $C_{11}H_{17}NO_3 \cdot HCl$: 247.72
4-[1-Hydroxy-2-(propan-2-ylamino)ethyl]benzene-1,2-diol hydrochloride [*51-30-9*]

Isoproterenol Hydrochloride, when dried, contains NLT 97.0% and NMT 101.5% of isoproterenol hydrochloride ($C_{11}H_{17}NO_3 \cdot HCl$).

Description Isoproterenol Hydrochloride occurs as a white crystalline powder. It is odorless.
It is freely soluble in water, sparingly soluble in ethanol(95), and practically insoluble in acetic acid(100), acetic anhydride, chloroform or ether.
It is gradually colored by air or light.

Identification (1) Determine the absorption spectra of solutions of Isoproterenol Hydrochloride and isoproterenol hydrochloride RS in 0.1 mol/L hydrochloric acid TS (1 in 20000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectrum of Isoproterenol Hydrochloride and isoproterenol hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 165 and 170 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Isoproterenol Hydrochloride in 20 mL of 0.1 mol/L hydrochloric acid TS; the resulting solution is colorless and clear.

(2) ***Sulfate***—Perform the test with 0.10 g of Isoproterenol Hydrochloride. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid (NMT 0.2%).

(3) ***Heavy metals***—Proceed with 1.0 g of Isoproterenol Hydrochloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Isoproterenone***—Weigh 50 mg of Isoproterenol Hydrochloride, and dissolve in 0.01 mol/L hydrochloric acid TS to make exactly 25 mL. Determine the absorbance of this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at a wavelength of 310 nm is NMT 0.040.

Loss on drying NMT 1.0% (1 g, in vacuum, silica gel, 4 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.125 g of Isoproterenol Hydrochloride, and dissolve in sodium hydrogen sulfate (3 in 1000) to make exactly 25 mL. Take 5.0 mL of this solution, add 0.17 mol/L acetic acid to make exactly 100 mL, and use it as the test solution. Separately, weigh accurately an appropriate amount of isoproterenol hydrochloride RS, and add the mobile phase to make a solution containing 2.5 mg per mL. Take 5.0 mL of this solution, add 0.17 mol/L acetic acid to make a solution containing 0.25 mg per mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of isoproterenol hydrochloride, A_T and A_S, in each solution.

$$\text{Amount (mg) of isoproterenol hydrochloride } (C_{11}H_{17}NO_3 \cdot HCl) = 0.5 \times C \times \frac{A_T}{A_S}$$

C: Concentration of the standard solution (μg/mL)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 278 nm).

Column: A stainless steel column, about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography.

Mobile phase: 0.17 mol/L acetic acid

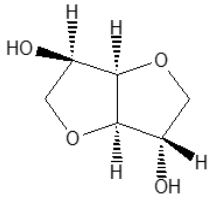
Flow rate: 1.5 mL/min

System suitability

System repeatability: Repeat the test 6 times according to the above conditions with 10 μL each of the standard solution; the relative standard deviation of the peak area is NMT 3.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Isosorbide
이소소르비드



$C_6H_{10}O_4$: 146.14

(3*S*,3a*R*,6*R*,6a*R*)-2,3,3a,5,6,6a-Hexahydrofuro[3,2-b]furan-3,6-diol [*652-67-5*]

Isosorbide contains NLT 98.5% and NMT 101.0% of isosorbide ($C_6H_{10}O_4$), calculated on the anhydrous basis.

Description Isosorbide occurs as white crystals or grains. It is odorless or has a slightly characteristic odor and a bitter taste.
It is very soluble in water or methanol, freely soluble in ethanol(95), and slightly soluble in ether.
It is hygroscopic.

Identification (1) Dissolve 0.1 g of Isosorbide in 6 mL of diluted sulfuric acid (1 in 2) by heating on a steam bath. After cooling, add 1 mL of potassium permanganate (1 in 30), shake well to mix, and heat on a steam bath until the color of the potassium permanganate disappears. To this solution, add 10 mL of 2,4-dinitrophenylhydrazine TS, and heat on a steam bath; orange precipitates are formed.

(2) To 2 g of Isosorbide, add 30 mL of pyridine and 4 mL of benzoyl chloride, and boil under a reflux condenser for 50 minutes. After cooling, add this solution slowly to 100 mL of cold water. Filter the produced precipitate with a glass filter, wash with water, recrystalize 2 times with ethanol(95), and dry in a desiccator (in vacuum, silica gel) for 4 hours; the melting point is 102 to 103 ℃.

(3) Determine the infrared spectra of Isosorbide and isosorbide RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +45.0° and +46.0° (5 g, calculated on the anhydrous basis, water, 50 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Transfer 25 g of Isosorbide into the Nessler tube, and dissolve in water to make 50 mL; the resulting solution is clear, and the color is not more intense than the following control solution.

Control Solution—To a mixture of 1.0 mL of cobaltous(II) chloride hexahydrate colorimetric stock solution, 3.0 mL of colorimetric stock solution, and 2.0 mL of copper(II) sulfate pentahydrate colorimetric stock solution, and add water to make 10.0 mL. Take 3.0 mL of this solution, and add water to make 50 mL.

(2) ***Sulfate***—Perform the test with 2.0 g of Isosorbide. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid VS (NMT 0.024%).

(3) ***Heavy metals***—Proceed with 5.0 g of Isosorbide according to Method 1, and perform the test. Prepare the control solution with 2.5 mL of lead standard solution (NMT 5 ppm).

(4) ***Arsenic***—Prepare the test solution with 1.0 g of Isosorbide according to Method 1, and perform the test (NMT 2 ppm).

(5) ***Related substances***—Dissolve 0.10 g of Isosorbide in 10 mL of methanol and use this solution as the test solution. Pipet 2 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethanol(95) and cyclohexane (1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly a solution of ninhydrin in a mixture of ethanol(95) and sulfuric acid (9 : 1) on the plate, and heat at 105 ℃ for 30 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Water NMT 1.5% (2 g, volumetric titration, direct titration).

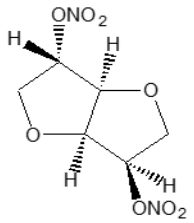
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 10 g of Isosorbide, calculated on the anhydrous basis, and dissolve in water to make exactly 100 mL. Determine the optical rotation α_D with this solution at the layer length of 100 mm at 20 ± 1 ℃.

$$\text{Amount (mg) of isosorbide } (C_6H_{10}O_4) = \alpha_D \times 2.1978$$

Packaging and storage Preserve in tight containers.

Isosorbide Dinitrate
이소소르비드질산염



$C_6H_8N_2O_8$: 236.14

(3*R*,3a*S*,6*S*,6a*S*)-6-(Nitrooxy)-hexahydrofuro[3,2-b]furan-3-yl nitrate[*87-33-2*]

Isosorbide Dinitrate contains NLT 95.0% and NMT 101.0% of isosorbide dinitrate ($C_6H_8N_2O_8$), calculated on the anhydrous basis.

Description Isosorbide Dinitrate occurs as white crystals or a crystalline powder. It is odorless and has a slightly nitric acid-like odor.

It is very soluble in *N*,*N*-dimethylformamide or acetone, freely soluble in chloroform or toluene, soluble in methanol, ethanol(95), or ether, and practically insoluble in water.

It explodes when rapidly heated or subjected to shock.

Identification (1) To 10 mg of Isosorbide Dinitrate, add 1 mL of water, and dissolve in 2 mL of sulfuric acid carefully. After cooling, layer 3 mL of iron(II) sulfate TS to this solution and allow to stand for 5 to 10 minutes; a brown band forms at the interface.

(2) To 0.1 g of Isosorbide Dinitrate, add 6 mL of diluted sulfuric acid (1 in 2), and dissolve on a steam bath by heating. After cooling, add 1 mL of potassium permanganate (1 in 30), shake well to mix, and heat on a steam bath until the color of the potassium permanganate disappears. To this solution, add 10 mL of 2,4-dinitrophenylhydrazine TS, and heat on a steam bath; orange precipitates are formed.

Optical rotation $[\alpha]_D^{20}$: Between +134° and +139° (1 g, calculated on the dried basis, ethanol(95), 100 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Isosorbide Dinitrate in 10 mL of acetone; the resulting solution is colorless and clear.

(2) ***Nitrate***—Dissolve 50 mg of Isosorbide Dinitrate in 30 mL of toluene, and extract 3 times each with 20 mL of water. Combine the water layer, wash twice each with 20 mL of toluene, take the water layer, and add water to make 100 mL. Use this solution as the test solution. Transfer 5 mL of nitric acid standard solution and 25 mL of the test solution into a separate Nessler tube, add 60 mL of Griess-Romijin's nitric acid reagent, shake well to mix, and allow to stand for 30 minutes. Observe the solution from the side of the Nessler tube; the color of the test solution is not more intense than that of the standard solution.

(3) ***Sulfate***—Dissolve 1.5 g of Isosorbide Dinitrate in 15 mL of *N*,*N*-dimethylformamide, and add 60 mL of water. After cooling, filter. Wash the paper 3 times each with 20 mL of water, combine the washings with the filtrate, and add water to make 150 mL. To 40 mL of this solution, add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid VS (NMT 0.048%).

(4) ***Heavy metals***—Dissolve 1.0 g of Isosorbide Dinitrate in 30 mL of acetone, and add 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 1.0 mL of lead standard solution, 30 mL of acetone, 2 mL of dilute acetic acid, and water to make 50 mL (NMT 10 ppm).

Water NMT 1.5% (0.3 g, volumetric titration, direct titration).

Assay Weigh accurately about 0.1 g of Isosorbide Dinitrate, transfer into a Kjeldahl flask for nitrogen determination, dissolve in 10 mL of methanol, and add 3 g of Devarda's alloy and 50 mL of water. Connect the distillation apparatus for nitrogen determination. Pipet 25 mL of 0.05 mol/L sulfuric acid, transfer into the collector, add 5 drops of bromocresol green-methyl red TS, and dip the bottom end of the cooler into this solution. Add 15 mL of sodium hydroxide solution (1 in 2) with the funnel, wash carefully with 20 mL of water, immediately close the pinch cock on the rubber tube, and distill slowly by passing through the water vapor condenser until about 100 mL of distillate is obtained. Remove the bottom end of the cooler from the surface of the liquid, wash the part with a small amount of water, and titrate with 0.1 mol/L sodium hydroxide VS. However, the endpoint of the titration is when the red solution turns reddish purple to bluish green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L sulfuric acid VS
= 11.807 mg of $C_6H_8N_2O_8$

Packaging and storage Preserve in light-resistant, tight containers in a cold place.

Isosorbide Dinitrate Tablets
이소소르비드질산염 정

Isosorbide Dinitrate Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of isosorbide dinitrate ($C_6H_8N_2O_8$: 236.14).

Method of preparation Prepare as directed under Tablets, with Isosorbide Dinitrate.

Identification Weigh an amount of Isosorbide Dinitrate

Tablets, previously powdered, equivalent to 0.1 g of isosorbide dinitrate according to the labeled amount, add 50 mL of ether, shake well to mix, and then filter. Take 5 mL of the filtrate, evaporate the ether carefully, add 1 mL of water, and carefully dissolve in 2 mL of sulfuric acid. After cooling, superimpose 3 mL of iron(II) sulfate TS on this solution, and allow to stand for 5 to 10 minutes; a brown band forms at the interface.

Purity ***Nitrate***—Weigh accurately an amount of Isosorbide Dinitrate Tablets, previously powdered, equivalent to 50 mg of isosorbide dinitrate according to the labeled amount, transfer into a separatory funnel, add 30 mL of toluene, and shake well to mix. Then, extract 3 times each with 20 mL of water, and perform the test as directed in Purity (2) under Isosorbide Dinitrate.

Disintegration Meets the requirements. However, for sublingual preparations, the time of the test is 2 minutes, and omit the use of the auxiliary disk.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Isosorbide Dinitrate Tablets, and powder. Weigh accurately an amount, equivalent to about 5 mg of isosorbide dinitrate ($C_6H_8N_2O_8$), dissolve with the mobile phase, add 5.0 mL of the internal standard solution, and add the mobile phase to make exactly 20 mL. Then, filter, and use this filtrate as the test solution. Separately, weigh accurately about 0.2 g of isosorbide dinitrate RS (25%, diluted with lactose), and dissolve with the mobile phase to make exactly 50 mL. Pipet 5 mL of this solution, add 5.0 mL of the internal standard solution, add the mobile phase to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, of isosorbide dinitrate to the peak area of the internal standard, respectively.

$$\text{Amount (mg) isosorbide dinitrate } (C_6H_8N_2O_8) = \text{Amount (mg) of isosorbide dinitrate RS} \times \frac{Content\ (\%)\ of\ \text{isosorbide dinitrate in RS}}{100} \times \frac{Q_T}{Q_S} \times \frac{1}{10}$$

Internal standard solution—Weigh 3 g of nitroglycerine RS (10%, diluted with lactose), dissolve in the mobile phase to make 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: Ordinary temperature

Mobile phase: To a mixture of methanol and 0.005 mol/L triethylamine (50 : 50), add acetic acid to adjust the pH to 5.0.

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; isosorbide dinitrate and the internal standard are eluted in this order with the resolution not being less than 2.0.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area ratios is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Isotonic Sodium Chloride Injection
생리식염 주사액

0.9% Sodium Chloride Injection
Isotonic Saline

Isotonic Sodium Chloride Injection is an aqueous solution for injection. Isotonic Sodium Chloride Injection contains NLT 0.85% and NMT 0.95% of sodium chloride (NaCl: 58.44).

Method of preparation

Sodium chloride	9 g
Water for Injection	A sufficient quantity
Total volume	1000 mL

Prepare as directed under Injections, with the above ingredients.
No preservative is added.

Description Isotonic Sodium Chloride Injection occurs as a clear, colorless liquid and has a slightly saline taste.

Identification Isotonic Sodium Chloride Injection responds to the Qualitative Analysis for sodium salt and chloride.

pH Between 4.5 and 8.0.

Purity (1) ***Heavy metals***—Concentrate 100 mL of Isotonic Sodium Chloride Injection on a steam bath to make about 40 mL, and add 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 2 mL of dilute acetic acid and water to 3.0 mL of lead standard solution to make 50 mL (NMT 0.3 ppm).

(2) ***Arsenic***—Prepare the test solution with 20 mL of Isotonic Sodium Chloride Injection, and perform the test (NMT 0.1 ppm).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.50 EU/mL of Glucose Injection.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

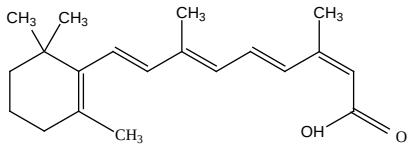
Extractable volume of injections Meets the requirements.

Assay Measure exactly 20 mL of Isotonic Sodium Chloride Injection, add 30 mL of water, and titrate with 0.1 mol/L silver nitrate VS with vigorous shaking (indicator: 3 drops of fluorescein sodium TS).

Each mL of 0.1 mol/L silver nitrate VS
= 5.844 mg of NaCl

Packaging and storage Preserve in hermetic containers. Plastic containers for aqueous injections may be used.

Isotretinoin
이소트레티노인



$C_{20}H_{28}O_2$: 300.44

(2*Z*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,4,6,8-tetraenoic acid [*4759-48-2*]

Isotretinoin contains NLT 98.0% and NMT 102.0% of isotretinoin ($C_{20}H_{28}O_2$), calculated on the dried basis.

Description Isotretinoin occurs as yellow crystals.
It is soluble in chloroform, sparingly soluble in ethanol(95), 2-propanol, or polyethylene glycol 400, and practically insoluble in water.

Identification (1) Determine the absorption spectra of solutions of Isotretinoin and isotretinoin RS in a solution of 0.01 mol/L hydrochloric acid TS in 2-propanol (1 in 1000) (1 in 25000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Isotretinoin and isotretinoin RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Isotretinoin according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Tretinoin***—Weigh accurately about 25 mg of Isotretinoin, dissolve in a small amount of dichloromethane, add isooctane to make exactly 100 mL, and use this solution as the test solution. Separately, dissolve about 25 mg of tretinoin RS in a small amount of dichloromethane, add isooctane to make exactly 100 mL. To 1.0 mL of this solution, and add isooctane to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of tretinoin of each solution, A_T and A_S, according to the automatic integration method; the amount of tretinoin is NMT 1.0%.

$$\text{Content (\%) of tretinoin} = 10 \times \frac{C}{W} \times \frac{A_T}{A_S}$$

C: Concentration (μg/mL) of tretinoin in the standard solution

W: Amount (mg) of Isotretinoin taken

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 352 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with porous silica gel for liquid chromatography (3 to 10 μm in particle diameter).

Mobile phase: A mixture of isooctane, 2-propanol, and acetic acid(100) (99.65 : 0.25 : 0.1).

Flow rate: 1 mL/min

System suitability

System performance: Dissolve 25 mg of isotretinoin RS in a small amount of dichloromethane, add isooctane to make 100 mL, and use this solution as the system suitability stock solution. To 1 mL of standard stock solution, add the system suitability stock solution to make 100 mL, and use this solution as the system suitability solution. Proceed with 20 μL of this solution according to the above conditions; the relative retention time of the peaks of isotretinoin and tretinoin are about 0.84 and 1.0, respectively, and the resolution between the two peaks is NLT 2.0.

System repeatability: Repeat the test 5 times with 20 μL each of the system suitability solutions according to the above conditions; the relative standard deviation of the peak area of tretinoin is NMT 2.0%.

Loss on drying NMT 0.5% (1 g, room temperature, in vacuum, 16 hours).

Residue on ignition NMT 0.1% (1 g).

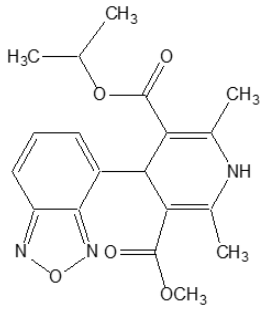
Assay Weigh accurately about 0.24 g of Isotretinoin, dissolve in 50 mL of *N*,*N*-dimethylformamide, and titrate with 0.1 mol/L sodium methoxide VS [indicator: 3 drops of a solution of titration in *N*,*N*-dimethylformamide (1 in 100)]. The endpoint of the titration is when the solution

turns green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium methoxide VS
= 30.04 mg of $C_{20}H_{28}O_2$

Packaging and storage Preserve in light-resistant, tight containers, and fill with an inert gas.

Isradipine
이스라디핀



$C_{19}H_{21}N_3O_5$: 371.39
3-Methyl 5-propan-2-yl 4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate
[*75695-93-1*]

Isradipine contains NLT 98.0% and NMT 102.0% of Isradipine ($C_{19}H_{21}N_3O_5$), calculated on the dried basis.

Description Isradipine occurs as a yellow fine crystalline powder.
It is freely soluble in acetone, soluble in methanol or acetonitrile, and practically insoluble in *n*-hexane or water.

Identification (1) Determine the infrared spectra of Isradipine and isradipine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 166 and 170 ºC.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Isradipine according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Weigh exactly 50 mg of Isradipine, dissolve in 5.0 mL of methanol, add the mobile phase to make exactly 25 mL, and use this solution as the test solution. Weigh exactly 6 mg of Isradipine RS, dissolve in 5 mL of methanol, and add the mobile phase to make exactly 100 mL. To 5 mL of this solution, add the mobile phase to make exactly 50 mL and use the resulting solution as the standard solution. Perform the test with each 25 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas other than isradipine; the total area of all peaks obtained from the test solution is not greater than 4 times the peak area of isradipine from the standard solution (1.2%), the largest peak area other than the isradipine peak from the test solution is not greater than 1.6 times the peak area of isradipine from the standard solution (0.5%), and the area of other individual peaks from the test solution is not greater than the peak area of isradipine from the standard solution (0.3%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Mobile phase: A mixture of water, methanol and tetrahydrofuran (50 : 40 : 10).

Column: A stainless steel column about 4.6 mm in internal diameter and 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 3 μm to 10 μm in particle diameter).

Flow rate: 1.7 mL/min

System suitability

System performance: Weigh 0.2 g of isradipine RS and 10 mg of isradipine related substance I RS, dissolve in 5 mL of methanol, and add the mobile phase to make 100 mL. To 5.0 mL of this solution, add the mobile phase to make 50 mL and use this solution as the system suitability solution. Perform the test with 25 μL of this solution according to the above operating conditions; the resolution of the peaks of Isradipine and isradipine related substance I is NLT 1.5.

System repeatability: Repeat the test five times with 25 μL each of the system suitability solution according to the above operating conditions; the relative standard deviation of the Isradipine peak areas is NMT 1.5%.

Time span of measurement: NLT 3 times of the retention time of Isradipine peak.

Loss on drying NMT 0.2% (105 ℃, 4 hours, constant mass).

Residue on ignition NMT 0.1% (1 g).

Assay Use light-resistant containers in this procedure. Weigh accurately about 20 mg of Isradipine, dissolve in 20 mL of methanol, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately a suitable amount of isradipine RS and isradipine related substance I [isopropylmethyl 4-(4-benzofurzanyl)-2,6-dimethyl-3,5 -pyridinedicarboxylate] RS, dissolve in methanol, and add the mobile phase so that the resulting solutions contain 0.2 mg of isradipine RS and 10 μg of isradipine related substance I RS per mL, respectively. Use these solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of isradipine.

Amount (mg) of isradipine ($C_{19}H_{21}N_3O_5$)

$$= 100 \times C \times \frac{A_T}{A_S}$$

C: Concentration (mg/mL) of isradipine in the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 326 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of water, methanol and tetrahydrofuran (50 : 40 : 10).

Flow rate: 1.7 mL/min

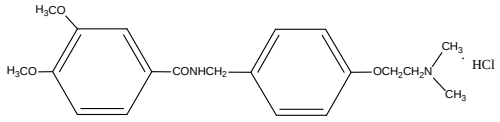
System suitability

System performance: Perform the test with 25 μL of the standard solution according to the above operating conditions; the resolution of the peaks of isradipine and isradipine related substance I is NLT 1.5.

System repeatability: Repeat the test five times with 25 μL each of the standard solution according to the above conditions; the relative standard deviation of the Isradipine peak areas is NMT 1.5%.

Packaging and storage Preserve in light-resistant, tight containers.

Itopride Hydrochloride
이토프리드염산염



$C_{20}H_{26}N_2O_4 \cdot HCl$: 394.90

N-[[4-[2-(Dimethylamino)ethoxy]phenyl]methyl]-3,4-dimethoxy-benzamide hydrochloride (1:1), [*122892-31-3*]

Itopride Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of itopride hydrochloride ($C_{20}H_{26}N_2O_4 \cdot HCl$).

Description Itopride Hydrochloride occurs as white to pale yellow crystals or a crystalline powder.

It is odorless.

It is very soluble in water, freely soluble in methanol or acetic acid(100), slightly soluble in ethanol(95), and practically insoluble in ether.

The pH of a solution of 1 g of Itopride Hydrochloride in 10 mL of water is between 4.0 and 5.0.

Identification (1) Weigh 0.1 g of Itopride Hydrochloride, dissolve in 3 mL of citric acid-acetic acid TS, and heat on a steam bath; the solution exhibits a dark reddish purple color.

(2) Determine the absorption spectrum of a solution of Itopride Hydrochloride in 0.1 mol/L hydrochloric acid TS (1 in 80000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 256 nm and 260 nm and no absorption between 277 nm and 281 nm.

(3) Determine the infrared spectra of Itopride Hydrochloride and itopride hydrochloride RS, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) Dissolve 0.4 g of Itopride Hydrochloride in 20 mL of water, add 2 mL of ammonia TS, shake and mix. If necessary, filter the precipitate collected by scratching the inner wall of the column with a glass rod to remove. Acidify the filtrate with dilute acetic acid; the resulting solution responds to the Qualitative Analysis for chloride.

Melting point Between 193 and 198 °C.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Itopride Hydrochloride in 10 mL of water; the solution is clear and colorless to pale yellow.

(2) ***Heavy metals***—Proceed with 2.0 g of Itopride Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 0.2 g of Itopride Hydrochloride in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution and add methanol to make exactly 20 mL. Pipet 1 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the standard solution. With the test solution and the standard solution, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, methanol, ammonia water(28) and water (18 : 4 : 2 : 1) to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not larger or more intense than the spots from the standard solution.

Loss on drying NMT 0.10% (2 g, 105 °C, 2 hours).

Residue on ignition NMT 0.10% (1 g).

Assay Weigh accurately about 0.5 g of Itopride Hydrochloride, dissolve in 2 mL of acetic acid(100), add 100 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 39.49 mg of $C_{20}H_{26}N_2O_4 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight

containers.

Itopride Hydrochloride Tablets
이토프리드염산염 정

Itopride Hydrochloride Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of itopride hydrochloride ($C_{20}H_{26}N_2O_4$·HCl: 394.90).

Method of preparation Prepare as directed under Tablets, with Itopride Hydrochloride.

Identification (1) Weigh an amount of Itopride Hydrochloride Tablets, previously powdered, equivalent to about 0.2 g of itopride hydrochloride ($C_{20}H_{26}N_2O_4$·HCl), add 10 mL of methanol, shake vigorously to mix, and then centrifuge. Take 0.5 mL of the clear supernatant, remove methanol in the vacuum, then add 3 mL of citric acid-acetic acid TS to the residue, and heat on a steam bath; the resulting solution exhibits a dark reddish purple color.

(2) Determine the absorption spectrum of a solution of Itopride Hydrochloride Tablets in 0.1 mol/L hydrochloric acid TS (1 in 80000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 256 nm and 260 nm and no absorption between 277 nm and 281 nm.

(3) Weigh an amount of Itopride Hydrochloride Tablets, previously powered, equivalent to about 0.2 g of itopride hydrochloride ($C_{20}H_{26}N_2O_4$·HCl: 394.90), add 10 mL of methanol, shake vigorously to mix, and then centrifuge. Use the clear supernatant as the test solution. Separately, dissolve 0.02 g of itopride hydrochloride RS in 1 mL of methanol, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, methanol, strong ammonia water and water (18 : 4 : 2 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values of the spots obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 tablet of Itopride Hydrochloride Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of 0.1 mol/L hydrochloric acid TS as the dissolution medium. Filter the medium 45 minutes after starting the test and use this solution as the test solution. Separately, weigh accurately about 5.5 mg of itopride hydrochloride RS, dissolve in 0.1 mol/L hydrochloric acid TS to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and determine the peak areas, A_T and A_S, of itopride hydrochloride in each solution. The dissolution rate in 45 minutes is NLT 80%.

Dissolution rate (%) of the labeled amount of itopride hydrochloride ($C_{20}H_{26}N_2O_4$·HCl)
= Amount (mg) of itopride hydrochloride RS
$$\times \frac{A_T}{A_S} \times \frac{1}{C} \times 300$$

C: Labeled amount (mg) of itopride hydrochloride ($C_{20}H_{26}N_2O_4$·HCl) in 1 tablet

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Itopride Hydrochloride Tablets, and powder. Weigh accurately an amount, equivalent to about 50 mg of itopride hydrochloride ($C_{20}H_{26}N_2O_4$·HCl), and add the mobile phase to make exactly 50 mL. After filtering this solution, discard the first 10 mL of the filtrate, pipet 10 mL of the subsequent filtrate, transfer into a 100-mL volumetric flask, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of itopride hydrochloride RS, proceed in the same manner as the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of itopride hydrochloride in each solution.

Content (%) of the labeled amount of itopride hydrochloride ($C_{20}H_{26}N_2O_4$·HCl)
= Amount (mg) of itopride hydrochloride RS$\times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 257 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: To 13.6 g of potassium dihydrogen phosphate, add water to make 1 L, then take 800 mL of this solution, and add 200 mL of acetonitrile.

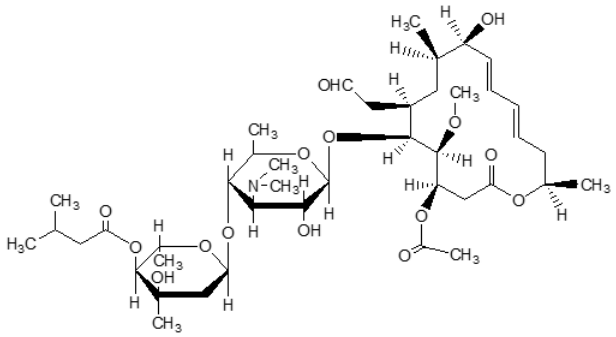
Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of itopride hydrochloride is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Josamycin
조사마이신



$C_{42}H_{69}NO_{15}$: 827.99

[(2*S*,3*S*,4*R*,6*S*)-6-[(2*R*,3*S*,4*R*,5*R*,6*S*)-6-[[(4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-4-Acetyloxy-10-hydroxy-5-methoxy-9,16-dimethyl-2-oxo-7-(2-oxoethyl)-1-oxacyclohexadeca-11,13-dien-6-yl]oxy]-4-(dimethylamino)-5-hydroxy-2-methyloxan-3-yl]oxy-4-hydroxy-2,4-dimethyloxan-3-yl] 3-methylbutanoate [*16846-24-5*]

Josamycin is a macrolide compound with antimicrobial activity produced by the growth of *Streptomyces narbonensis* var. *josamyceticus*.

Josamycin contains NLT 900 μg and NMT 1100 μg (potency) per mg of josamycin ($C_{42}H_{69}NO_{15}$: 827.99), calculated on the dried basis.

Description Josamycin occurs as a white to yellowish white powder.
It is very soluble in methanol or ethanol(95), and very slightly soluble in water.

Identification (1) Determine the absorption spectra of solutions of Josamycin and josamycin RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Dissolve 5 mg each of Josamycin and josamycin RS in 1 mL of methanol, add diluted methanol (1 in 2) to make 100 mL, and use these solutions as the test solution and the standard solution, respectively. With 10 μL each of the test solution and standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions; the retention time of josamycin from the test solution is the same as that of josamycin from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed under the operating conditions under the Purity (2).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Josamycin according to Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(2) ***Related substances***—Dissolve 50 mg of Josamycin in 5 mL of methanol, add diluted methanol (1 in 2) to make 50 mL, and use this solution as the test solution. Perform the test with 10 μL of the test solution as directed under the Liquid Chromatography according to the following conditions, and determine each peak area. Calculate the amount of each peak other than josamycin by the percentage peak area method; the amount is NMT 6% and the sum of all peak areas other than josamycin is NMT 20%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 231 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 50 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 119 g of sodium perchlorate hydrate in water to make 1000 mL, and adjust the pH to 2.5 with 1 mol/L hydrochloric acid TS. To 600 mL of this solution, add 400 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of josamycin is about 10 minutes.

System suitability

Test for required detectability: Pipet 3 mL of the test solution, add dilute methanol (1 in 2) to make exactly 50 mL, and use this solution as the system suitability solution. Pipet 2 mL of the system suitability solution, and add dilute methanol (1 in 2) to make exactly 20 mL. Confirm that the peak area of josamycin obtained from 10 μL of this solution is equivalent to 8 to 12% of the peak area of josamycin from the system suitability solution.

System performance: Dissolve 0.05 g of Josamycin in 50 mL of 0.1 mol/L potassium dihydrogen phosphate TS (pH 2.0), and allow to stand at 40 °C for 3 hours. Adjust the pH of this solution to 6.8 to 7.2 with 2 mol/L sodium hydroxide TS, and add 50 mL of methanol. Proceed with 10 μL of this solution under the above operating conditions; the resolution between the peaks of josamycin and josamycin S_1, eluted at the relative retention time of about 0.9 is NLT 1.5.

System repeatability: Repeat the test 6 times with 10 μL each of the system suitability solution under the above operating conditions; the relative standard deviation of the peak areas of josamycin is NMT 1.5%.

Time span of measurement: About 4 times the retention time of josamycin after the solvent peak.

Loss on drying NMT 1.0% (0.5 g, in vacuum, phosphorus pentoxide, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay ***Cylinder plate method*** (1) Medium: Agar medium for seed and base layer Use the medium of the Potency assay (A) (2) (a) ① ⓐ.

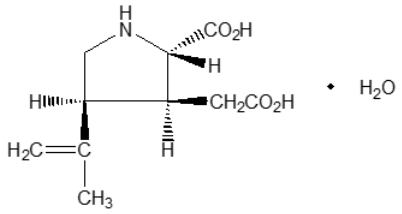
(2) Test organism: Use *Bacillus subtilis* ATCC 6633

as the test organism.

(3) Weigh accurately about 30 mg (potency) of Josamycin, dissolve in 5 mL of methanol, add sterile purified water to make exactly 100 mL, and use this solution as the test stock solution. Pipet a suitable amount of the test stock solution, dilute it with sterile purified water so that the solution contains 30.0 μg and 7.5 μg (potency) per mL, and use these solutions as the high concentration test solution and the low concentration test solution, respectively. Separately, weigh accurately about 30 mg (potency) of josamycin RS, dissolve in 5 mL of methanol, add sterile purified water to make exactly 100 mL, and use this solution as the standard stock solution. Store the standard stock solution at a temperature NMT 5 °C, and use it within 7 days. Pipet a suitable amount of the standard stock solution, dilute with sterile purified water so that the solution contains 30.0 μg and 7.5 μg (potency), and use these solutions as the high concentration standard solution and the low concentration standard solution, respectively. Perform the test with these solutions as directed in (A) (8) under Microbial Assays for Antibiotics.

Packaging and storage Preserve in light-resistant, tight containers.

Kainic Acid Hydrate
카인산수화물



Kainic Acid $C_{10}H_{15}NO_4 \cdot H_2O$: 231.25
(2*S*,3*S*,4*S*)-3-(Carboxymethyl)-4-prop-1-en-2-ylpyrrolidine-2-carboxylic acid hydrate

Kainic Acid Hydrate, when dried, contains NLT 99.0% and NMT 101.0% of kainic acid ($C_{10}H_{15}NO_4$: 213.23).

Description Kainic Acid Hydrate occurs as white crystals or a crystalline powder. It is odorless and has a sour taste.

It is sparingly soluble in water or warm water, very slightly soluble in ethanol(95) and acetic acid(100), and practically insoluble in ether.

It is soluble in dilute hydrochloric acid or sodium hydroxide TS.

Dissolve 1.0 g of Kainic Acid Hydrate in 100 mL of water; the pH of this solution is between 2.8 and 3.5.

Melting point—About 252 °C (with decomposition).

Identification (1) Take 5 mL of an aqueous solution of Kainic Acid Hydrate (1 in 5000), add 1 mL of ninhydrin TS, and warm on a steam bath between 60 and 70 ℃ for 5 minutes; the resulting solution exhibits a yellow color.

(2) Dissolve 50 mg of Kainic Acid Hydrate in acetic acid(100), and add 0.5 mL of bromine TS; the color of the test solution disappears immediately.

Optical rotation $[\alpha]_D^{20}$: Between -13° and -17° (0.5 g, water, 50 mL, 200 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Kainic Acid Hydrate in 10 mL of water; the solution is colorless and clear.

(2) ***Chloride***—Transfer 0.5 g of Kainic Acid Hydrate into platinum crucible, dissolve in 5 mL of sodium carbonate TS, evaporate to dryness on a steam bath, and ignite by heating slowly almost to incineration. After cooling, dissolve 12 mL of dilute nitric acid by warming, and filter. Wash the residue with 15 mL of water, combine the washings with the filtrate, and add water to make 50 mL. Use this solution as the test solution and perform the test.

Control solution—To 0.30 mL of 0.01 mol/L hydrochloric acid, add 5 mL of sodium carbonate TS, and proceed in the same manner as the test solution (NMT 0.021%).

(3) ***Sulfate***—To 0.5g of Kainic Acid Hydrate, add 40 mL of water, and dissolve by warming. After cooling, add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.30 mL of 0.005 mol/L sulfuric acid (NMT 0.028%).

(4) ***Ammonium***—Perform the test with 0.25 g of Kainic Acid Hydrate. Prepare the control solution with 5.0 mL of ammonium standard solution (NMT 0.02%).

(5) ***Heavy metals***—Proceed with 1.0 g of Kainic Acid Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(6) ***Arsenic***—Weigh 1.0 g of Kainic Acid Hydrate, and dissolve in 5 mL of dilute hydrochloric acid. Use this solution as the test solution, and perform the test (NMT 2 ppm).

(7) ***Related substances***—Weigh 0.10 g of Kainic Acid Hydrate, dissolve in exactly 10 mL of water, and use this solution as the test solution. Pipet 2 mL of this solution, and add water to make exactly 100 mL. Take 1.0 mL of this solution, add water to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Next, develop the plate with the upper layer of a mixture of water, 1-butanol, and acetic acid(100) (5 : 4 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly a solution of ninhydrin in acetone (1 in 50) on the plate, and dry at 80 ℃ for 5 minutes; the spots other than the principal spot obtained from the test

solution are not more intense than the spots from the standard solution.

Loss on drying Between 6.5% and 8.5% (1 g, 105 ºC, 4 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately 0.4 g of Kainic Acid Hydrate, previously dried, dissolve in 50 mL of warm water, cool, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 10 drops of bromothymol blue TS).

Each mL of 0.1 mol/L sodium hydroxide VS
= 21.323 mg of $C_{10}H_{15}NO_4$

Packaging and storage Preserve in tight containers.

Kallidinogenase
칼리디노게나제

[*9001-01-8*]

Kallidinogenase is an enzyme obtained from pancreas of healthy pigs and has the effect of decomposing kininogen to release kinins. It contains NLT 25 units of kallidinogenase in 1 mg.

It is generally diluted with Lactose Hydrate, etc.

Kallidinogenase contains NLT 90.0% and NMT 110.0% of the labeling unit.

Description Kallidinogenase occurs as a white to pale brown powder. It is odorless or has a faint, characteristic odor.

It is freely soluble in water and practically insoluble in ethanol(95) or ether.

The pH of an aqueous solution of Kallidinogenase (1 in 300) is between 5.5 and 7.5.

Identification (1) Weigh accurately an appropriate amount of Kallidinogenase according to the labeled amount, dissolve in 0.05 mol/L phosphate buffer solution of pH 7.0, and prepare a solution containing 10 Units of kallidinogenase in 1 mL. Pipet 5 mL of this solution, and add exactly 1 mL of the Trypsin Inhibitor TS and additional 0.05 mol/L phosphate buffer solution of pH 7.0 to make exactly 10 mL. Pipet 4 mL each of this solution, and transfer to each test tube. Add exactly 1 mL of aprotinin TS on one side and 1 mL of 0.05 mol/L phosphate buffer solution of pH 7 on the other side, allow to stand at room temperature for 20 minutes, and use these solutions as the test solution (1) and the test solution (2). Separately, pipet 1 mL of trypsin inhibitor TS, and add 0.05 mol/L phosphate buffer solution of pH 7.0 to make exactly 10 mL. Pipet 4 mL each of this solution, and transfer to each test tube. Add exactly 1 mL of aprotinin TS on one side and 1 mL of 0.05 mol/L phosphate buffer solution of pH 7 on the other side, allow to stand at room temperature for 20 minutes, and use these solutions as the test solutions (3) and (4), respectively. Next, add exactly 2.5 mL of substrate reagent TS (1) for kallidinogenase assay previously warmed for 5 minutes at 30 ± 0.5 ℃, put in a cell with the layer length of 1 cm, and add exactly 0.5 mL of the test solution 1 warmed for 5 minutes at 30 ± 0.5 ℃ while starting a stopwatch at the same time. Perform the test as directed under the Ultraviolet-visible Spectroscopy using water at 30 ± 0.5 ℃ as the control solution, and determine the absorbances, $A_{1\text{-}2}$ and $A_{1\text{-}6}$, at the wavelength of 405 nm, exactly after 2 minutes and 6 minutes. Perform the same procedure for the test solutions (2), (3) and (4), and determine the absorbances $A_{2\text{-}2}$, $A_{2\text{-}6}$, $A_{3\text{-}2}$, $A_{3\text{-}6}$, $A_{4\text{-}2}$, and $A_{4\text{-}6}$. Calculate of the value of I according to the following equation; the value I is less than 0.2.

$$\mathrm{I} = \frac{(A_{1-6} - A_{1-2}) - (A_{3-6} - A_{3-2})}{(A_{2-6} - A_{2-2}) - (A_{4-6} - A_{4-2})}$$

(2) Take exactly 2.9 mL of substrate reagent TS (2) for kallidinogenase assay previously warmed for 5 minutes at 30 ± 0.5℃, put in a cell with the layer length of 1 cm, and add exactly 0.1 mL of the test solution obtained from the Assay while starting a stopwatch at the same time. Perform the test as directed under the Ultraviolet-visible Spectroscopy at 30 ± 0.5 ℃, and determine a change in absorbance at the wavelength of 253 nm for 4 minutes to 6 minutes. However, add exactly 1 mL of trypsin inhibitor TS separately, and add 0.05 mol/L phosphate buffer solution of pH 7.0 to make exactly 10 mL. Pipet 0.1 mL of this solution, add to a solution prepared by taking exactly 2.9 mL of substrate reagent TS (2) for kallidinogenase assay previously warmed for 5 minutes at 30 ± 0.5℃, and use this solution as the control solution. Calculate a quantity of change in absorbance *A* per minute when the rate of change in absorbance is constant. Calculate of the value R according to the following equation; the value is between 0.12 and 0.16.

$$R = \frac{A}{0.0383} \times \frac{1}{a \times b}$$

a: Amount (mg) of Kallidinogenase in 1 mL of the test solution

b: Units of kallidinogenase in 1 mg of Kallidinogenase obtained in the Assay

Inactivity Determine the nitrogen content of Kallidinogenase according to the Nitrogen Determination, convert 1 mg of nitrogen into 6.25 mg of protein, and calculate the inactivity from the number of units obtained from the Assay; the result is NLT 100 units of Kallidinogenase per mg of protein.

Purity (1) ***fat***—Add 20 mL of ether to 1.0 g of Kallidinogenase, extract for 30 minutes while shaking occasionally, filter, and wash with 10 mL of ether. Combine the filtrate and the washings to evaporate, and dry for 2 hours at 105 °C; the amount is NMT 1 mg.

(2) ***Kininase***—(i) bradykinin solution: Weigh an appropriate amount of bradykinin solution, and dissolve

in the gelatin-phosphate buffer solution of pH 7.4 to prepare a solution containing 0.200 μg of bradykinin in 1 mL.

(ii) Kallidinogenase solution: Weigh accurately an appropriate amount of Kallidinogenase according to the labeling unit, and dissolve in the gelatin-phosphate buffer solution of pH 7.4 to prepare a solution containing 1 unit of Kallidinogenase in 1 mL.

(iii) Test solution: Pipet 0.5 mL of bradykinin solution, warm for 5 minutes at 30 ± 0.5 ℃, add accurately 0.5 mL of the kallidinogenase solution previously warmed for 5 minutes at 30 ± 0.5℃, and shake immediately to mix. Allow this solution to stand at 30 ± 0.5 ℃ for 150 seconds exactly, add exactly 0.2 mL of trichloroacetic acid solution (1 in 5), and shake to mix. Boil for 3 minutes, cool with cold water immediately, centrifuge, and allow to stand at room temperature for 15 minutes. Pipet 0.5 mL of the clear supernatant, add accurately 0.5 mL of gelatin-tris buffer solution of pH 8.0, and shake to mix. Pipet 0.1 mL of this solution, add accurately 0.9 mL of trichloroacetic acid-gelatin-tris buffer solution, and shake to mix. Pipet 0.2 mL of this solution, mix exactly 0.6 mL of trichloroacetic acid-gelatin-tris buffer solution, and use this solution as the test solution.

(iv) Control solution: Take 0.5 mL of gelatin-phosphate buffer solution of pH 7.4, proceed with it in the same manner as (c), and use this solution as the control solution.

(v) Procedure: Add 0.1 mL of anti-bradykinin antibody TS to anti-rabbit antibody-coated wells of a 96-well microplate, shake to mix, and allow to stand at a constant temperature of about 25 °C for 1 hour. Remove the anti-bradykinin antibody TS, and add 0.3 mL of phosphate buffer solution for microplate washing to remove. Repeat this procedure 3 times, and remove the solution thoroughly. Add 100 μL each of the test solution and the control solution, and 50 μL of gelatin-phosphate buffer solution of pH 7.0, shake to mix, and allow to stand at a constant temperature of about 25 °C for 1 hour. Next, add 50 μL of peroxidase-labeled bradykinin TS, shake to mix, and allow to stand overnight in a cool place. Remove the reaction solution, and add 0.3 mL of phosphate buffer solution for microplate washing to remove. Repeat this procedure 4 times to remove the solution thoroughly, add 100 μL of substrate solution for peroxidase assay, and allow to stand at a constant temperature of about 25 °C for 30 minutes exactly while protected from light. Add 100 μL of diluted sulfuric acid (23 in 500), shake to mix, and determine the absorbance at the wavelengths between 490 nm and 492 nm. Separately, weigh an appropriate amount of bradykinin, dissolve in pH 7.0 gelatin-phosphate buffer solution to prepare solutions containing exactly 100, 25, 6.25, 1.56, 0.39 and 0.098 ng in 1 mL, and use these solutions as the standard solution (1), the standard solution (2), the standard solution (3), the standard solution (4), the standard solution (5) and the standard solution (6), respectively. Also, use 1 mL of gelatin-phosphate buffer solution of pH 7.0 as the standard solution (7). Put 50 μL each standard solution and 100 μL of trichloroacetic acid-gelatin-tris buffer solution in the well, and proceed in the same manner as the test solution and the control solution below. Prepare a calibration curve from the amount and the absorbance of bradykinin in the standard solution, and calculate the amount of bradykinin, B_T (pg) and B_S (pg), of the test solution and the control solution. The absorbance of this test is usually determined by using a spectrophotometer for microplate. Take care of contamination and scratch since the well is a spectrophotometric cell. Also, put a certain exact amount of solution into the well since the layer length varies according to the quantity of the solution.

(vi) Interpretation: Calculate the value R according to the following equation; the value is NLT 0.8.

$$\mathrm{R} = \frac{B_\mathrm{T}}{B_\mathrm{S}}$$

(3) ***Trypsin-like substance***—Pipet 4 mL of the sample stock solution obtained from Assay, add exactly 1 mL of trypsin inhibitor TS and additional 0.05 mol/L phosphate buffer solution of pH 7.0 to make exactly 10 mL, and use this solution as the test solution. Take exactly 2.5 mL of substrate reagent TS (1) for kallidinogenase assay previously warmed for 5 minutes at 30 ± 0.5℃, put in a cell with the layer length of 1 cm, and add exactly 0.5 mL of the test solution warmed for 5 minutes at 30 ± 0.5℃ while starting a stopwatch at the same time. Perform the test as directed under the Ultraviolet-visible Spectroscopy using water as the control solution at 30 ± 0.5 ℃, and determine the absorbances, A_2 and A_6, at the wavelength of 405 nm, exactly after 2 minutes and 6 minutes. Separately, pipet 4 mL of the sample stock solution, add 0.05 mol/L phosphate buffer solution of pH 7.0 to make exactly 10 mL, and use this solution as the control solution. With the control solution, perform the same test as the test solution to determine the absorbances A'_2 and A'_6. Calculate the value T according to the following equation; the value is NMT 0.05.

$$\mathrm{T} = \frac{(A'_6 - A'_2) - (A_6 - A_2)}{(\mathrm{A}'_6 - \mathrm{A}'_2)}$$

(4) ***Protease***—Weigh accurately an appropriate amount of Kallidinogenase according to the labeled amount, dissolve by adding 0.05 mol/L phosphate buffer solution of pH 7.0, prepare a solution containing 1 unit of kallidinogenase in 1 mL, and use this solution as the test solution. Take exactly 1 mL of the test solution, put in a test tube, and allow to stand at 35 ± 0.5 ℃ for 5 minutes. Next, take exactly 2.9 mL of substrate reagent TS (3) for kallidinogenase assay previously warmed at 35 ± 0.5℃, add to the test solution in a test tube, and allow to react at 35 ± 0.5 ℃ for exactly 20 minutes. Add exactly 5 mL of trichloroacetic acid TS, shake well to mix, allow to stand at a room temperature for 1 hour, and filter through a membrane filter with a pore size of 5 μm. Discard the first 3 mL of the filtrate, perform the test with the subsequent filtrate as directed under the Ultraviolet-visible Spectroscopy using water as the control solution within 2

hours, and determine the absorbance A at the wavelength of 280 nm. Separately, take exactly 1 mL of the test solution, add exactly 5 mL of trichloroacetic acid TS, and shake well to mix. Add exactly 5 mL of substrate reagent TS (3) for kallidinogenase assay, and perform the test in the same manner to determine the absorbance A_0. Determine A - A_0 from the values obtained previously; the result is NMT 0.2.

Loss on drying NMT 2.0% (0.5 g, in vacuum, phosphorus pentoxide, 4 hours).

Residue on ignition NMT 3.0% (0.5 g, between 650 and 750 ℃).

Kinin-releasing activity (a) ***Kallidinogenase solution*** —Weigh accurately an appropriate amount of Kallidinogenase according to the labeling unit, dissolve in 0.02 mol/L phosphate buffer solution of pH 8.0, and prepare a solution containing 0.1 unit of kallidinogenase in 1 mL. In addition, use glass containers to prepare this solution.

(b) ***Test solution***—Pipet 0.5 mL of kininogen TS, warm for 5 minutes at 30 ± 0.5 ℃, add exactly 0.5 mL of kallidinogenase solution previously warmed for 5 minutes at 30 ± 0.5℃, and shake immediately to mix. Allow this solution to stand at 30 ± 0.5 ℃ for 2 minutes exactly, add exactly 0.2 mL of trichloroacetic acid solution (1 in 5), and shake to mix. Boil for 3 minutes, cool with iced water immediately, centrifuge, allow to stand at room temperature for 15 minutes. Pipet 0.5 mL of the clear supernatant, add accurately 0.5 mL of gelatin-tris buffer solution of pH 8.0, and shake to mix. Pipet 0.1 mL of this solution, add exactly 1.9 mL of trichloroacetic acid-gelatin-tris buffer solution, shake to mix, and use this solution as the test solution.

(c) ***Procedure***—Determine the amount of kinins per well, B (pg), with the test solution as directed under the purity (2). Calculate the Kinin-releasing activity per unit of Kallidinogenase according to the following equation; the result is NLT 500 ng bradykinin equivalent/min/unit.

Kinin-releasing activity per unit of Kallidinogenase (ng bradykinin equivalent/min/unit)
= B × 4.8

Determination Weigh accurately an appropriate amount of Kallidinogenase according to the labeling unit, dissolve in the 0.05 mol/L phosphate buffer solution of pH 7.0, prepare a solution containing about 10 unit of kallidinogenase in 1 mL, and use this solution as the sample stock solution. Pipet 4 mL of the sample stock solution, add exactly 1 mL of the trypsin inhibitor TS and additional 0.05 mol/L phosphate buffer solution of pH 7.0, to make exactly 10 mL, and use this solution as the test solution. Take exactly 2.5 mL of substrate reagent TS (1) for kallidinogenase assay previously warmed for 5 minutes at 30 ± 0.5℃, put in a cell with the layer length of 1 cm, and add exactly 0.5 mL of the test solution warmed for 5 minutes at 30 ± 0.5℃ while starting a stopwatch at the same time. Perform the test as directed under the Ultraviolet-visible Spectroscopy, using water as the control solution at 30 ± 0.5 ℃, and determine the absorbances, A_{T2} and A_{T6}, at the wavelength of 405 nm, exactly after 2 minutes and 6 minutes. Separately, dissolve kallidinogenase RS by adding 0.05 mol/L phosphate buffer solution of pH 7.0, prepare a solution containing exactly 10 units in 1 mL, and use this solution as the standard stock solution. Pipet 4 mL of this solution, add exactly 1 mL of trypsin inhibitor TS and additional 0.05 mol/L phosphate buffer solution of pH 7.0 to make exactly 10 mL, and use this solution as the standard solution. Pipet 0.5 mL of the standard solution, perform the same test as the test solution, and determine the absorbances, A_{S2} and A_{S6}, after 2 minutes and 6 minutes exactly. Separately, pipet 1 mL of trypsin inhibitor TS, and add 0.05 mol/L phosphate buffer solution of pH 7.0 to make exactly 10 mL. Pipet 0.5 mL of this solution, perform the same test as the test solution, and determine the absorbances, A_{02} and A_{06}, after 2 minutes and 6 minutes exactly.

$$\text{Units of kallidinogenase in 1 mg of Kallidinogenase} = \frac{(A_{T6} - A_{T2}) - (A_{06} - A_{02})}{(A_{S6} - A_{S2}) - (A_{06} - A_{02})} \times \frac{W_S}{a} \times \frac{1}{b}$$

W_S: Amount of kallidinogenase RS taken (unit)
a: Volume of the standard stock solution (mL)
b: Amount of Kallidinogenase in 1 mL of the sample stock solution (mg)

Packaging and storage Preserve in tight containers.

Kallidinogenase Tablets
칼리디노게나제 정

Kallidinogenase Tablets contains NLT 90.0% and NMT 130.0% of the labeled potency of kallidinogenase.

Method of preparation Prepare as directed under Tablets, with Kallidinogenase.

Identification Perform the test as directed under the Assay; it shows a positive response.

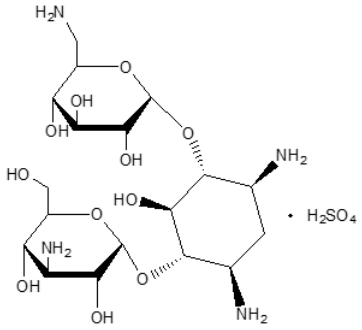
Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the contents of NLT 20 tablets of Kallidinogenase Tablets, and powder. Perform the test as directed under the Assay under Kallidinogenase in Japanese Pharmacopoeia.

Packaging and storage Preserve in well-closed containers.

Kanamycin Monosulfate
카나마이신일황산염



$C_{18}H_{36}N_4O_{11}\cdot H_2SO_4$: 582.58

(2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Aminomethyl)-6-{[(1*R*,2*R*,3*S*,4*R*,6*S*)-4,6-diamino-3-{[(2*S*,3*R*,4*S*,5*S*,6*R*)-4-amino-3,5-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy}-2-hydroxycyclohexyl]oxy}oxane-3,4,5-triol monosulfate [*25389-94-0*]

Kanamycin Monosulfate is the sulfate of aminoglycoside compound having antibacterial activity produced by cultivating *Streptomyces kanamyceticus*.

Kanamycin Monosulfate contains NLT 750 μg and NMT 832 μg (potency) of kanamycin ($C_{18}H_{36}N_4O_{11}$: 484.50) per mg, calculated on the dried basis.

Description Kanamycin Monosulfate occurs as a white crystalline powder.
It is freely soluble in water and practically insoluble in ethanol(99.5).

Identification (1) Dissolve 50 mg of Kanamycin Monosulfate in 3 mL of water, and add 6 mL of anthrone TS; the resulting solution exhibits bluish purple color.

(2) Dissolve 20 mg each of Kanamycin Monosulfate and kanamycin monosulfate RS in 1 mL of water, respectively, and use these solutions as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with the clear supernatant of a mixture of chloroform, ammonia water(28) and methanol (2 : 1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly 0.2% ninhydrin-water saturated 1-butanol TS on the plate and heat the plate at 100 ℃ for 10 minutes; the principal spot obtained from the test solution and the spots obtained from the standard solution are purple and have the same R_f value.

(3) To an aqueous solution of Kanamycin Monosulfate (1 in 5), add 1 drop of barium chloride TS; a white precipitate forms.

Optical rotation $[\alpha]_D^{20}$: Between +112° and +123° (0.2 g calculated on the dried basis, water, 20 mL, 100 mm).

pH Dissolve 0.1 g of Kanamycin Monosulfate in 10 mL of water; the pH of this solution is between 6.5 and 8.5.

Purity (1) ***Sulfate***—Weigh accurately 0.25 g of Kanamycin Monosulfate, dissolve in 100 mL of water, and adjust the pH to 11.0 with ammonia water(28). To this solution, add exactly 10 mL of 0.1 mol/L barium chloride VS, and titrate with 0.1 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: phthalein purple, 0.5 mg). However, when the color of the solution begins to change, add 50 mL of ethanol(99.5), and the endpoint of the titration is when the bluish purple color of this solution turns colorless. Perform a blank test in the same manner. Kanamycin Monosulfate contains NLT 15.0% and NMT 17.0% of sulfate (SO_4^{2-}), calculated on the dried basis.

Each mL of 0.1 mol/L barium chloride VS
= 9.606 mg of sulfate (SO_4^{2-})

(2) ***Heavy metals***—Proceed with 2.0 g of Kanamycin Monosulfate according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Prepare the test solution with 2.0 g of Kanamycin Monosulfate according to Method 4 and perform the test (NMT 1 ppm).

(4) ***Related substances***—Weigh accurately 0.30 g of Kanamycin Monosulfate, dissolve in water to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately 45 mg of kanamycin monosulfate RS, dissolve it in water to make exactly 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 1 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with potassium dihydrogen phosphate solution (3 in 40) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly a solution of ninhydrin in 1-butanol (1 in 100) on the plate, and heat at 110 ℃ for 10 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 4.0% (5 g, in vacuum, NMT 0.67 kPa, 60 ℃, 3 hours).

Residue on ignition NMT 0.5% (1 g).

Sterility It meets the requirements when used in a sterile preparation. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of a sterile preparation.

Bacterial endotoxins Less than 0.50 EU per mg of kanamycin when used for the manufacturing of sterile preparations.

Abnormal toxicity Dissolve 2 mg of Kanamycin Mono-

sulfate in 0.5 mL of water for injection, and inject intravenously for 15 to 30 seconds to each of 5 healthy mice weighing 17 g to 22 g. Use animals in which no abnormalities are observed for NLT 5 days prior to the test. No animals die when observed for 24 hours after administration. If 1 animal dies, repeat the test with 5 animals, and make sure that no animal dies when observed for 24 hours.

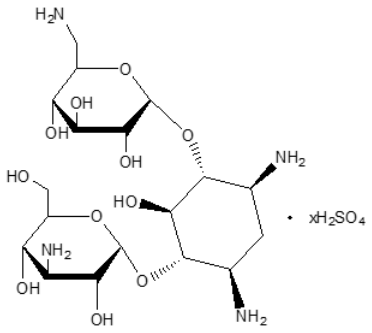
Assay ***Cylinder-plate method*** (1) Medium: Agar media for seed and base layer Use the culture medium in (A) (2) (a) ① ⓐ under the Microbial Assays for Antibiotics.

(2) Test organism: Use *Bacillus subtilis* ATCC 6633 as the test organism.

(3) Weigh accurately about 20 mg (potency) of Kanamycin Monosulfate and dissolve in water to make exactly 50 mL. Take exactly an appropriate amount of this solution, dilute with 0.1 mol/L phosphate buffer solution (pH 8.0) to make two solutions containing each 20.0 μg and 5.0 μg (potency) per mL, and use these solutions as the high concentration test solution and the low concentration test solution, respectively. Separately, dry an appropriate amount of kanamycin monosulfate RS, weigh accurately about 20 mg of kanamycin monosulfate RS, dissolve in diluted phosphate buffer solution, pH 6.0 (1 in 2) to make exactly 50 mL, and use this solution as the standard stock solution. Store the standard stock solution at 5 to 15 °C and use them within 30 days. Take exactly an appropriate amount of this standard stock solution, dilute with 0.1 mol/L phosphate buffer solution (pH 8.0) to obtain solutions containing each 20.0 μg and 5.0 μg (potency) per mL, and use these solutions as the high concentration standard solution and the low concentration standard solution, respectively. With these solutions, perform the test according to (A)(8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in well-closed containers.

Kanamycin Sulfate
카나마이신황산염



$C_{18}H_{36}N_4O_{11}\cdot xH_2SO_4$

(2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Aminomethyl)-6-{[(1*R*,2*R*,3*S*,4*R*,6*S*)-4,6-diamino-3-{[(2*S*,3*R*,4*S*,5*S*,6*R*)-4-amino-3,5-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy}-2-hydroxycyclohexyl]oxy}oxane-3,4,5-triol sulfate [*25389-94-0*]

Kanamycin Sulfate is the sulfate of aminoglycoside compound having antibacterial activity produced by cultivating *Streptomyces kanamyceticus*. Kanamycin Sulfate contains NLT 690 μg and NMT 740 μg (potency) of kanamycin ($C_{18}H_{36}N_4O_{11}$: 484.50) per mg, calculated on the dried basis.

Description Kanamycin Sulfate occurs as a white to yellowish white powder.
It is very soluble in water and practically insoluble in ethanol(99.5).

Identification (1) Dissolve 20 mg each of Kanamycin Sulfate and kanamycin sulfate RS in 1 mL of water, and use these solutions as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of chloroform, ammonia water(28), and methanol (2 : 1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly 0.2% ninhydrin-water saturated 1-butanol TS on the plate and heat the plate at 100 ℃ for 10 minutes; the principal spot obtained from the test solution and the spots obtained from the standard solution are purplish brown and have the same R_f value.

(2) An aqueous solution of Kanamycin Sulfate (1 in 10) responds to the Qualitative Analysis (1) for sulfate.

Optical rotation $[\alpha]_D^{20}$: Between +103° and +115° (0.5 g calculated on the dried basis, water, 50 mL, 100 mm).

pH Dissolve 1.0 g of Kanamycin Sulfate in 20 mL of water; the pH of this solution is between 6.0 and 7.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.5 g of Kanamycin Sulfate in 5 mL of water; the solution is clear and colorless to pale yellow.

(2) ***Heavy metals***—Proceed with 1.0 g of Kanamycin Sulfate according to Method 4 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(3) ***Arsenic***—Prepare the test solution with 2.0 g of Kanamycin Sulfate according to Method 3 and perform the test (NMT 1 ppm).

(4) ***Related substances***—Dissolve 0.30 g of Kanamycin Sulfate in water to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately 9.0 mg of kanamycin monosulfate RS, dissolve in water to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 1 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate

with potassium dihydrogen phosphate solution (3 in 40) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly a solution of ninhydrin in 1-butanol (1 in 100) on the plate, heat at 110 ℃ for 10 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 5.0% (0.5 g, NMT 0.67 kPa, 60 ℃, 3 hours).

Sterility It meets the requirements when used in a sterile preparation. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of a sterile preparation.

Pyrogen It meets the requirements when used in a sterile preparation. Weigh an appropriate amount of Kanamycin Sulfate, make the solution so that each mL contains 10 mg, and use the solution as the test solution. However, inject the test solution into a rabbit by 1.0 mL per kg of the rabbit weight.

Assay Cylinder plate method Perform the test according to the Assay under Kanamycin Monosulfate. However, weigh accurately about 20 mg (potency) of Kanamycin Sulfate, and dissolve it in water to make exactly 50 mL.

Packaging and storage Preserve in tight containers.

Kanamycin Sulfate for Injection
주사용 카나마이신황산염

Kanamycin Sulfate for Injection is a preparation for injection, which is dissolved before use. It contains NLT 90.0% and NMT 120.0% of the labeled amount of kanamycin ($C_{18}H_{36}N_4O_{11}$: 484.50).

Method of preparation Prepare as directed under Injections, with Kanamycin Sulfate.

Description Kanamycin Sulfate for Injection occurs as a white powder.

Identification (1) Dissolve 50 mg of Kanamycin Sulfate for Injection in 3 mL of water, and add 2 mL of anthrone TS; the solution exhibits a bluish purple color.

(2) Dissolve 20 mg of Kanamycin Sulfate for Injection in 2 mL of 1/15 mol/L phosphate buffer solution (pH 5.6), add 1 mL of ninhydrin TS, and boil; the solution exhibits a bluish purple color.

(3) Dissolve 10 mg of Kanamycin Sulfate for Injection in 1 mL of water, add 1 mL of a solution of ninhydrin in 1-butanol (1 in 500) and 0.5 mL of pyridine, heat on a steam bath for 5 minutes, and then add 1 mL of water; the solution exhibits a deep violet color.

pH Dissolve Kanamycin Sulfate for Injection in water to make 50 mg (potency) per mL; the pH of the solution is between 6.0 and 8.5.

Loss on drying NMT 5.0% (0.1 g, 0.7 kPa, 60 ℃, 3 hours).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.50 EU per mg (potency) of kanamycin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

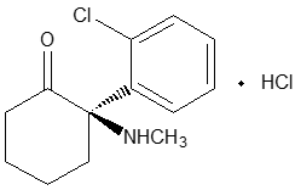
Assay ***Cylinder plate method*** (1) Medium: Agar media for seed and base layer Use the medium in (A) (2) (a) ① ⓐ under the Microbial Assays for Antibiotics.

(2) Test organism: Use *Bacillus subtilis* ATCC 6633 as the test organism.

(3) Weigh accurately about 0.1 g (potency) of Kanamycin Sulfate for Injection according to the labeled potency, add sterile purified water, shake to mix, and make exactly 200 mL. Take an appropriate amount of this solution, dilute to contain exactly 20 μg and 5 μg (potency) per mL with 0.1 mol/L phosphate buffer solution (pH 8.0), and use these solutions as the high-dose test solution and the low-dose test solution, respectively. Separately, take an appropriate amount of kanamycin sulfate RS, dry, weigh accurately about 20 mg (potency), and dissolve in 0.05 mol/L phosphate buffer solution (pH 6.0) to prepare a standard stock solution containing exactly 400 μg (potency) per mL. Keep this standard stock solution at 5 to 15 ℃, and use within 30 days. Take an appropriate amount of this standard stock solution and dilute with 0.1 mol/L phosphate buffer solution (pH 6.0) to contain 20 μg and 5 μg (potency) per mL, and use these solutions as the high-dose standard solution and the low-dose standard solution, respectively. With these solutions, perform the test according to (A) (8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in hermetic containers.

Ketamine Hydrochloride
케타민염산염



and enantiomer

$C_{13}H_{16}ClNO \cdot HCl$: 274.19
2-(2-Chlorophenyl)-2-(methylamino)cyclohexan-1-one hydrochloride [*1867-66-9*]

Ketamine Hydrochloride, when dried, contains NLT 99.0% and NMT 101.0% of ketamine hydrochloride ($C_{13}H_{16}ClNO \cdot HCl$).

Description Ketamine Hydrochloride occurs as white crystals or a crystalline powder.
It is very soluble in formic acid, freely soluble in water or methanol, sparingly soluble in ethanol(95) or acetic acid(100), and practically insoluble in acetic anhydride or ether.
An aqueous solution of Ketamine Hydrochloride (1 in 10) shows no optical rotation.

Melting point—About 258 °C (with decomposition).

Identification (1) Determine the absorption spectra of solutions of Ketamine Hydrochloride and ketamine hydrochloride RS in 0.1 mol/L hydrochloric acid TS (1 in 3000) as directed under the Ultraviolet-visible spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Ketamine Hydrochloride and ketamine hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Ketamine Hydrochloride (1 in 10) responds to the Qualitative Analysis (2) for chloride.

pH Dissolve 1.0 g of Ketamine Hydrochloride in 10 mL of freshly boiled and cooled water. The pH of this solution is between 3.5 and 4.5.

Absorbance $E_{1cm}^{1\%}$ (269 nm): Between 22.0 and 24.5 (30 mg, after drying, 0.1 mol/L hydrochloric acid TS, 100 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Ketamine Hydrochloride in 5 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Ketamine Hydrochloride as directed under the Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Ketamine Hydrochloride as directed under the Method 1 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.5 g of Ketamine Hydrochloride in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of the test solution, add methanol to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of cyclohexane and isopropylamine (49 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly Dragendorff's TS on the plate. (; the spots other than the major spot obtained from the test solution are not more intense than the spots from the standard solution as dry the plate and spray evenly hydrogen peroxide TS on the plate.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

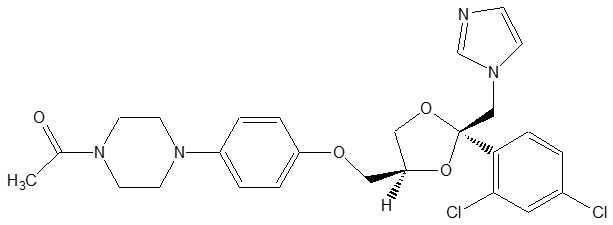
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Ketamine Hydrochloride, previously dried, dissolve in 1 mL of formic acid, add 70 mL of a mixture of acetic anhydride and acetic acid(100) (6 : 1), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 27.419 mg of $C_{13}H_{16}ClNO \cdot HCl$

Packaging and storage Preserve in tight containers.

Ketoconazole
케토코나졸



and enantiomer

$C_{26}H_{28}Cl_2N_4O_4$: 531.43
1-[4-(4-{[2-(2,4-Dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy}phenyl)piperazin-1-yl]ethan-1-one [*65277-42-1*]

Ketoconazole, when dried, contains NLT 98.0% and NMT 102.0% of ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$).

Description Ketoconazole occurs as a white powder.
It is soluble in methanol, sparingly soluble in ethanol(95), and practically insoluble in water.

Identification Determine the infrared spectra of Ketoconazole and ketoconazole RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared spectrophotometry; both spectra exhibit the similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -1° and +1° (0.4 g,

methanol, 10 mL, 100 mm).

Melting point Between 148 and 152 ℃.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Ketoconazole as directed under the Method 2 under the Heavy Metals and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) **Related substances**—Dissolve 0.10 g of Ketoconazole in 10 mL of methanol and use this solution as the test solution. Pipet 5 mL of this solution and add methanol to make exactly 100 mL. Pipet 1 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; each peak area other than the peak of ketoconazole from the test solution is not greater than 2/5 of the peak area of ketoconazole from the standard solution. Also, the total area of the peaks other than the peak of ketoconazole from the test solution is not greater than the peak area of ketoconazole from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 10 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: Acetonitrile

Mobile phase B: Tetrabutylammonium hydrogen sulfate solution (17 in 5000).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 10	5 → 50	95 → 50
10 - 15	50	50

Flow rate: 2.0 mL/min

System suitability

Test for required detectability: Pipet 2 mL of the standard solution and add methanol to make exactly 20 mL. Confirm that the peak area of ketoconazole obtained from 10 μL of this solution is equivalent to between 7% and 13% of the peak area of ketoconazole obtained from the standard solution.

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; the number of theoretical plates and symmetry factor of the peak of ketoconazole are NLT 40000 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times according to the above conditions with 10 μL of the standard solution each time; the relative standard deviation of the peak areas of ketoconazole is NMT 2.5%.

Time span of measurement: From the solvent peak until 15 minutes after introduction.

Loss on drying NMT 0.5% (1 g, vacuum, 80 ℃, 4 hours).

Residue on ignition NMT 0.1% (2 g).

Assay Weigh accurately about 0.2 g of Ketoconazole, dissolve in 40 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 26.572 mg of $C_{26}H_{28}Cl_2N_4O_4$

Packaging and storage Preserve in well-closed containers.

Ketoconazole Solution
케토코나졸 액

Ketoconazole Solution contains NLT 90.0% and NMT 110.0% of the labeled amount of ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$: 531.43).

Method of preparation Prepare as directed under the Liquids, with Ketoconazole.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

pH Between 6.0 and 8.0.

Assay Pipet an amount of Ketoconazole Solution equivalent to 0.2 g of ketaconazole ($C_{26}H_{28}Cl_2N_4O_4$) according to the labeled amount, and add a mixture of methanol and dichloromethane (1 : 1) to make 50 mL. Take 5.0 mL of this solution, add 5.0 mL of the internal standard solution, add a mixture of methanol and dichloromethane (1 : 1) to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of ketaconazole RS, add 5.0 mL of the internal standard solution, and add a mixture of methanol and dichloromethane (1 : 1) to make 50 mL. Use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of ketaconazole to the internal standard, respectively.

Amount (mg) of ketaconazole ($C_{26}H_{28}Cl_2N_4O_4$)

$$= \text{Amount (mg) of ketaconazole RS} \times \frac{A_T}{A_S} \times 10$$

Internal standard solution—Weigh an appropriate amount of terconazole, and dissolve in a mixture of methanol and dichloromethane (1 : 1) to prepare a solution containing 5 mg per mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 3 μm to 10 μm in particle diameter).

Column temperature: Room temperature

Mobile phase: A mixture of methanol solution of diisopropylamine (1 in 500) and ammonium acetate solution (1 in 200) (70 : 30).

Flow rate: 3 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution under the above conditions; the relative peak retention time of ketoconazole and terconazole are about 0.6 and 1.0, respectively, with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 20 mL each of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of ketoconazole and terconazole is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Ketoconazole Tablets
케토코나졸 정

Ketoconazole Tablets contains NLT 90.0% and NMT 110.0% of labeled amount of ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$: 531.43).

Method of preparation Prepare as directed under Tablets, with Ketoconazole.

Identification Weigh the amount of powdered Ketoconazole Tablets, equivalent to about 50 mg of ketoconazole according to the labeled amount, add 50 mL of chloroform, shake for 2 minutes, filter, and use the filtrate as the test solution. Separately, dissolve an appropriate amount of ketoconazole RS in chloroform to make a solution containing 1 mg per mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of *n*-hexane, ethyl acetate, methanol, water and acetic acid(100) (42: 40 : 15 : 2 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Observe the plate under the ultraviolet light (main wavelength: 254nm); the R_f values of the principal spots obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 tablet of Ketoconazole Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of 0.1 mol/L hydrochloric acid TS as the dissolution medium. Take NLT 20 mL of the dissolved solution 30 minutes after starting the dissolution text and filter through a membrane filter with a pore size of 0.45 μ. Discard the first 10 mL of the filtrate, pipet V mL of the subsequent filtrate, add the dissolution medium to make exactly V' mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of ketoconazole RS, dissolve it in the dissolution medium to make it the same concentration as the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorption maximum wavelength of about 270 nm as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as a control solution. It meets the requirements when the dissolution rate of Ketoconazole Tablets in 30 minutes is NLT 80% (Q).

Dissolution rate (%) with respect to the labeled amount of ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$)

$$= CS \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 90000$$

C_S: Concentration (mg/mL) of the standard solution

C: Labeled amount (mg) of ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$) in 1 tablet

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Ketoconazole Tablets, and powder. Weigh accurately an amount of this powder, equivalent to about 0.2 g of ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$), put it in a centrifuge tube, add exactly 50 mL of a mixture of methanol and dichloromethane (1 : 1), shake to mix on a shaker for 30 minutes, and centrifuge. Pipet 5 mL of the clear supernatant, add exactly 5 mL of the internal standard solution, put the mixture of methanol and dichloromethane (1 : 1) to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of ketoconazole RS, add exactly 5 mL of the internal standard solution, add the mixture of methanol and dichloromethane (1 : 1) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of ketoconazole to the peak area of the internal standard.

Amount (mg) of ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$)

$$= \text{Amount (mg) of ketoconazole RS} \times \frac{Q_T}{Q_S} \times 10$$

Internal standard solution—Weigh an appropriate amount of terconazole RS and dissolve it in the mixture of methanol and dichloromethane (1 : 1) to make a solution containing 5 mg per mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of diisopropylamine in methanol (1 in 500) and ammonium acetate solution (1 in 200) (7 : 3).

Flow rate: 3 mL/min

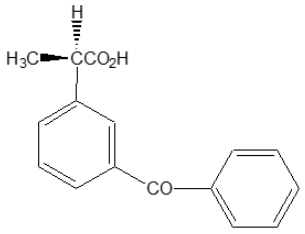
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above operating conditions; ketoconazole and terconazole are eluted in this order with resolution being NLT 2.0.

System repeatability: Perform the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratios is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Ketoprofen
케토프로펜



and enantiomer

$C_{16}H_{14}O_3$: 254.28

2-(3-Benzoylphenyl)propanoic acid [*22071-15-4*]

Ketoprofen, when dried, contains NLT 99.0% and NMT 100.5% of ketoprofen ($C_{16}H_{14}O_3$).

Description Ketoprofen occurs as a white crystalline powder.

It is very soluble in methanol, freely soluble in ethanol(95) or acetone, and practically insoluble in water.

A solution of Ketoprofen in ethanol(99.5) (1 in 100) shows no optical rotation.

It is colored by light to pale yellow.

Identification (1) Determine the absorption spectra of Ketoprofen and ketoprofen RS in methanol (1 in 200000) as directed under the Ultraviolet-visible spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectrum of Ketoprofen and ketoprofen RS, previously dried, as directed in the potassium bromide disk method under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 94 and 97 ºC.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Ketoprofen in 10 mL of acetone; the solution is clear and the color is not more intense than the following control solution.

Control solution—Add dilute hydrochloric acid (1 in 10) to a mixture of 0.6 mL of cobaltous(II) chloride hexahydrate colorimetric stock solution and 2.4 mL of iron(III) chloride hexahydrate colorimetric stock solution to make 100 mL.

(2) ***Heavy metals***—Proceed with 2.0 g of Ketoprofen according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Perform the test using a light-resistant container, protected from direct sunlight. Dissolve 20 mg of Ketoprofen in 20 mL of the mobile phase and use this solution as the test solution. Pipet 1.0 mL of this solution and add the mobile phase to make exactly 50 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the peaks areas of relative retention time about 1.5 times and about 0.3 times that of ketoprofen from the test solution are not greater than 4.5 times and 2 times, respectively, the peak area of ketoprofen from the standard solution. In addition, the peak areas of ketoprofen and about 1.5 times and about 0.3 times the relative retention time of ketoprofen from the test solution are not greater than the peak area of ketoprofen from the standard solution, and the sum of these areas is not greater than 2 times the peak area of ketoprofen from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 233 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 68.0 g of potassium dihydrogen phosphate in water to make 1000 mL; add phosphoric acid to this solution and adjust pH to 3.5. Add

430 mL of acetonitrile and 550 mL of water to 20 mL of this solution.

Flow rate: Adjust the flow rate so that the retention time of ketoprofen is about 7 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution and add the mobile phase to make exactly 10 mL. Confirm that the peak area of ketoprofen obtained from 20 μL of this solution is equivalent to 9% to 11% of the peak area of ketoprofen obtained from the standard solution.

System performance: Proceed with 20 μL of the standard solution under the above operating conditions; the number of theoretical plates and symmetry factor of the peak of ketoprofen are NLT 8000 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area for ketoprofen is NMT 2.0%.

Time span of measurement: About 7 times the retention time of ketoprofen.

Loss on drying NMT 0.5% (0.5 g, in vacuum, 60 ℃, 24 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of ketoprofen, previously dried, dissolve in 25 mL of ethanol(95), add 25 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry) Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 25.428 mg of $C_{16}H_{14}O_3$

Packaging and storage Preserve in light-resistant, tight containers.

Ketoprofen Injection
케토프로펜 주사액

Ketoprofen Injection is an aqueous solution for injection, which contains NLT 95.0% and NMT 105.0% of the labeled amount of ketoprofen ($C_{16}H_{14}O_3$: 254.28).

Method of preparation Prepare as directed under Injections, with Ketoprofen.

Identification (1) Weigh an amount of Ketoprofen Injection, equivalent to 10 mg of ketoprofen according to the labeled amount, add ethanol to make 10 mL, and use this solution as the test solution. Separately, weigh 10 mg of ketoprofen RS, dissolve in 10 mL of ethanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made using silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of toluene, ethyl acetate, ethanol and acetic acid (50 : 20 : 10 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the colors and the Rf values obtained from the test solution and the standard solution are the same.

(2) Determine the absorption spectrum of the test solution in the Assay as directed under the Ultraviolet-visible Spectroscopy using methanol as a control solution; it exhibits a maximum absorbance around 255 nm.

pH Between 6.1 and 8.1.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

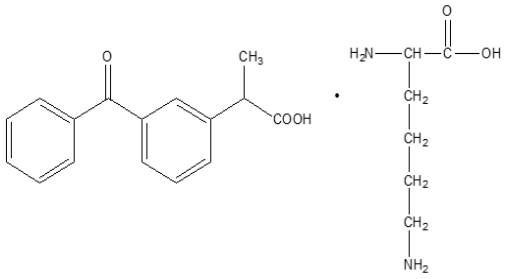
Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Ketoprofen Injection, equivalent to 50 mg of ketoprofen ($C_{16}H_{14}O_3$) according to the labeled amount, and add methanol to make exactly 250 mL. Take 5 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of ketoprofen RS, previously dried to a constant mass in vacuum at 60 ℃, add methanol to make exactly 250 mL. Pipet 5 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using methanol as a control solution and determine the absorbances, A_T and A_S, at 255 nm.

$$\text{Amount (mg) of ketoprofen } (C_{16}H_{14}O_3) = \text{Amount (mg) of ketoprofen RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in light-resistant, hermetic containers.

Ketoprofen Lysinate
케토프로펜리신



$C_{22}H_{28}N_2O_5$: 400.47
L-Lysine 3-benzoyl-α-methylbenzeneacetate (1:1),
[*57469-78-0*]

Ketoprofen Lysinate, when dried, contains NLT 98.0% and NMT 101.0% of ketoprofen lysinate ($C_{22}H_{28}N_2O_5$: 400.47).

Description Ketoprofen Lysinate occurs as a white crystalline powder.
It is very soluble in water.

Melting point—Between 161 and 165 ℃ (with decomposition).

Identification (1) Weigh 10 mg of Ketoprofen Lysinate, and dissolve in 5 mL of pH 5.25 acetate buffer solution, add ninhydrine glycol monoethylether solution, and heat for a few minutes; the solution exhibits a bluish purple color.

(2) Determine the absorption spectra of an aqueous solution of Ketoprofen Lysinate (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; a maximum is exhibited at near 260 nm, and $E_{1cm}^{1\%}$ is 410 ± 15.

(3) Determine the infrared spectra of Ketoprofen Lysinate and ketoprofen lysinate RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) Weigh 20 mg each of Ketoprofen Lysinate and ketoprofen lysinate RS, dissolve in 100 mL of water, respectively, and use these solutions as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Develop the plate with a mixture of isooctane, 1-butanol and acetic acid(100) (210 : 90 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the spot of the test solution exhibits an R_f value and color corresponding to that of the standard solution.

pH Between 6.5 and 7.5 (10% aqueous solution).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Ketoprofen Lysinate in 10 mL of water; the resulting solution is colorless and clear.

(2) ***Chloride***—Weigh 166.7 mg of Ketoprofen Lysinate, dissolve in 15 mL of water, and use this solution as the test solution. Prepare the control solution with 10 mL of sodium chloride solution and 5 mL of water (NMT 0.03%).

(3) ***Sulfate***—Weigh 1.0 g of Ketoprofen Lysinate, dissolve in water, add 1.0 mL of acetic acid, then add water to make 50 mL, and take 10 mL of this solution. Use this solution as the test solution. Separately, add water to 0.711 g of potassium sulfate to make 1000 mL, take 0.1 mL of this solution, add water to make 100 mL, and take 10 mL of this solution. Use this solution as the control solution. To the test solution and the control solution, add 0.75 mL of ethanol and 0.5 mL of barium chloride solution (25%), allow it to stand for 30 seconds, then add 0.3 mL acetic acid TS to each, and perform the test under the Sulfate (NMT 0.02%).

(4) ***Heavy metals***—Proceed with 1.0 g of Ketoprofen Lysinate, and perform the test as directed under Method 1. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

Loss on drying NMT 1.0% (1 g, 105 ℃, constant mass).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.5 g of Ketoprofen Lysinate, previously dried, place in a beaker, and dissolve in 100 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 20.024 mg of $C_{22}H_{28}N_2O_5$

Packaging and storage Preserve in tight containers.

Ketoprofen Lysinate Capsules
케토프로펜리신 캡슐

Ketoprofen Lysinate Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of ketoprofen lysinate ($C_{22}H_{28}N_2O_5$: 400.47).

Method of preparation Prepared as directed under Capsules, with Ketoprofen Lysinate.

Identification (1) Weigh an amount of Ketoprofen Lysinate Capsules equivalent to about 50 mg of ketoprofen lysinate according to the labeled amount, dissolve in 5 mL of water by shaking, filter, and use the filtrate as the test solution. Weigh about 20 mg of ketoprofen lysinate RS, dissolve in 2 mL of water, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatog-

raphy. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made using silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of isoctane, dioxane and acetic acid(100) (200 : 100 : 1) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the Rf values obtained from the test solution and the standard solution are the same.

(2) Determine the absorption spectrum of the test solution obtained under Assay as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum absorbance at the wavelength of 260 ± 1 nm.

Disintegration Meets the requirements.

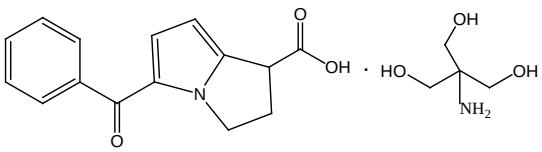
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the contents of NLT 20 capsules of Ketoprofen Lysinate Capsules. Weigh accurately an amount, equivalent to about 50 mg of ketoprofen lysinate ($C_{22}H_{28}NaO_2$), transfer to a 250-mL volumetric flask, add 200 mL of water, dissolve by shaking for 30 minutes, and add water to make 250 mL. Filter the resulting solution, discard 25 mL of the first filtrate, pipet 5.0 mL of the subsequent filtrate, add water to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of ketoprofen lysinate RS, proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 260 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of ketoprofen lysinate } (C_{22}H_{28}N_2O_5) = \text{Amount (mg) of ketoprofen lysinate RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in well-closed containers.

Ketorolac Tromethamine
케토롤락트로메타민염



$C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$: 376.40
2-Amino-2-(hydroxymethyl)propane-1,3-diol;
5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid [*74103-07-4*]

Ketorolac Tromethamine contains NLT 98.5% and NMT 101.5% of ketorolac tromethamine ($C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$), calculated on the dried basis.

Description Ketorolac Tromethamine occurs as a white crystalline powder.
It is freely soluble in water and methanol, slightly soluble in ethanol(95), ethanol(99.5) and tetrahydrofuran, and practically insoluble in acetonitrile, acetone, dichloromethane, toluene, ethyl acetate, 1,4-dioxane, hexane or butanol.

Melting point—Between 165 and 170 ℃ (with decomposition).

Identification (1) Determine the absorption spectra of solutions of Ketorolac Tromethamine and ketorolac tromethamine RS in methanol (1 in 100000) as directed under the Ultraviolet-visible spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Ketorolac Tromethamine and ketorolac tromethamine RS according to the potassium bromide disk method as directed under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 50 mg each of Ketorolac Tromethamine and ketorolac tromethamine RS in 10 mL of a mixture of dichloromethane and methanol (2:1), to make 10 mL, and use these solutions the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 40 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of dichloromethane, acetone and acetic acid(100) (95 : 5 : 2) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Evenly spray the plate with a solution of 0.3 g of ninhydrin dissolved in 10 mL of ethanol(95), and heat for 2 to 5 minutes at 150 ℃; yellow spots with pink to violet edges appear around the drops of the test solution and the standard solution.

pH Dissolve 1 g of Ceftazidime Hydrate in 100 mL of water; the pH of this solution is between 5.7 and 6.7.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Ketorolac Tromethamine as directed under the Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Take 10 μL of the test solution and perform the test as directed under the Liquid Chromatography according to the following conditions and determine the areas of the peaks by the automatic integration method to determine the amounts of each related substances; ketorolac 1-keto derivatie or ketorolac 1-hydroxy derivative are NMT 0.1%, each of the other related substances is NMT 0.5%, and total related substances are NMT 1.0%.

$$\text{Content (\%) of related substances} = 100 \times rf_1 \times \frac{A_i}{A_S}$$

rf: The correction factor for each related substance

with respect to the ketorolac peak

Ketorolac 1-keto analog: 0.52

Ketorolac 1-hydroxy analog: 0.67

Peak of related substance whose relative retention time with respect to the ketorolac peak is 0.54: 2.2.

Peak of related substance whose relative retention time with respect to the ketorolac peak is 0.66: 0.91.

A_i: Peak area of each related substance

A_S: Sum of all related substance peaks and the major peak of ketorolac

Operating conditions

Follow the conditions under the Assay for the test solution, the standard solution, the resolution solution, detector, column, column temperature, mobile phase, flow rate and system suitability.

Time span of measurement: About 3 times the retention time of ketorolac.

Loss on drying NMT 0.5% (1 g, 60 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Dissolve about 50 mg each of Ketorolac Tromethamine and ketorolac tromethamine RS, accurately weighed, in a mixture of water and tetrahydrofuran (70 : 30) to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. The test solution and the standard solution are protected from light. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of each solution.

$$\text{Amount (mg) of ketorolac tromethamine } (C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3) = \text{Amount (mg) of ketorolac tromethamine RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 313 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of ammonium phosphate buffer solution and tetrahydrofuran (70 : 30).

Flow rate: 1.5 mL/min

System suitability

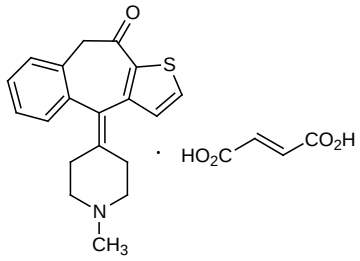
System performance: Add 100 mL of water, 100 mL of dichloromethane, 30 mg of ketorolac tromethamine RS and 1 mL of 1 mol/L hydrochloric acid to a 250 mL separatory funnel, shake and let stand. Transfer the bottom dichloromethane layer to a flask and discard the upper layers. Expose the dichloromethane extract to direct sunlight for 10 to 15 minutes, transfer 1.0 mL of the solution to a vial, evaporate to dryness under an air or nitrogen atmosphere, and dissolve the residue in 1.0 mL of a mixture of water and tetrahydrofuran (70 : 30). Store the solution refrigerated, and test according to the above conditions; ketorolac 1-keto derivative and ketorolac 1-hydroxy derivative are identified and can be used when suitable for the resolution test. Proceed with 10 μL of this solution according to the above conditions; the relative retention time of the peaks of ketorolac 1-hydroxy derivative and ketorolac 1-keto derivative with respect to the ketorolac peak are 0.63 and 0.89, respectively, and the resolution between the two peaks is NLT 1.5. In addition, proceed with 10 μL of the standard solution under the above operating conditions; the number of theoretical plates is NLT 5500.

System repeatability: Repeat the test 5 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of ketorolac is NMT 1.5%.

Ammonium phosphate buffer—Dissolve 5.75 g of ammonium dihydrogen phosphate in water to make 1000 mL, then add phosphoric acid to adjust pH to 3.0. If necessary, adjust the flow rate so that the retention time of the ketorolac peak is between 8 and 12 minutes.

Packaging and storage Preserve in light-resistant, tight containers.

Ketotifen Fumarate
케토티펜푸마르산염



$C_{19}H_{19}NOS \cdot C_4H_4O_4$: 425.50

(*E*)-But-2-enedioic acid; 2-(1-methylpiperidin-4-ylidene)-6-thiatricyclo[8.4.0.0^{3,7}]tetradeca-1(10),3(7),4,11,13-pentaen-8-one [*34580-14-8*]

Ketotifen Fumarate, when dried, contains NLT 99.0% and NMT 101.0% of ketotifen fumarate ($C_{19}H_{19}NOS \cdot C_4H_4O_4$).

Description Ketotifen Fumarate occurs as a white to bright yellow crystalline powder. It is sparingly soluble in methanol or acetic acid(100), and slightly soluble in ethanol(99.5) or acetic anhydride.

Melting point—About 190 °C (with decomposition).

Identification (1) Proceed with 0.03 g of Ketotifen Fumarate as directed under the Oxygen Flask Combustion, using 20 mL of water as the absorbent; the test solution obtained responds to the Qualitative Analysis for sulfate.

(2) Determine the absorption spectra of solutions of Ketotifen Fumarate and ketotifen fumarate RS in methanol (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Ketotifen Fumarate and ketotifen fumarate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Chloride***—Dissolve 0.6 g of Ketotifen Fumarate in 2.5 mL of sodium carbonate TS in a crucible, dry by heating on a steam bath, then ignite at 500 ℃. Dissolve the residue in 15 mL of water, filter as needed, neutralize with diluted nitric acid (3 in 10), then add 6 mL of dilute nitric acid and add water to make 50 mL. Use this as the test solution and perform the test as directed under the Chloride. As the matching fluid, add 0.25 mL of 0.01 mol/L hydrochloric acid and 2.5 mL of sodium carbonate TS, then add diluted nitric acid (3 in 10) equivalent to the amount used for preparation of the test solution, add 6 mL of dilute nitric acid, then add water to make 50 mL (NMT 0.015%).

(2) ***Heavy metals***—Proceed with 1.0 g of Ketotifen Fumarate as directed under the Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve 0.10 g of Ketotifen Fumarate in 10 mL of a mixture of methanol and ammonia TS (99 : 1), and use this solution as the test solution. Pipet 1 mL of this solution and add a mixture of methanol and ammonia TS (99 : 1) to make exactly 25 mL. Pipet 1 mL of this solution and add a mixture of methanol and ammonia TS (99 : 1) to make 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of acetonitrile, water and ammonia water(28) (90 : 10 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray evenly Dragendorff TS for spraying and hydrogen peroxide TS on the plate; the number of the spots other than the principal spot from the test solution is NMT 4, and the spots other than the principal spot are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh exactly about 0.35 g of Ketotifen Fumarate, previously dried, dissolve in 80 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 42.55 mg of $C_{19}H_{19}NOS{\cdot}C_4H_4O_4$

Packaging and storage Preserve in tight containers.

Ketotifen Fumarate Syrup
케토티펜푸마르산염 시럽

Ketotifen Fumarate contains NLT 90.0% and NMT 110.0% of the labeled amount of ketotifen fumarate ($C_{19}H_{19}NOS{\cdot}C_4H_4O_4$: 425.50).

Method of preparation Prepare as directed under Syrups, with Ketotifen Fumarate.

Identification Take an amount of Ketotifen Fumarate Syrup equivalent to 5 mg of ketotifen fumarate, transfer to a separatory funnel, extract 3 times with 50 mL of ether each, and combine the ether extracts. Evaporate to dryness in vacuum. Dissolve the residue in methanol to make 5 mL, and use this solution as the test solution. Separately, weigh about 5 mg of ketotifen fumarate RS, dissolve in 5 mL of methanol, and use this solution as the standard solution. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography as directed under the Thin Layer Chromatography. Next, develop the plate with a mixture of acetonitrile, water and strong ammonia water (90 : 10 : 1) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm), and the R_f values of the spots from the test solution and the standard solution are the same.

pH Between 4.0 and 6.0.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Shake Ketotifen Fumarate Syrup well to mix, pipet an amount equivalent to about 1.38 mg of ketotifen fumarate ($C_{19}H_{19}NOS{\cdot}C_4H_4O_4$), and transfer to a 50-mL volumetric flask. Add water to the gauge line, mix, and use this solution as the test solution. Separately, weigh accurately about 13.8 mg of ketotifen fumarate RS, place in a 50-mL volumetric flask, dissolve in water to the gauge line, and mix. Then take 1.0 mL of the resulting solution, add water to make 10 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of ketotifen fumarate from each solution.

Amount (mg) of ketotifen fumarate ($C_{19}H_{19}NOS{\cdot}C_4H_4O_4$)
= Amount (mg) of ketotifen fumarate RS$\times \frac{A_T}{A_S} \times \frac{1}{10}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of methanol, water and triethylamine (65 : 35 : 0.35).

Flow rate: 2.0 mL/min

Packaging and storage Preserve in well-closed containers.

Ketotifen Fumarate Tablets
케토티펜푸마르산염 정

Ketotifen Fumarate Tablets contains NLT 90.0% and NMT 110.0% of the labeled amount of ketotifen fumarate ($C_{19}H_{19}NOS \cdot C_4H_4O_4$: 425.50).

Method of preparation Prepare as directed under Tablets, with Ketotifen Fumarate.

Identification Weigh the amount of Ketotifen Fumarate Tablets, equivalent to about 5 mg of ketotifen fumarate according to the labeled amount, add 5 mL of methanol, shake to mix for 15 minutes, filter, and use the filtrate as the test solution. Separately, weigh about 5 mg of ketotifen fumarate RS, dissolve in 5 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made using silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of acetonitrile, water and strong ammonia water (90 : 10 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray Dragendorff's TS or 3% hydrogen peroxide solution on the plate or examine the plate under ultraviolet light (main wavelength: 254 nm); the colors and the Rf values obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 tablet of Ketotifen Fumarate Tablets at 120 revolutions per minute according to Method 1 under the Dissolution, using 500 mL of 0.1 mol/L hydrochloric acid as the dissolution medium. Take 20 mL of the dissolved solution 30 minutes after starting the test, filter, and use this solution as the test solution. Separately, weigh accurately about 14 mg of ketotifen fumarate RS, put it into a 500-mL volumetric flask, dissolve with 0.1 mol/L hydrochloric acid to fill up to the gauge line, and mix. Pipet 2 mL of this solution, add 0.1 mol/L hydrochloric acid to make 20 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution at the wavelength of 300 nm as directed under the Ultraviolet-visible Spectroscopy, using 0.1 mol/L hydrochloric acid as a control solution. Meets the requirements if the amount dissolved of Ketotifen Fumarate Tablets in 30 minutes is NLT 80%.

Amount dissolved (%) with respect to the labeled amount of ketotifen fumarate ($C_{19}H_{19}NOS \cdot C_4H_4O_4$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 100$$

W_S: Amount (mg) of ketotifen fumarate RS

C: Labeled amount (mg) of ketotifen fumarate ($C_{19}H_{19}NOS \cdot C_4H_4O_4$) in 1 tablet

Uniformity of dosage units It meets the requirements when the Content uniformity test is performed according to the following method. Take 1 tablet of Ketotifen Fumarate Tablets, add 25.0 mL of a mixture of water and ethanol (1 : 1), stir it for 20 minutes, centrifuge at 4000 rpm for 15 minutes, take 5.0 mL of the clear supernatant, add the mixture of water and ethanol (1 : 1) to make 25 mL, and use this solution as the test solution. Separately, weigh accurately about 13.8 mg of ketotifen fumarate RS, put it into a 250-mL volumetric flask, dissolve with the mixture of water and ethanol to fill up to the gauge line, and mix. Take 10.0 mL of the resulting solution, add a mixture of water and ethanol (1 : 1) to make 50 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, at a wavelength of 300 nm as directed under the Ultraviolet-visible Spectroscopy, using a mixture of water and ethanol (1 : 1) as a control solution.

Amount (mg) of ketotifen fumarate ($C_{19}H_{19}NOS \cdot C_4H_4O_4$)

$$= \text{Amount (mg) of ketotifen fumarate RS} \times \frac{A_T}{A_S} \times \frac{1}{10}$$

Assay Weigh accurately the contents of NLT 20 tablets of Ketotifen Fumarate Tablets, weigh accurately an amount equivalent to about 10 mg of ketotifen fumarate ($C_{19}H_{19}NOS \cdot C_4H_4O_4$), and put it in a 100-mL volumetric flask, add 90 mL of a mixture of 0.1 mol/L hydrochloric acid and acetonitrile (1 : 1), and sonicate it for 5 minutes on an ultrasonic shaker. Add 0.6 mL of triethylamine, shake to mix for 5 minutes, add the mixture of 0.1 mol/L hydrochloric acid and acetonitrile (1 : 1) to fill up to the gauge line, mix, filter, and use the filtrate as the test solution. Separately, weigh accurately about 10 mg of ketotifen fumarate RS, and proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area, A_T and A_S, of ketotifen fumarate in each solution.

Amount (mg) of ketotifen fumarate ($C_{19}H_{19}NOS \cdot C_4H_4O_4$)

$$= \text{Amount (mg) of ketotifen fumarate RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer

(wavelength: 280 nm).

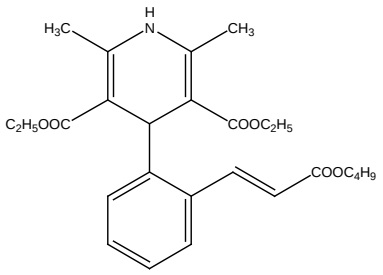
Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of methanol, water, and trietylamine (65 : 35 : 0.35).

Flow rate: 2.0 mL/min

Packaging and storage Preserve in well-closed containers.

Lacidipine
라시디핀



$C_{26}H_{33}NO_6$: 455.54

Diethyl-2,6-dimethyl-4-[2-[(*E*)-3-[(2-methylpropan-2-yl)oxy]-3-oxoprop-1-enyl]phenyl]-1,4-dihydro-pyridine-3,5-dicarboxylate [*103890-78-4*]

Lacidipine contains NLT 97.5% and not more 102.0% of lacidipine ($C_{26}H_{33}NO_6$), calculated on the anhydrous basis and solvent-free basis.

Description Lacidipine occurs as a white to pale yellow crystalline powder.

It is very soluble in acetone or dichloromethane, sparingly soluble in ethanol(99.5) and practically insoluble in water.

Melting point—About 178 °C.

Identification (1) Determine the infrared spectra of Lacidipine and lacidipine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Purity (1) ***2-Propanol***—Weigh accurately about 1.0 g of Lacidipine, dissolve in the internal standard solution to make exactly 50 mL, and use this solution as the test solution. Pipet 2 μL of 2-propanol, add the internal standard solution to make exactly 100 mL, and use this solution as the standard solution. Perform the test solution with 1 μL each of the test solution and the standard solution according to the following conditions as directed under the Gas Chromatography, and calculate the content (%) of 2-propanol (NMT 0.5%).

Internal standard solution—Pipet 2 μL of toluene and dissolve in dimethylacetamide to make exactly 100 mL.

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A stainless steel column about 0.25 mm in internal diameter and about 30 cm in length, packed with 5% phenylmethylsilicone polymer for gas chromatography (0.25 μm in particle diameter).

Column temperature: Maintain the initial temperature to 40 ℃ for 1 minute, increase to 100 ℃ with a velocity of 2 ℃ every minute, increase to 200 ℃ with a velocity of 25 ℃ every minute, and maintain the temperature for the next 5 minutes.

Carrier gas: Nitrogen

Sample injection port temperature: 250 ℃

Detector temperature: 250 °C

Flow rate: 1.0 mL/minute

System suitability

System performance: Proceed with 1 μL of the standard solution according to the above conditions; the two peaks are clearly separated, and the retention time of 2-propanol and toluene is about 6.2 minutes and 3.5 minutes, respectively.

(2) ***Related substances***—Weigh accurately about 10.0 mg of Lacidipine and dissolve in ethanol(99.5) to make exactly 100 mL. Take 1.0 mL of this solution, add the mobile phase to make exactly 5 mL, and use this solution as the test solution. Take 1.0 mL of the test solution, add the mobile phase to make exactly 500 mL, and use the test solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution according to the above conditions; the peak area of lacidipine related substances I is not greater than 2 times the major peak area from the standard solution (0.2%, relative correction factor:2), and the area of related substances is not greater than the major peak area from the standard solution (0.2%). Also, determine lacidipine related substances I with the relative correction factor and determine the amount of other related substances using the standard solution; the amount of total related substances is NMT 0.5%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm)

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with cyanosilyl silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of *n*-hexane and ethanol(99.5) (97 : 3). Adjust so that the retention time of lacidipine is about 10 minutes.

Flow rate: About 2.0 mL per minute.

Water NMT 0.2% (0.5 g, coulometric titration).

Assay Weigh accurately about 10.0 mg each of Lacidipine and Lacidipine RS and dissolve in ethanol(99.5) to make exactly 10 mL. Take 5.0 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the test solution and the standard solution, respectively. Perform the test with 20 μL of each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of lacidipine.

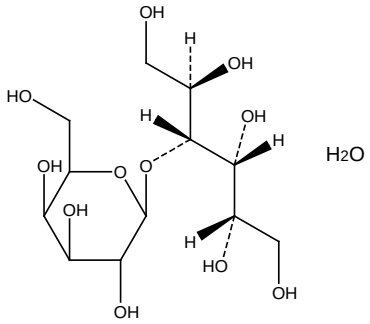
$$\text{Amount (mg) of lacidipine } (C_{26}H_{33}NO_6) = \text{Amount (mg) of lacidipine RS} \times \frac{A_T}{A_S}$$

Operating conditions and system suitability

Proceed as directed according to the operating conditions of the related substances.

Packaging and storage Preserve in well-closed containers.

Lactitol Hydrate
락티톨수화물



$C_{12}H_{24}O_{11}\cdot H_2O$: 362.34

(2*S*,3*R*,4*R*,5*R*)-4-[(2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-Trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyhexane-1,2,3,5,6-pentolhydrate [*81025-04-9*]

Lactitol Hydrate contains NLT 98.0% and NMT 101.0% of lactitol ($C_{12}H_{24}O_{11}$: 344.31), calculated on the anhydrous basis.

Description Lactitol Hydrate occurs as white or light brown crystals. It is odorless and has a slightly sweet taste without an aftertaste.

Identification Determine the infrared spectra of Lactitol Hydrate and Lactitol Hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Heavy metals***—Proceed with about 4.0 g of Lactitol Hydrate according to Method 1 and perform the test. Prepare the control solution with 2.5 mL of lead standard solution (NMT 5 ppm).

(2) ***Reducing sugar***—Dissolve about 0.5 g of Lactitol Hydrate in 2.0 mL of water and use this solution as the test solution. Separately, use 2.0 mL of glucose TS with a concentration of 0.5 g/L as the standard solution. Add 1 mL of alkaline copper tartrate TS to each solution at the same time, heat, and cool. At this time, the turbidity of the test solution is not more intense than the standard solution with reddish brown precipitation (as glucose, NMT 0.2%).

(3) ***Related substances***—Weigh accurately about 1 g of Lactitol Hydrate, dissolve in water to make 100 mL, and use this solution as the test solution. Separately, weigh accurately 30 mg of Lactitol RS, add water to make 100 mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution as directed in the automatic integration method; the relative retention time for lactitol peak of the test solution is 0.53 for lactose, 0.58 for glucose, 0.67 for galactose, 0.72 for lactitol, 1.55 for galactitol, and 1.68 for sorbitol. Determine the amount of galactitol, sorbitol, lactitol, lactose, glucose and galactose on lactitol according to the following formula; the amount of the total related substances is NMT 1.5%.

$$\text{Content (\%) of any other individual related substances} = 100 \times \frac{C_S}{C_T} \times \frac{A_i}{A_S}$$

C_S: Concentration (mg/mL) of lactitol in the standard solution

C_T: Concentration (mg/mL) of Lactitol Hydrate in the test solution

A_i: Peak area of each related substances in the test solution

A_S: Peak area of lactitol in the standard solution

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

Water Between 4.5% and 5.5% (volumetric titration, direct titration).

Residue on ignition NMT 0.5% (1 g).

Assay Weigh accurately about 1 g of Lactitol Hydrate, dissolve in water to make 100 mL, and use this solution as the test solution. Separately, weigh accurately 0.1 g of Lactitol RS, dissolve in water to make 10 mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions. Determine the peak areas, A_T and A_S, of lactitol in the test solution and the standard solution, respectively.

Amount (mg) of lactitol ($C_{12}H_{24}O_{11}$)
= Concentration (mg/mL) of lactitol in the standard solution $\times \frac{A_T}{A_S} \times 100$

Operating conditions

Detector: A differential refractometer

Column: A stainless steel column about 7.8 mm in internal diameter and about 30 cm in length, packed with strongly acidic ion exchange resin for liquid chromatography (9 μm in particle diameter).

Column temperature: A constant temperature of about 85 °C.

Mobile phase: Water

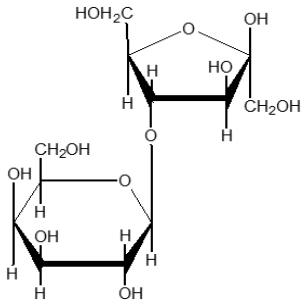
Flow rate: About 0.7 mL per minute.

System suitability

System repeatability: Repeat the test 6 times with 25 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of lactitol is NMT 1.0%

Packaging and storage Preserve in tight containers.

Lactulose
락툴로오스



$C_{12}H_{22}O_{11}$: 342.30

(2*S*,3*R*,4*S*,5*R*,6*R*)-2-[(2*R*,3*S*,4*S*,5*R*)-4,5-Dihydroxy-2,5-*bis*(hydroxymethyl)oxolan-3-yl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol [*4618-18-2*]

Lactulose is an aqueous solution, which is obtained from isomerizing lactose in alkaline and purified with ion exchange resin.

Lactulose contains NLT 50.0% and NMT 56.0% of lactulose ($C_{12}H_{22}O_{11}$).

Description Lactulose occurs as a colorless to pale yellow clear viscous solution. It is odorless and has a sweet taste.

It is miscible with water or formamide.

Identification (1) Add 10 mL of water to about 0.7 g of Lactulose, put 10 mL of ammonium heptamolybdate (VI) tetrahydrate (1 in 25) and 0.2 mL of acetic acid(100), and heat on a steam bath for between 5 and 10 minutes; the resulting solution exhibits a blue color.

(2) Mix about 0.3 g of Lactulose and 30 mL of water, add 16 mL of 0.5 mol/L iodine TS, and immediately add 2.5 mL of 8 mol/L sodium hydroxide TS, allow it to stand for 7 minutes, and put 2.5 mL of diluted sulfuric acid (3 in 20). Add the saturated sodium sulfite solution until the solution turns pale yellow, add 3 drops of methyl orange TS, neutralize with the sodium hydroxide solution (4 in 25), and add water to make 100 mL. Take 10 mL of this solution, add 5 mL of Fehling's TS, and boil for 5 minutes; the red precipitate is formed.

Specific gravity d_{20}^{20}: Between 1.320 and 1.360.

pH Dissolve 2.0 g of Lactulose in 15 mL of water; the pH of this solution is between 3.5 and 5.5.

Purity (1) ***Heavy metals***—Proceed with about 5.0 g of Lactulose and perform the test according to Method 4. Prepare the control solution with 2.5 mL of lead standard solution (NMT 5 ppm).

(2) ***Arsenic***—Proceed with about 1.0 g of Lactulose according to Method 1 and perform the test (NMT 2 ppm).

(3) ***Other sugars***—Determine the peak height of galactose and lactose from chromatograms of the test solution and the standard solution in Assay and determine the peak height ratios, Q_{Ta} and Q_{Tb}, of galactose and lactose against the peak height of the internal standard in the test solution and the peak height ratios Q_{Sa} and Q_{Sb} of galactose and lactose against the peak height of the internal standard in the standard solution; the amount of galactose is NMT 11% and the amount of lactose is NMT 6%.

Amount (mg) of galactose ($C_6H_{12}O_6$)
= Amount (mg) of D-galactose $\times \frac{Q_{Ta}}{Q_{Sa}}$

Amount (mg) of lactose ($C_{12}H_{22}O_{11}\cdot H_2O$)
= Amount (mg) of lactose hydrate $\times \frac{Q_{Tb}}{Q_{Sb}}$

Loss on drying NMT 35.0% (0.5 g, in vacuum, 80 ℃, 5 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 1 g of Lactulose, dissolve in 10 mL of internal standard solution, add water to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 0.5 g of Lactulose RS, about 80 mg of D-galactose and about 40 mg of lactose, add exactly 10 mL of internal standard solution to make 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution according to the following conditions as directed under the Liquid Chromatography, and determine the peak height ratios, Q_T and Q_S, of lactulose to that of the peak height of the internal standard.

Amount (mg) of lactulose ($C_{12}H_{22}O_{11}$)

$$= \text{Amount (mg) of lactulose RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—D-mannitol solution (1 in 20).

Operating conditions

Detector: A differential refractometer

Column: A stainless steel column about 8 mm in internal diameter and about 50 cm in length, packed with gel-type strongly acidic ion-exchange resin for liquid chromatography (cross-linking: 6%) (11 μm in particle diameter).

Column temperature: A constant temperature of about 75 °C.

Mobile phase: Water

Flow rate: Adjust the flow rate so that the retention time of lactulose is about 18 minutes.

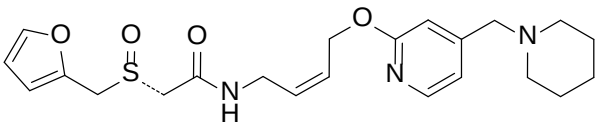
System suitability

System performance: Proceed with 20 μL of the standard solution under the above operating conditions; lactulose and the internal standard are eluted in this order with the resolution between their peaks being NLT 8.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to above operating conditions; the relative standard deviation of the ratios of peak height of lactulose, galactose and lactose to that of the internal standard is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Lafutidine
라푸티딘



and enantiomer

$C_{22}H_{29}N_3O_4S$: 431.55

2-[(RS)-Furan-2-ylmethylsulfinyl]-N-{4-[4-(piperidin-1-ylmethyl)pyridin-2-yl] oxy-(2Z) but-2-en-1-yl} acetamide *[206449-93-6]*

Lafutidine, when dried, contains NLT 99.0% and NMT 101.0% lafutidine ($C_{22}H_{29}N_3O_4S$).

Description Lafutidine occurs as a white to pale yellowish white crystalline powder.

It is freely soluble in acetic acid(100), soluble in methanol, sparingly soluble in ethanol(99.5) and practically insoluble in water.

A solution of Lafutidine in methanol (1 in 100) shows no optical rotation.

It shows polymorphism.

Identification (1) Determine the absorption spectra of solutions of Lafutidine and lafutidine RS in methanol (1 in 20000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Lafutidine and lafutidine RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Heavy metals***—Proceed with about 2.0 g of Lafutidine as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Dissolve about 0.10 g of Lafutidine in 100 mL of the mobile phase and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution as directed in the automatic integration method; the peak area of lafutidine related substance I with a relative retention time of about 0.85 to lafutidine in the test solution is not lager than 3/10 of the peak area of lafutidine in the standard solution (NMT 0.3%). The peak area other than lafutidine in the test solution and the peak from above is not lager than 1/10 of the peak area of lafutidine in the standard solution (NMT 0.1%). The sum of peak areas other than lafutidine in the test solution is not lager than 2/5 of the peak area of lafutidine in the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 0.87 g of sodium 1-pentanesulfonate in dilute phosphoric acid (1 in 1000) to make 1000 mL. To 850 mL of this solution, add 150 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of lafutidine is about 15 minutes.

Time span of measurement: About 6 times the retention time of lafutidine.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution and add the mobile phase to make exactly 20 mL. Confirm that the peak area of lafutidine obtained from 5 μL of this solution is equivalent to 3.5% to 6.5% of the peak area of lafutidine in the standard solution.

System performance: Proceed with 5 μL of the standard solution under the above operating conditions; the number of theoretical plates and symmetry factor of

the peak of lafutidine are NLT 8000 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 5 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of lafutidine is NMT 2.0%.

Loss on drying NMT 0.5% (1 g, in vacuum, NMT 0.67 kPa, 60 ℃, phosphorus (V) oxide, 4 hours).

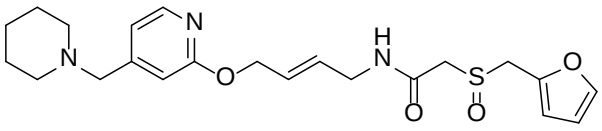
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Lafutidine, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

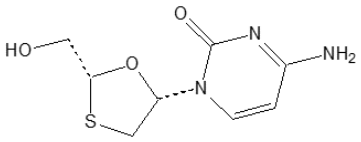
Each mL of 0.1 mol/L perchloric acid VS
= 21.58 mg of $C_{22}H_{29}N_3O_4S$

Packaging and storage Preserve in tight containers.

Note Lafutidine related substance I : (±)-2-(furfurylsulfinyl)-N-[4-[4-(piperidinomethyl)-2-pyridin]oxy-(E)-2-butenyl]acetamide



Lamivudine
라미부딘



$C_8H_{11}N_3O_3S$: 229.26

4-Amino-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2-one [*134678-17-4*]

Lamivudine contains NLT 98.0% and NMT 102.0% of lamivudine ($C_8H_{11}N_3O_3S$), calculated on the anhydrous basis and solvent-free basis.

Description Lamivudine occurs as a white solid.
It is soluble in water.

Melting point—About 176 °C.

Identification (1) Determine the infrared spectra of Lamivudine and Lamivudine RS, as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak obtained from the test solution in the Lamivudine isomer test is the same as that of the major peak from the resolution solution.

Purity (1) ***Color of the solution***—Perform the test with the aqueous solution of Lamivudine (1 in 20) as directed under the Ultraviolet-visible Spectroscopy at the wavelength of 440 nm, with a layer length of 4 cm; the absorbance is NMT 0.0015.

(2) ***Heavy metals***—Weight about 1.0 g of Lamivudine, put into a flask, set the angle of the flask to about 45°, and mix after adding 8 mL of sulfuric acid and 10 mL of nitric acid. Apply low heat until the reaction starts, add 8 mL of sulfuric acid and 10 mL of nitric acid again, increase the temperature, and heat until the solution turns black. After cooling, add 2 mL of nitric acid, and heat again until the solution turns black. Continue heating until the solution does not get darker and heat strongly again until rich fumes are formed. After cooling, add 5 mL of water, and heat until rich fumes are formed, and continue heating until the amount of residue is NLT 2 mL and NMT 3 mL. After cooling, add 5 mL of water and confirm the color of the solution. If the color is yellow, add 1 mL of strong hydrogen peroxide, heat until rich fumes are formed, and continue until the residue is NLT 2 mL and NMT 3 mL. If the solution still exhibits a yellow color, add 5 mL of water and 1 mL of strong hydrogen peroxide, and repeat the procedure until the solution turns colorless. After cooling, and dilute it with water so the total amount is NMT 25 mL, and transfer to a 50-mL Nessler tube. Adjust the pH to between 3.0 and 4.0 with dilute ammonia water and add water to dilute to 40 mL. Add 2 mL of acetate buffer solution, pH 3.5 and 1.2 mL of thioacetamide TS, mix, add water to make 50 mL, and use this solution as the test solution. Separately, prepare the control solution in the same manner as the preparation of the test solution with 2 mL of lead standard solution at the same time. Allow the solution to stand for 2 minutes and compare on a white background; the brown color from the test solution is not more intense than the color from the standard solution (NMT 20 ppm).

If reading is difficult, filter slowly with a low pressure using a filter with a pore size of 0.45 μm, and compare the color of the filter paper.

System suitability: Proceed in the same manner as the preparation of the test solution without adding the sample separately, and use this solution as the blank test solution. The control solution has a slightly brownish color compared to the blank test solution. Add 2 mL of lead standard solution in the test solution and use the solution as the system suitability solution. The system suitability solution is more intense than or equal to the control solution.

(3) ***Lamivudine isomer***—Weigh accurately about 25 mg of Lamivudine, dissolve in water to make 100 mL, and use this solution as the test solution. Perform the test with about 10 μL of the test solution according to the following conditions as directed under the Liquid Chromatography, determine the areas of the major peaks and the amount of lamivudine isomer; the amount of lamivu-

dine isomer is NMT 0.3%.

$$\text{Content (\%) of lamivudine isomer} = 100 \times \frac{A_\text{i}}{A_\text{i} + A_\text{S}}$$

A_i: Peak area of lamivudine isomer
A_S: Peak area of lamivudine

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with betacyclodextrin silica gel (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of 0.1 mol/L ammonium acetate solution and methanol (95 : 5).

Melting point—Between 15 and 30 ℃.

Flow rate: About 1.0 mL per minute.

System suitability

System performance: Dissolve the content of 1 vial of lamivudine resolution mixture I RS in 5 mL of water, wash the vial with 2 mL each of water, and add water to make 10 mL. Proceed with 10 μL of this solution according to the above operating conditions; the relative retention times are about 1.0 for lamivudine and about 1.2 for lamivudine isomer, and the resolution between the peak of lamivudine and that of lamivudine isomer is NLT 1.5.

0.1 mol/L ammonium acetate solution—Dissolve about 7.7 g of ammonium acetate in water to make 1000 mL.

(4) ***Residual solvent***—Weigh accurately about 5 g of Lamivudine, add 10 mL of internal standard solution, add a mixture of water and dimethylsulfoxide (1 : 1) to make exactly 100 mL, and use this solution as the test solution. To 10 mL of the internal standard solution, add exactly 100 μL each of ethanol(99.5), isopropyl acetate, methanol and triethylamine, add a mixture of water and dimethylsulfoxide (1 : 1) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 0.5 μL each of the test solution and the standard solution according to the following conditions as directed under the Gas Chromatography, determine the peak areas of the test solution and the standard solution, and determine the content of residual solvent in Lamivudine; the amount of ethanol is NMT 0.2%, isopropyl acetate is NMT 0.2%, triethylamine is NMT 0.1% and the total residual solvent is NMT 0.3%.

$$\text{Content (\%) of residual solvent} = 10 \times \frac{C}{W} \times \frac{Q_\text{i}}{Q_\text{S}}$$

C: Concentration (mg/mL) of each component in the standard solution
W: Amount of Lamivudine taken (g)
Q_i: Peak area ratio of each component of the internal standard solution in the test solution
Q_S: Peak area ratio of each component of the internal standard solution in the standard solution

Pipet 1 mL of 2-pentanone, the internal standard solution, and add a mixture of dimethylsulfoxide and water to make 100 mL.

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A fused silica column about 0.53 mm in internal diameter and about 50 m in length, packed with dimethylsiloxane (5 μm in particle diameter).

Column temperature: Maintain at 70 ℃ for the first 3 minutes, increase by 30 ℃ every minute until 200 ℃, and keep the temperature for 6.5 minutes.

Carrier gas: Hydrogen

Flow rate: 320 mL/minute

Sample injection port temperature: 150 ℃

Detector temperature: 250 ℃

(5) ***Related substances***—Weigh accurately about 25 mg of Lamivudine, dissolve in the mobile phase of the Assay to make exactly 100 mL, and use this solution as the test solution. Weigh accurately an appropriate amount of salicylic acid, dissolve in the mobile phase, dilute appropriately so the solution contains 0.625 μg per mL, and use it as the salicylic acid solution. Perform the test with 10 μL each of the test solution and the salicylic acid solution according to the conditions in the Assay as directed under the Liquid Chromatography and determine the peak area of the test solution and the salicylic acid solution; the amount of salicylic acid in Lamivudine is NMT 0.1% when calculated according to formula (1). Determine the amount of other related substances according to formula (2); the related substances with the relative retention time of about 0.4 are NMT 0.3%, the related substances with the relative retention time of about 0.9 are NMT 0.2%, the other related substances are NMT 0.1%, and the total amount of related substances is NMT 0.6%.

$$\text{Content (\%) of salicylic acid} = 10 \times \frac{C}{W} \times \frac{A_\text{T}}{A_\text{S}} \quad (1)$$

C: Concentration (μg/mL) of salicylic acid in the salicylic acid solution
W: Amount (mg) of Lamivudine taken
A_T: Peak area of salicylic acid from the test solution
A_S: Peak area of salicylic acid from the salicylic acid solution

$$\text{Content (\%) of other related substances} = 100 \times \frac{A_\text{I}}{A_\text{S}} \quad (2)$$

A_I: Peak area of related substances other than the salicylic acid from the test solution
A_S: Total area of all peaks from the test solution

Water NMT 0.2% (1 g, coulometric titration).

Assay Weigh accurately about 25 mg each of Lamivudine and Lamivudine RS, dissolve in a mixture of 0.025 mol/L ammonium acetate buffer solution and methanol (95 : 5) to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the area of the major peak, A_T and A_S in the test solution and the standard solution.

$$\text{Amount (mg) of lamivudine } (C_8H_{11}N_3O_3S) = \text{Amount (mg) of lamivudine RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 277 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of 0.025 mol/L ammonium acetate buffer solution and methanol (95 : 5).

Column temperature: A constant temperature of about 35 °C.

Flow rate: About 1.0 mL per minute.

System suitability

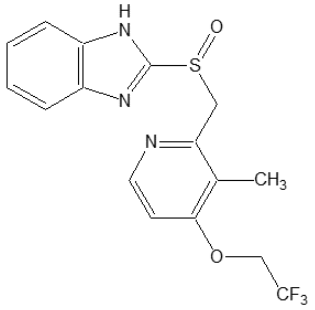
System performance: Dissolve 2 mL of the mobile phase in the content of 1 vial of lamivudine resolution mixture II RS, and proceed with 10 μL of this solution according to the above operating conditions; the relative retention times are about 1.0 for lamivudine and 0.9 for lamivudine isomer, respectively, and the resolution between the peak of lamivudine and that of lamivudine isomer is NLT 1.5.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak area is NMT 2.0%.

0.025 mol/L ammonium acetate buffer solution—Weigh about 1.9 g of ammonium acetate, dissolve in 900 mL of water, adjust the pH to 3.8 ± 0.2 with acetic acid, and add water to make 1000 mL.

Packaging and storage Preserve in light-resistant, well-closed containers.

Lansoprazole
란소프라졸



$C_{16}H_{14}F_3N_3O_2S$: 369.36

2-[[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl]-1*H*-benzimidazole [*103577-45-3*]

Lansoprazole contains NLT 99.0% and NMT 101.0% of lansoprazole ($C_{16}H_{14}F_3N_3O_3S$), calculated on the anhydrous basis.

Description Lansoprazole occurs as a white or brown crystalline powder.

It is freely soluble in *N*,*N*-Dimethylformamide, soluble in methanol, sparingly soluble in ethanol(99.5), very slightly soluble in ether and practically insoluble in water.

Melting point—About 166 °C (with decomposition).

Identification (1) Determine the absorption spectra of solutions of Lansoprazole and Lansoprazole RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Lansoprazole and Lansoprazole RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity ***Related substances***—Weigh accurately about 0.125 g of Lansoprazole, dissolve in methanol to make exactly 50 mL, take 1.0 mL of this solution, and add a mixture of mobile phase A and mobile phase B (9 : 1) to make exactly 10 mL. Use this solution as the test solution. Prepare the test solution before use. Separately, weigh accurately about 25 mg of Lansoprazole RS, dissolve in methanol to make 100 mL, and add methanol to 5.0 mL of this solution to make exactly 50 mL. Add a mixture of mobile phase A and mobile phase B (9 : 1) to 1.0 mL of this solution to make exactly 10 mL, and use this solution as the standard solution. Mix 9 mL of a mixture of mobile phase A and mobile phase B (9 : 1) with 1 mL of methanol, and use it as the blank test solution. Perform the test with 40 μL each of the test solution, the standard solution and the blank test solution according to the following conditions by the percentage peak area method under the Liquid Chromatography. Other than the peak from the blank test solution, determine the peak area of each related substance, A_i other than the major peak

from the test solution and the major peak from the standard solution, A_S; the amount of the total related substances is NMT 1.0%.

$$\text{Content (\%) of individual related substances} = 50 \times \frac{C}{W} \times \frac{A_i}{A_S}$$

C: Concentration (μg/mL) of lansoprazole in the standard solution

W: Amount of Lansoprazole taken (mg)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 285 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Use mobile phases A and B to control stepwise or based on the gradient elution as follows.

Mobile phase A: Water

Mobile phase B: A mixture of acetonitrile, water and triethylamine (160 : 40 : 1). Adjust the pH to 7.0 by adding phosphoric acid.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 40	90 → 20	10 → 80
40 - 50	20	80
50 - 51	20 → 90	80 → 10
51 - 60	90	10

Flow rate: 0.8 mL/minute

System suitability

System performance: Weigh 5 mg of Lansoprazole RS and 5 mg of Lansoprazole related substance I {2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridin]methyl]sulfinyl]benzimidazole}, dissolve in methanol to make 200 mL, add a mixture of mobile phase A and mobile phase B (9 : 1) to 1.0 mL of this solution to make 10 mL. Proceed with 40 μL of this solution; the resolution between the peaks of lansoprazole and lansoprazole related substance I is NLT 6.

System repeatability*:* Weigh accurately about 2.5 mg of lansoprazole related substance I RS, dissolve in methanol to make 100 mL, take 1.0 mL of this solution, and add a mixture of mobile phase A and mobile phase B (9 : 1) to make 10 mL. Repeat the test 6 times with 40 μL of this solution under the above operating conditions; the relative standard deviation of the peak area of related substance I is NMT 3%.

Water NMT 0.1% (1.0 g, volumetric titration, direct titration). However, use 50 mL of a mixture of pyridine and ethylene glycol (9 : 1 or 8 : 2) as a vehicle.

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately 50 mg each of Lansoprazole and Lansoprazole RS and dissolve in the internal standard solution to make exactly 10 mL. To 1.0 mL of these solutions, add a mixture of water, acetonitrile and triethylamine (60 : 40 : 1), in which pH is adjusted to 10 with phosphoric acid, to make exactly 50 mL, and use each solution as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution according to the following operating conditions as directed under the Liquid Chromatography, and determine the ratio of peak areas for lansoprazole, Q_T and Q_S, to the internal reference for each solution.

$$\text{Amount (mg) of lansoprazole } (C_{16}H_{14}F_3N_3O_2S) = \text{Amount (mg) of lansoprazole RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh 25 mg of 4′-ethoxyacetophenone and dissolve in a mixture of water, acetonitrile and triethylamine (60 : 40 : 1), in which pH is adjusted to 10 with phosphoric acid, to make 10 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 285 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of water, acetonitrile and triethylamine (60 : 40 : 1). Adjust the pH to 7.0 by adding phosphoric acid.

Flow rate: 1 mL/min

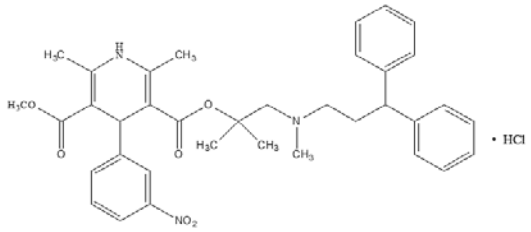
System suitability

System performance: Weigh 5 mg of Lansoprazole RS and 5 mg of Lansoprazole related substance I RS and dissolve in a mixture of water, acetonitrile, and triethylamine (60 : 40 : 1), in which pH is adjusted to 10 with phosphoric acid, to make 50 mL. Proceed with 10 μL of this solution according to the above conditions; the resolution between the peaks of lansoprazole and the related substance I is NLT 5.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of lansoprazole is NMT 0.5%

Packaging and storage Preserve in light-resistant, well-closed containers.

Lercanidipine Hydrochloride
레르카니디핀염산염



$C_{36}H_{41}N_3O_6 \cdot HCl$: 648.21

3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-2-[(3,3-diphenylpropyl)methylamino]-1,1-dimethylethylmethylester hydrochloride, [*132866-11-6*]

Lercanidipine Hydrochloride contains NLT 99.0% and NMT 101.0% of lercanidipine hydrochloride ($C_{36}H_{41}N_3O_6 \cdot HCl$: 648.21), calculated on the dried basis.

Description Lercanidipine Hydrochloride is light yellow crystals or a crystalline powder and is odorless.
It is very soluble in chloroform and methanol, soluble in ethanol(95), sparingly soluble in acetone, and practically insoluble in water.

Identification (1) Determine the absorption spectra of Lercanidipine Hydrochloride and lercanidipine hydrochloride RS as directed under the ATR method under the Mid-infrared Spectroscopy in the General Tests of the Korean Pharmacopoeia (KP); both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Perform the test as directed under the Liquid Chromatography in Related substances; the peak retention time from the test solution and the standard solution is the same.

Melting point Between 185 and 190 ℃.

Loss on drying NMT 1.0% (1 g, 105 °C, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Clarity and color of solution Dissolve 0.5 g of Lercanidipine Hydrochloride in chloroform to make 10 mL; the resulting solution exhibits a yellow color and is clear.

Related substances (1) ***Thin layer chromatography***—Perform as directed under the following test method; the total impurity is NMT 0.5%, the single impurity is NMT 0.2%, and the single unidentified impurity is NMT 0.1%. Weigh about 0.5 g of Lercanidipine Hydrochloride, dissolve in 10 mL of chloroform, and use this solution as the test solution (A). Pipet 0.1 mL (B), 0.2 mL (C), and 0.5 mL (D) of this solution, add chloroform to each to make 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography in the General Tests of the pharmacopoeia. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform, methanol and acetic acid (90 : 7 :3) as a developing solvent to a distance of about 15 cm, and dry the plate. Expose the plate under ultraviolet rays (main wavelength: 254 mm), confirm the spots, spray Dragendorff's TS, spray again 3% hydrogen peroxide solution, and confirm the spots. The color of the total spots other than the principal spot from the test solution are not more intense than the spot from the standard solution D. Other than the principal spot from the test solution, the spot of single impurity 1, 2, 3, and 5 spot (relative R_f value - lercanidipine hydrochloride : 1, impurity 1 : 1.5, impurity 2 : 0.5, impurity 3 : 2.0, impurity 5 : 1.7) is not more intense than the spot from the standard solution C, and the spot of single unidentified impurity, other than the spot of impurity, 1, 2, 3 and 5 is not more intense than the spot from the standard solution B.

(2) ***Liquid chromatography***—Weigh 10 mg of Lercanidipine Hydrochloride, dissolve in 10 mL of acetonitrile to make exactly 10 mL, and use this solution as the test solution. Pipet 0.2 mL of the test solution, dissolve in acetonitrile to make exactly 100 mL, and use this solution as the diluted test solution. Separately, weigh accurately about 100 mg of lercanidipine hydrochloride RS, dissolve in acetonitrile to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution, the diluted test solution, the standard solution and the blank test solution (acetonitrile) according to the following operating conditions as directed under the Liquid Chromatography, and determine the amount of related substances; the amount of related substances I, III, IV and V is NMT 0.2%, respectively, the amount of any other individual related substances is NMT 0.1%, and the amount of total related substances is NMT 0.5%.

$$\text{Content (\%) of each related substance} = 0.2 \times (A_i / A_S) / RF$$

A_i: Peak area of each related substance in the test solution

A_s: Peak area of lercanidipine hydrochloride in the diluted test solution

RF: Response factor of each related substance

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and phosphoric acid (675 : 325).

Flow rate: 1.5 mL/minute

Running time: 30 minutes

System suitability

System performance: Weigh 100 mg of the standard solution and 1 mg of related substance III, add ace-

tonitrile to make 100 mL, take 10 μL of this resulting solution, and perform the test according to the above operating conditions; the resolution between lercanidipine hydrochloride and related substance III is NLT 1.5.

Related substance III—1,1-dimethyl-2-[(3,3-diphenylpropyl)methylamino] ethylmethyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate

<Relative retention time and response factor of each related substance>

Name	Relative retention Time	Response factor (*RF*)
Related substance I	0.16	1.14
Related substance V	0.25	1.88
Related substance III	0.90	0.47
Lercanidipine hydrochloride	1.00	1.00
Related substance IV	1.24	0.83

Assay Weigh accurately about 500 mg of Lercanidipine Hydrochloride, dissolve in 15 mL of formic acid, add 35 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 64.82 mg of $C_{36}H_{41}N_3O_6 \cdot HCl$

Packaging and storage Preserve in tight containers.

Lercanidipine Hydrochloride Tablets
레르카니디핀염산염 정

Lercanidipine Hydrochloride Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of lercanidipine hydrochloride ($C_{36}H_{41}N_3O_6 \cdot HCl$: 648.205).

Method of preparation Prepare as directed under Tablets, with Lercanidipine Hydrochloride.

Identification The retention time of the major peak obtained from the test solution and the standard solution from the Assay and the ultraviolet absorption spectrum between 200 nm and 400 nm are the same.

Uniformity of dosage units Meets the requirements.

Dissolution Perform the test with 1 tablet of Lercanidipine Hydrochloride Tablets at 50 revolutions per minute according to Method 2 under the Dissolution using 900 mL of 0.1 mol/L hydrochloric acid TS of 0.3 w/v% polysorbate 80 as the dissolution medium. Take the solution 45 minutes after starting the dissolution test and filter. Use this filtrate as the test solution. Separately, weigh accurately about 10 mg of lercanidipine hydrochloride RS, add 10 mL of acetonitrile, and dissolve it. Add the dissolution medium to make the same concentration as that of the test solution, and use this solution as the standard solution. Prepare the test solution and the standard solution before use. Inject 20 μL of the test solution and the standard solution as directed by the following assay of content or potency. Meets the requirements if the dissolution rate of Lercanidipine Hydrochloride Tablets in 45 minutes is NLT 75%.

Dissolution rate (%) with respect to the labeled amount of lercanidipine hydrochloride ($C_{36}H_{41}N_3O_6 \cdot HCl$)
$= A_T / A_S \times C_S \times 1 / C \times 90000$

C_S: Concentration (mg/mL) of the standard solution
C: Labeled amount (mg) of lercanidipine hydrochloride ($C_{36}H_{41}N_3O_6 \cdot HCl$) in 1 tablet

System suitability
System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of lercanidipine hydrochloride is NMT 2.0%.

Assay Weigh accurately the mass of NLT 20 tables of Lercanidipine Hydrochloride Tablets and powder. Weigh accurately an amount equivalent to 80 mg of lercanidipine hydrochloride ($C_{36}H_{41}N_3O_6 \cdot HCl$) and put it into 200 mL of volumetric flask. Add 20 mL of 0.01 mol/L hydrochloric acid and sonicate for about 15 minutes. Add 100 mL of methanol and sonicate for about 15 minutes. Cool at room temperature and add methanol to make exactly 200 mL. Filter this solution to have a clear supernatant. Pipet 10.0 mL of the clear supernatant, and add the mobile phase to make exactly 100 mL. Use this solution as the test solution. Separately, weigh accurately 80 mg of lercanidipine hydrochloride RS and put it into a 200-mL volumetric flask containing 100 mL of methanol, dissolve in 20 mL of 0.01 mol/L hydrochloric acid, and add methanol to make exactly 200 mL. Pipet 10 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Prepare the test solution and the standard solution before use. Perform the test with 15 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas, A_T and A_S of lercanidipine hydrochloride, for the test solution and the standard solution, respectively.

Amount (mg) of lercanidipine hydrochloride ($C_{36}H_{41}N_3O_6 \cdot HCl$)
= Amount (mg) of lercanidipine hydrochloride $\times A_T / A_S$

Operating conditions
Detector: An ultraviolet absorbance photometer (wavelength: 240 nm). However, a photo-diode array detector (200 nm to 400 nm) is used when the Identifica-

tion is performed.

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 um in particle diameter), or an equivalent column.

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of acetonitrile and 0.15 mol/L sodium perchlorate solution (adjusted the pH to 3.0 with perchloric acid) (61 : 39).

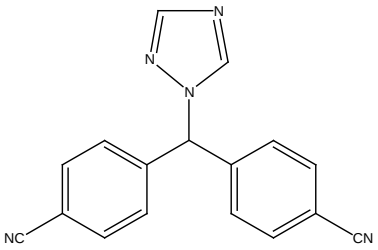
Flow rate: 1.3 mL/min

System suitability

System repeatability: Repeat the test 6 times with 15 μL each of the standard solutions according to the above operating conditions; the relative standard deviation of the peak area of lercanidipine hydrochloride is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Letrozole
레트로졸



$C_{17}H_{11}N_5$: 285.30

4-[(4-Cyanophenyl)-(1,2,4-triazol-1-yl)methyl]benzonitrile [*112809-51-5*]

Letrozole contains NLT 98.0% and NMT 102.0% of letrozole ($C_{17}H_{11}N_5$), calculated on the anhydrous basis.

Description Letrozole occurs as white to pale yellow crystals or a crystalline powder.
It is freely soluble in dichloromethane, slightly soluble in ethanol(95), and practically insoluble in water.

Identification (1) Determine the infrared spectra of Letrozole and Letrozole RS, as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Letrozole according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Weigh accurately about 25 mg of Letrozole, dissolve in 75 mL of acetonitrile, add water to make exactly 250 mL, and use this solution as the test solution. Separately, weigh accurately 10 mg of Letrozole RS, dissolve by adding 30 mL of acetonitrile, and put water to make exactly 100 mL. To 5.0 mL of this solution, add a mixture of water and acetonitrile (7 : 3) to make exactly 50 mL. To 5.0 mL of this solution, add a mixture of water and acetonitrile (7 : 3) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 15 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak area of the major peak. The letrozole related substance I (4,4-(1*H*-1,3,4-triazol-1-ylmethylene)dibenzonitrile) obtained from the test solution is NMT 0.3%, 4,4′,4″methylidentribenzonitrile is NMT 0.2%, other related substances are NMT 0.1%, and the sum of all related substances is NMT 0.3% (the relative retention time of 4,4′,4″methanetriyltribenzonitrile is about 2.4).

$$\text{Content (\%) of related substances} = \frac{A_i}{A_S} \times \frac{C_S}{C_T}$$

A_T: Peak area of each related substance obtained from the test solution

A_S: The area of the major peak obtained from the standard solution

C_S: Concentration (mg/L) of letrozole in the standard solution

C_T: Concentration (mg/mL) of letrozole in the test solution

Operating conditions

For detector, column, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

System performance: Weigh 2 mg of letrozole related substance I RS and 10 mg of Letrozole RS each, dissolve in 30 mL of acetonitrile, and add water to make 100 mL. To 5.0 mL of this solution, add a mixture of water and acetonitrile (7 : 3) to make 50 mL. Proceed with 15 μL of this solution according to the above conditions; the relative retention times for letrozole related substance I and letrozole are about 0.67 and 1.0, respectively, with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 15 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of letrozole is NMT 10.0%.

Water NMT 0.3% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 20 mg each of Letrozole and letrozole RS, dissolve in 30 mL of acetonitrile, and dissolve by adding water to make exactly 100 mL. To 5.0 mL of these solutions, add a mixture of water and ace-

tonitrile (7 : 3) to make exactly 100 mL, and use these solutions as the test solution and standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of letrozole.

$$\text{Amount (mg) of letrozole } (C_{17}H_{11}N_5) = \text{Amount (mg) of letrozole RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm)

Column: A stainless steel column about 4.6 mm in internal diameter and about 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Use the mobile phases A and B to control stepwise or based on the gradient elution as follows.

Mobile phase A: Water

Mobile phase B: Acetonitrile

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0	70	30
0 - 25	70 → 30	30 → 70

Flow rate: 1.0 mL/min

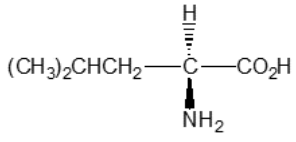
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the symmetry factor of the peak of letrozole is between 0.8 and 1.5.

System repeatability: Repeat the test 5 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of letrozole is NMT 2.0%.

Packaging and storage Preserve in tight containers.

L-Leucine
L-류신



$C_6H_{13}NO_2$: 131.17

(2*S*)-2-Amino-4-methylpentanoic acid [*61-90-5*]

L-Leucine, when dried, contains NLT 98.5% and NMT 101.0% of L-leucine ($C_6H_{13}NO_2$).

Description L-Leucine occurs as white crystals or a crystalline powder. It is odorless or has a slightly characteristic odor and has a bitter taste.

It is freely soluble in formic acid, sparingly soluble in water and practically insoluble in ethanol(95).

It dissolves in dilute hydrochloric acid.

Identification Determine the infrared spectra of L-Leucine and L-Leucine RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +14.5° and +16.0° (after drying, 1 g, 6 mol/L hydrochloric acid TS, 25 mL, 100 mm).

pH Dissolve 1.0 g of L-Leucine in 100 mL of water; the pH of this solution is between 5.5 and 6.5.

Purity (1) ***Clarity and color of solution*—**Dissolve 0.5 g of L-Leucine in 10 mL of 1 mol/L hydrochloric acid TS; the solution is clear and colorless.

(2) ***Chloride*—**Dissolve 0.5 g of L-Leucine in 40 mL of water and 6 mL of dilute nitric acid and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.021%).

(3) ***Sulfate*—**Dissolve 0.6 g of L-Leucine in 40 mL of water and 1 mL of dilute hydrochloric acid and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid (NMT 0.028%).

(4) ***Ammonium*—**Perform the test with 0.25 g of L-Leucine. Prepare the control solution with 5.0 mL of ammonium standard solution (NMT 0.02%).

(5) ***Heavy metals*—**Proceed with 1.0 g of L-Leucine according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(6) ***Iron*—**Dissolve 0.333 g of L-Leucine in water to make 45 mL, add 2 mL of hydrochloric acid, and use this solution as the test solution. To 1.0 mL of iron standard solution, add water to make 45 mL, add 2 mL of hydrochloric acid, and use this solution as the standard solution. Add 50 mg of ammonium peroxydisulfate and 3 mL of 30% ammonium thiocyanate solution to the test solution and the standard solution, respectively, and mix. The color obtained from the test solution is not more intense than that obtained from the standard solution (NMT 30 ppm).

(7) ***Arsenic*—**Prepare the test solution with 1.0 g of L-Leucine according to Method 2 and perform the test (NMT 2 ppm).

(8) ***Related substances*—**Dissolve 0.10 g of L-Leucine in water by warming. After cooling, add water to make 25 mL and use this solution as the test solution. Perform the test as directed under Purity (8) of L-Isoleucine.

Loss on drying NMT 0.3% (1 g, 105 ℃, 3 hours).

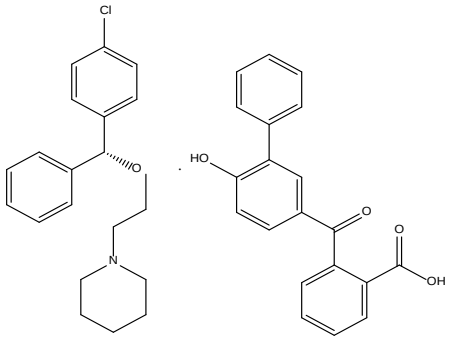
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.13 g of L-Leucine, previously dried, dissolve in 3 mL of formic acid, add 50 mL of acetic acid(100) and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 13.117 mg of $C_6H_{13}NO_2$

Packaging and storage Preserve in well-closed containers.

Levocloperastine Fendizoeate
레보클로페라스틴펜디조산염



$C_{20}H_{24}ClNO \cdot C_{20}H_{14}O_4$: 648.20

2-[(6-Hydroxy[1,1'-biphenyl]-3-yl)carbonyl]-benzoic acid compound with 1-[2-[(*S*)-(4-chlorophenyl)phenylmethoxy]ethyl]piperidine (1:1), [*220329-19-1*]

Levocloperastine Fendizoate contains NLT 95.0% and NMT 101.0% of levocloperastine fendizoate ($C_{20}H_{24}ClNO \cdot C_{20}H_{14}O_4$: 648.20), calculated on the anhydrous basis.

Description Levocloperastine Fendizoate occurs as white or pale yellow crystals or a crystalline powder. It is odorless.
It is slightly soluble in ethanol(95), methanol or pyridine, and practically insoluble in water and ether.

Identification (1) Determine the infrared spectra of Levocloperastine Fendizoeate and levocloperastine fendizoeate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve 20 mg of Levocloperastine Fendizoeate in ethanol(95) to make 100 mL, and determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 202 nm and 206 nm, between 250 nm and 254 nm, and between 286 nm and 290 nm.

Melting point Between 178 and 184 ℃.

Optical rotation $[\alpha]_D^{20}$: Between -4.5° and -5.0° (0.1 g as converted anhydride, dimethylformamide, 10 mL, 100 mm).

Purity (1) ***Chloride***—Add 50 mL of water to 2.0 g of Levocloperastine Fendizoeate, heat at 70 °C for 5 minutes, cool, and filter. Take 25 mL of the filtrate and add 6 mL of dilute nitric acid and water to make 50 mL. Use this as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.1%).

(2) ***Heavy metals***—Proceed with 1.0 g of Levocloperastine Fendizoeate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Dextrocloperastine fendizoate***—Weigh accurately about 10 mg of Levocloperastine Fendizoeate, dissolve it in 10 mL of chloroform, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Perform the test with 20 μL of the test solution as directed under the Liquid Chromatography according to the following conditions. The retention time of dextrocloperastine fendizoate and Levocloperastine Fendizoeate exhibit 6.5 minutes and 7.1 minutes, respectively. Determine the ratio of dextrocloperastine fendizoate by obtaining each peak area value; the amount of dextrocloperastine relative to the total cloperastine fendizoate should be NMT 4.0%.

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 226 nm).

Column: A stainless steel column with an internal diameter of about 4.0 mm and a length of about 25 cm, packed with octadecylsilanized silica gel for chiral separationliquid chromatography.

Mobile phase: A mixture of hexane and isopropanol (98 : 2).

Flow rate: 0.8 mL/min

(4) ***β-hydroxyethylpiperidine***—Weigh 0.5 g of Levocloperastine Fendizoeate, put it into a 25 mL volumetric flask, add 2 drops of dimethylamine, and add methanol to make 25 mL. Use this solution as the test solution. Separately, weigh 10 mg of *β*-hydroxyethylpiperidine, add methanol to make exactly 100 mL, and use it as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol, acetone and water (98.5 : 1 : 0.5) to a distance of about 15 cm, and air-dry the plate. Apply iodine vapor to the plate; the spots other than the main spots obtained from the test solution are not darker than the spots from the standard

solution.

(5) ***Other Related Substances I***—Weigh accurately 200 mg of Levocloperastine Fendizoeate, add 2 drops of dimethylamine, add methanol to make 10 mL, and use this solution as the test solution. Separately, weigh accurately 20 mg of levocloperastine fendizoeate RS, add 2 drops of dimethylamine, and add methanol to make 10 mL. Pipet 1 mL of this solution, add methanol to make 20 mL, and use this solution as the standard solution. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography, develop the plate with a mixture of ethyl acetate, methanol, 30% ammonia water and water (30 : 10 : 10 : 2) to a distance of 10 cim, and air-dry the plate. Apply ultraviolet light (main wavelength: 254 nm); the spots other than the main spots obtained from the test solution are not larger or darker than the spots from the standard solution (NMT 0.5%).

(6) ***Other Related Substances II***—Weigh accurately about 200 mg of Levocloperastine Fendizoeate, add 2 drops of dimethylamine, add methanol to make 10 mL, and use this solution as the test solution. Separately, weigh accurately 20 mg of levocloperastine fendizoate RS, add 2 drops of dimethylamine, and add methanol to make 10 mL. Pipet 1 mL of this solution, add methanol to make 20 mL, and use this solution as the standard solution. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of toluene, ethyl acetate, methanol, and 30% ammonia water (75 : 15 : 10 : 0.5) to a distance of about 10 cm, and air-dry the plate. Apply iodine vapor to the plate; spots other than the main spots obtained from the test solution are not larger or darker than those from the standard solution (NMT 0.5%).

Water NMT 1% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 1 g of Levocloperastine Fendizoeate, add 100 mL of acetic acid(100) for nonaqueous titration, warm to dissolve, and cool. Then titrate with 0.1 mol/L perchloric acid (indicator: 3 drops of methylrosaniline chloride TS). However, the endpoint of the titration is when the bluish purple color of the solution changes to blue. Perform a blank test in the same manner and make any necessary correction. Calculate the contents of Levocloperastine Fendizoeate by correcting for the purity of the isomer.

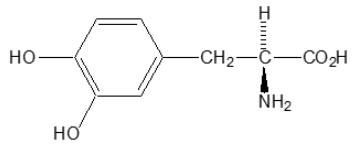
Each mL of 0.1 mol/L perchloric acid VS
= 64.82 mg of $C_{20}H_{24}ClNO \cdot C_{20}H_{14}O_4$

Amount of levocloperastine fendizoate ($C_{20}H_{24}ClNO \cdot C_{20}H_{14}O_4$) (%)
= 64.82 × 0.1 mol/L perchloric acid consumption (mL) × *F* / sampled amount (g)

F: Amount of Levocloperastine Fendizoeate relative to the total amount of cloperastine fendizoate (%)

Packaging and storage Preserve in tight containers.

Levodopa
레보도파



$C_9H_{11}NO_4$: 197.19

(2*S*)-2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid [*59-92-7*]

Levodopa, when dried, contains NLT 98.5% and NMT 101.0% of levodopa ($C_9H_{11}NO_4$).

Description Levodopa occurs as white or pale gray crystals or a crystalline powder, and is odorless.
It is freely soluble in formic acid, slightly soluble in water and practically insoluble in ethanol(95) or ether.
It is soluble in dilute hydrochloric acid.
The pH of the saturated solution of Levodopa is between 5.0 and 6.5.

Melting point—About 275 °C (with decomposition).

Identification (1) To 5 mL of the aqueous solution of Levodopa (1 in 1000), add 1 mL of ninhydrin TS and heat on a steam bath for 3 minutes; the resulting solution exhibits a purple color.

(2) To 2 mL of the aqueous solution of Levodopa (1 in 5000), add 10 mL of 4-Aminoantipyrine TS, and shake well to mix; the resulting solution exhibits a red color.

(3) With the solutions prepared by dissolving 3 mg of Levodopa and Levodopa RS in 0.001 mol/L hydrochloric acid TS to make 100 mL, determine the absorption spectra as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Optical rotation $[\alpha]_D^{20}$: Between -11.5° and -13.0° (after drying, 2.5 g, 1 mol/L hydrochloric acid TS, 50 mL, 100 mm).

Absorbance $E_{1cm}^{1\%}$ (280 nm): Between 136 and 146 (after drying, 30 mg, 0.001 mol/L hydrochloric acid TS, 1000 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Levodopa in 20 mL of 1 mol/L hydrochloric acid TS; the resulting solution is clear and colorless.

(2) ***Chloride***—Dissolve 0.5 g of Levodopa in 6 mL of dilute nitric acid and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.30 mL of 0.01 mol/L

hydrochloric acid (NMT 0.021%).

(3) ***Sulfate***—Dissolve about 0.40 g of Levodopa in 1 mL of dilute hydrochloric acid and 30 mL of water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.25 mL of 0.005 mol/L sulfuric acid (NMT 0.030%).

(4) ***Heavy metals***—Proceed with 1.0 g of Levodopa according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(5) ***Arsenic***—Dissolve about 1.0 g of Levodopa in 5 mL of dilute hydrochloric acid, use this solution as the test solution, and perform the test (NMT 2 ppm).

(6) ***Related substances***—Dissolve about 0.10 g of Levodopa in 10 mL of sodium metabisulfite TS and use this solution as the test solution. Pipet 1 mL of this solution and add sodium metabisulfite TS to make exactly 25 mL. Pipet 1 mL of this solution and add sodium metabisulfite TS to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate made of cellulose for thin-layer chromatography. Next, develop the plate with a mixture of *1*-butanol, water, acetic acid(100) and methanol (10 : 5 : 5 : 1) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly a solution of ninhydrin in acetone solution (1 in 50) on the plate and heat at 90 ℃ for 10 minutes; the spots other than the principal spot from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 0.3% (1 g, 105 °C, 3 hours).

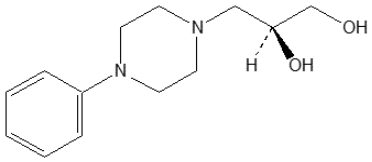
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately 0.3 g of Levodopa, previously dried, dissolve in 3 mL of formic acid, add 80 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 3 drops of methylrosaniline chloride TS). However, the endpoint of the titration is when the purple color of the solution turns to bluish green and then finally to green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 19.719 mg of $C_9H_{11}NO_4$

Packaging and storage Preserve in light-resistant, tight containers.

Levodropropizine
레보드로프로피진



$C_{13}H_{20}N_2O_2$: 236.31
(2*S*)-3-(4-Phenylpiperazin-1-yl)propane-1,2-diol [*99291-25-5*]

Levodropropizine, when dried, contains NLT 98.5% and NMT 101.0% of levodropropizine ($C_{13}H_{20}N_2O_2$).

Description Levodropropizine occurs as a white powder. It is freely soluble in dilute acetic acid and methanol and slightly soluble in water or ethanol(95).

Identification Determine the infrared spectra of Levodropropizine and Levodropropizine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

pH Dissolve 2.5 g of Levodropropizine in 100 mL of water by warming, and cool; the pH of the solution is NLT 9.2 and NMT 10.2.

Optical rotation $[\alpha]_D^{20}$: Between -30.0° and -33.5° (after drying, 1.5 g, 50 mL of 21 mg/mL hydrochloric acid, 100 mm).

Purity (1) ***Related substance I and related substances***—Dissolve 24.0 mg of Levodropropizine in the mobile phase to make 100 mL, and use this solution as the test solution. Separately, dissolve 12.0 mg of Levodropropizine related substance I (1-phenylpiperazine) in methanol to make exactly 100 mL, add the mobile phase to 1.0 mL of this solution to make exactly 100 mL, and use this solution as the standard solution (1). Pipet 0.5 mL of the test solution and 1.0 mL of the standard solution (1), add the mobile phase to make exactly 100 mL, and use this solution as the standard solution (2). Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions; the amount of related substance I obtained from the test solution is not greater than the peak area obtained from the standard solution (1) (0.5%), and the area of other individual peaks is not greater than 0.2 times the peak of related substances I obtained from the standard solution (1) (0.1%). However, exclude any peak areas that are NMT 0.02 times the peak area of related substance I obtained from the standard solution (1).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of phosphate buffer solution and methanol (88 : 12).

Flow rate: 1.5 mL/minute

System suitability

System performance: Proceed with 20 μL of the standard solution (2) according to the above operating conditions; the resolution between peaks of levodropropizine and related substance I is NLT 2.0.

Phosphate buffer solution—Dissolve 6.81 g of potassium dihydrogen phosphate in water to make 1000 mL, add phosphoric acid, and adjust the pH to 3.0.

(2) ***Related substance II*** —Prepare before use. Dissolve 50.0 mg of Levodropropizine in dichloromethane to make exactly 2.5 mL, and use this solution as the test solution. Separately, dissolve 0.20 g of levodropropizine related substance II {[2Rs)-oxirane-2-yl] methanol (glycidol)} in dichloromethane to make exactly 100 mL, add dichloromethane to 0.5 mL of this solution to make exactly 100 mL, and use this solution as the standard solution (1). Dissolve about 0.50 g of Levodropropizine in dichloromethane, add 0.5 mL of the standard solution (1), add dichloromethane to make exactly 2.5 mL, and use this solution as the standard solution (2). Perform the test as directed under the Gas Chromatography with 1 μL each of the test solution and the standard solution (2); the amount of related substance II obtained from the test solution is not greater than 0.5 times the peak area of related substance II obtained from the standard solution.

Operating conditions

Detector: A hydrogen flame-ionization detector

Column: A glass column about 0.53 mm in internal diameter and about 30 cm in length, packed with silica gel covered with for poly [(cyanopropyl)(phenyl)] [demethyl] siloxane for liquid chromatography (3 μm in particle diameter).

Sample injection port temperature: 170 ℃

Detector temperature: 250 °C

Carrier gas: Helium

Flow rate: 2.5 mL/minute

Split ratio: About 1 : 8.

(3) ***Isomer***—Dissolve 10.0 mg of Levodropropizine in 10.0 mL of a mixture of hexane and ethanol (6 : 4), add 1.0 mL of a mixture of hexane and ethanol (6 : 4) to this solution to make exactly 50 mL, and use this solution as the test solution. Separately, dissolve 10.0 mL of Levodropropizine RS in 10.0 mL of a mixture of hexane and ethanol (6 : 4), add a mixture of hexane and ethanol (6 : 4) to 1.0 mL of this solution to make exactly 50 mL, and use this solution as the standard solution (1). Dissolve 10.0 mg of levodropropizine related substance III [(2R)-3-(4-phenylpiperazin-1-yl)propane-1,2-diol (dextrodropropizine)] RS in 10.0 mL of a mixture of hexane and ethanol (6 : 4). To 1.0 mL of this solution, add a mixture of hexane and ethanol (6 : 4) to make exactly 50 mL, and use this solution as the standard solution (2). Pipet 1.0 mL of the standard solution (2), dissolve in a mixture of hexane and ethanol (6 : 4) to make exactly 50 mL, and use this solution as the standard solution (3). Mix 1 mL of the standard solution (1) and 1 mL of the standard solution (2), and use the solution as the standard solution (4). Perform the test with 20 μL each of the test solution, the standard solution (1), the standard solution (3) and the standard solution (4) according to the following conditions as directed under the Liquid Chromatography; the amount of related substance III obtained from the test solution is not greater than the peak area of related substance III obtained from the standard solution (3) (NMT 2%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with optical separation silica gel OD for liquid chromatography.

Mobile phase: A mixture of hexane, ethanol, and diethylamine (95 : 5 : 0.2).

Flow rate: 0.8 mL/minute

System suitability

System performance: Proceed with 20 μL of the standard solution (4) according to the above operation conditions; related substance III and levodropropizine are eluted in this order with the resolution between their peaks being NLT 2.0.

Loss on drying NMT 0.5% (0.5 g, 0.15-0.25 kPa, 60 ℃, oxidated (V), 4 hours).

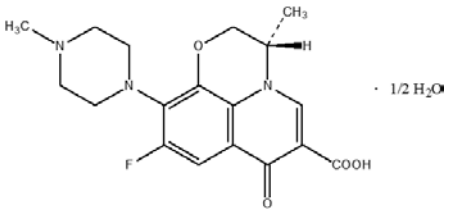
Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately 0.2 g of Levodropropizine, previously dried, dissolve in 50 mL of acetic acid(100), titrate with 0.1 mol/L perchloric acid VS, and determine the consumed volume in the second inflection point (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 11.82 mg of $C_{13}H_{20}N_2O_2$

Packaging and storage Preserve in light-resistant, well-closed containers.

Levofloxacin Hydrate
레보플록사신수화물



$C_{18}H_{20}FN_3O_4 \cdot 1/2H_2O$: 370.38

(3S)-9-Fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid hemihydrate. [*138199-71-0*]

Levofloxacin Hydrate contains NLT 99.0% and NMT 101.0% of levofloxacin ($C_{18}H_{20}FN_3O_4$), calculated on the anhydrous basis.

Description Levofloxacin Hydrate occurs as pale yellowish white to yellowish white crystals or a crystalline powder. It is odorless and has a bitter taste.

It is soluble in acetic acid(100), sparingly soluble in water or methanol, slightly soluble in ethanol, and practically insoluble in ether.

It is affected by light.

Melting point—Between 222 and 230 °C (with decomposition).

Identification (1) Proceed with about 10 mg of Levofloxacin Hydrate as directed under the Oxygen Flask Combustion, using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as the absorbent; the obtained test solution responds to the Qualitative Analysis (2) for fluoride.

(2) Weigh about 10 mg of Levofloxacin Hydrate to powder, dissolve in 2 to 3 drops of dilute hydrochloric acid and 5 mL of water, and add 1 mL of reinecke salt TS; a pale red precipitate develops.

(3) Determine the infrared spectra of Levofloxacin Hydrate as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; it exhibits absorption at the wavenumbers of about 3,430 cm^{-1}, 3,040 cm^{-1}, 2,800 cm^{-1}, 1,724 cm^{-1}, 1,622 cm^{-1}, 1,521 cm^{-1}, 1,471 cm^{-1}, 1,051 cm^{-1} and 803 cm^{-1}.

Optical rotation $[\alpha]_D^{20}$: Between -92° and -100° (calculated on the anhydrous basis, 0.1 g, methanol, 10 mL, 100 mm).

pH The pH of the aqueous solution of Levofloxacin Hydrate (1 in 100) is between 6.8 and 7.6.

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g of Levofloxacin Hydrate in 10 mL of water; the solution is clear and exhibits a pale yellow to yellow color.

(2) ***Heavy metals***—Proceed with 2.0 g of Levofloxacin Hydrate according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Proceed with 2.0 g of Levofloxacin Hydrate according to Method 3 under Arsenic and perform the test (NMT 1 ppm).

(4) ***Related substances***—Perform the test using a light-resistant container. Weigh accurately 50 mg of Levofloxacin Hydrate, dissolve in 10 mL of a mixture of water and methanol (1 : 1), and use this solution as the test solution. Pipet 1 mL of this solution, and add a mixture of water and methanol (1 : 1) to make exactly 10 mL. Pipet 1 mL of this solution, add a mixture of water and methanol (1 : 1) to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each of the solutions according to the automatic integration method; the peak area with the relative retention time to the peak of levofloxacin of about 1.2 in the test solution is not greater than 2/5 times the peak area of levofloxacin in the standard solution, and the peak areas other than the peak of levofloxacin and the peak with the relative retention time to levofloxacin of about 1.2 in the test solution are not greater than 1/5 of the peak area of levofloxacin in the standard solution. Also, the sum of peak areas other than levofloxacin and other than the peak with the relative retention time to levofloxacin of about 1.2 in the test solution is not greater than 3/10 of the peak area of levofloxacin in the standard solution.

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 340 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 45 °C.

Mobile phase: Dissolve 1.76 g of L-valine, 7.71 g of ammonium acetate and 1.25 g of copper(II) sulfate pentahydrate in water, add water to make 1000 mL, and add 250 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of levofloxacin is about 22 minutes.

Time span of measurement: About 2 times the retention time of levofloxacin after the solvent peak.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution, and add a mixture of water and methanol (1 : 1) to make exactly 20 mL. Confirm that the peak area of levofloxacin obtained from 10 μL of this solution is equivalent to 4 to 6% of that of levofloxacin from the standard solution.

System performance: Weigh accurately 10 mg of Ofloxacin, and add a mixture of water and methanol (1 : 1) to make exactly 20 mL. Pipet 1 mL of this solution, and add a mixture of water and methanol (1 : 1) to make exactly 10 mL. Proceed with 10 μL of this solution according to the above conditions; the resolution between levofloxacin and the peak with the relative retention time to levofloxacin of about 1.2 is NLT 3.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the

above conditions; the relative standard deviation of the peak areas of levofloxacin is NMT 3.0%.

Water Between 2.1% and 2.7% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.10% (1.0 g).

Assay Weigh accurately about 0.25 g of Levofloxacin Hydrate, dissolve in 50 mL of acetic acid(100), and titrate with 0.05 mol/L of perchloric acid VS (potentiometric titration). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L perchloric acid VS
= 18.069 mg of $C_{18}H_{20}FN_3O_4$

Packaging and storage Preserve in light-resistant, tight containers.

Levofloxacin Ophthalmic Solution
레보플록사신 점안액

Levofloxacin Ophthalmic Solution is an aqueous ophthalmic solution.

Levofloxacin Ophthalmic Solution contains NLT 95.0% and NMT 107.0% of the labeled amount of levofloxacin hydrate ($C_{18}H_{20}FN_3O_4 \cdot 1/2H_2O$: 370.38).

Method of preparation Prepare as directed under Ophthalmic Solutions, with Levofloxacin Hydrate.

Description Levofloxacin Ophthalmic Solution occurs as a pale yellow to yellow, clear liquid.

Identification (1) Weigh an amount of Levofloxacin Ophthalmic Solution, equivalent to 5 mg of levofloxacin hydrate, according to the labeled amount, and add 0.1 mol/L hydrochloric acid TS to make 100 mL. Take 2 mL of this solution, add 0.01 mol/L hydrochloric acid TS to make 20 mL, and use this solution as the test solution. Determine the absorption spectra of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 225 and 229 nm and 292 and 296 nm.

(2) Weigh an amount of Levofloxacin Ophthalmic Solution, equivalent to 5 mg of levofloxacin hydrate, according to the labeled amount, dissolve in 5 mL of a mixture of water and methanol (1 : 1), and use this solution as the test solution. Separately, dissolve 10 mg of levofloxacin RS in 10 mL of a mixture of water and methanol (1 : 1), and use this solution as the standard solution. Take 10 μL each of the test solution and the standard solution, and perform the test as directed under the Liquid Chromatography according to the following conditions; the retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 340 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 45 °C.

Mobile phase: Dissolve 1.25 g of copper(II) sulfate pentahydrate, 1.76 g of L-valine, and 7.71 g of ammonium acetate in water, add water to make 1000 mL, and add 250 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of levofloxacin is about 22 minutes.

System suitability

System performance: Weigh 10 mg of ofloxacin, dissolve in 20 mL of a mixture of water and methanol (1 : 1), and add a mixture of water and methanol (1 : 1) to 1 mL of this solution to make 10 mL. Proceed with 10 μL of this solution according to the above conditions; the resolution between levofloxacin and the peak with the relative retention time to levofloxacin of about 1.2 is NLT 3.

Sterility It meets the requirements when tested as directed under the membrane filtration method.

Particulate contamination: Visible particles Meets the requirements.

Particulate matter in Ophthalmic Solutions Meets the requirements.

Assay Weigh accurately an amount of Levofloxacin Ophthalmic Solution equivalent to about 5 mg of levofloxacin hydrate ($C_{18}H_{20}FN_3O_4 \cdot 1/2H_2O$) according to the labeled amount, and add exactly 2 mL of the internal standard solution, then add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, determine water for levofloxacin RS in advance. Weigh accurately about 25 mg of levofloxacin RS, dissolve in water to make exactly 50 mL, and take exactly 10 mL of this solution. Add exactly 2 mL of the internal standard solution, then add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, QT and QS, of the peak area of levofloxacin to that of each solution internal standard.

Amount (mg) of levofloxacin hydrate ($C_{18}H_{20}FN_3O_4 \cdot 1/2H_2O$)
$= W_S \times Q_T / Q_S \times 1 / 5 \times 1.025$

WS: Amount (mg) of levofloxacin RS, calculated on the anhydrous basis

1.025: Conversion factor from levofloxacin hydrate

($C_{18}H_{20}FN_3O_4.1/2H_2O$) to levofloxacin anhydrous ($C_{18}H_{20}FN_3O_4$)

Internal standard solution—Naphazoline hydrochloride in the mobile phase (3 in 500).

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 280 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with 5 μm octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 13.61 g of potassium dihydrogen phosphate and 0.77 g of ammonium acetate in 900 mL of water, add 1 mol/L hydrochloric acid to adjust the pH to 3.0, and then add water to make 1000 mL. To 900 mL of this solution, add 100 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of levofloxacin is about 17 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; levofloxacin and the internal standard are eluted in this order with the resolution between these peaks being NLT 5.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the ratios of the peak area of levofloxacin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Levofloxacin Tablets
레보플록사신 정

Levofloxacin Tablets contains NLT 95.0% and NMT 105.0% of the labeled amount of levofloxacin ($C_{18}H_{20}FN_3O_4 \cdot 1/2H_2O$: 370.38).

Method of preparation Prepare as directed under Tablets, with Levofloxacin.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Dissolution Perform the test with 1 tablet of Levofloxacin Tablets at 50 revolutions per minute according to Method 1 under the Dissolution, using 900 mL of the first solution as the dissolution solution. Take the dissolved solution after 30 minutes from the start of the test, and filter. Discard the first 10 mL of the filtrate, take exactly V mL of the next filtrate, add the first solution in the Dissolution so that 1 mL contains about 40 μg of levofloxacin according to the labeled amount to make exactly V' mL, and use this solution as the test solution. Separately, weigh accurately about 40 mg of levofloxacin RS, and dissolve in the first solution in the Dissolution to make 100 mL. Pipet 10 mL of this solution, add the first solution in the Dissolution to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak areas, A_T and A_S of levofloxacin ($C_{18}H_{20}FN_3O_4 \cdot 1/2H_2O$) in each solution, respectively. Meets the requirements if the dissolution rate of Levofloxacin Tablets in 30 minutes is NLT 70%.

$$\text{The dissolution rate (\%) of the labeled amount of levofloxacin } (C_{18}H_{20}FN_3O_4 \cdot 1/2H_2O) = W_S \times V'/V \times A_T/A_S \times 1/C \times 90$$

*W*s: Amount (mg) of levofloxacin RS

C: Labeled amount (mg) of levofloxacin ($C_{18}H_{20}FN_3O_4 \cdot 1/2H_2O$) per tablet

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 294 nm).

Column: A stainless-steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 0.87 g of sodium 1-pentane sulfonate in 1000 mL of a mixture of 0.02 mol/L phosphate buffer solution, pH 2.4, and acetonitrile (8 : 2).

Flow rate: 1.0 mL/min

0.02 mol/L phosphate buffer solution, pH 2.4—Dissolve 3.1 g of sodium dihydrogen phosphate dihydrate in 1000 mL of water, and add diluted phosphoric acid (1 in 10) to adjust the pH to 2.4.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tables of Levofloxacin Tablets, and powder them. Weigh accurately an amount, equivalent to about 50 mg of levofloxacin ($C_{18}H_{20}FN_3O_4 \cdot 1/2H_2O$), and add the mobile phase to make 100 mL. After filtering this solution, take 10 mL of the filtrate, add the mobile phase to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of levofloxacin RS, and put it in the mobile phase to make 100 mL. Take 10 mL of this solution, add the mobile phase to make 100 mL, and use this solution as the standard solution. Perform the test as directed under the Liquid Chromatography with 10 μL each of the test and standard solutions under the following conditions, and determine the peak areas A_T and A of levofloxacin.

The amount (mg) of levofloxacin ($C_{18}H_{20}FN_3O_4 \cdot 1/2H_2O$)
= Amount (mg) of levofloxacin × $\frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 294 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 0.87 g of sodium 1-pentane sulfonate in 1000 mL of a mixture of 0.02 mol/L phosphate buffer solution, pH 2.4, and acetonitrile (8 : 2).

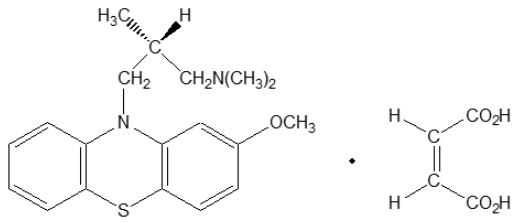
Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of levofloxacin is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Levomepromazine Maleate
레보메프로마진말레산염



$C_{19}H_{24}N_2OS \cdot C_4H_4O_4$: 444.54

(*Z*)-But-2-enedioic acid;(2*R*)-3-(2-methoxy phenothiazin-10-yl)-*N*,*N*,2-trimethylpropan-1-amine [*7104-38-3*]

Levomepromazine Maleate, when dried, contains NLT 98.0% and NMT 101.0% of levomepromazine maleate ($C_{19}H_{24}N_2OS \cdot C_4H_4O_4$).

Description Levomepromazine Maleate occurs as white crystals or a crystalline powder. It is odorless and has a bitter taste.

It is freely soluble in acetic acid(100), soluble in chloroform, sparingly soluble in methanol, slightly soluble in ethanol(95) or acetone, very slightly soluble in water, and practically insoluble in ether.

Melting point—Between 184 and 190 ℃ (with decomposition).

Identification (1) Dissolve 5 mg of Levomepromazine Maleate in 5 mL of sulfuric acid; the resulting solution exhibits a purple color and gradually turns to a dark purple color. To this solution, add 1 drop of potassium dichromate TS; the resulting solution exhibits a brownish orange color.

(2) Add 5 mL of sodium hydroxide TS and 20 mL of ether to 0.2 g of Levomepromazine Maleate, shake well to mix, take the ether layer, wash 2 times with 10 mL each of water, and add 0.5 g of anhydrous sodium sulfate. After filtering, evaporate ether in the filtration on a steam bath, and dry at 105 ℃ for 2 hours; the melting point is between 124 and 128 ℃.

(3) Add 5 mL of water and 2 L of ammonia water(28) to 0.5 g of Levomepromazine Maleate, extract 3 times with 5 mL of chloroform each, take the water layer, and evaporate to dryness. Add 2 to 3 drops of dilute sulfuric acid to the residue, add 5 mL of water, and extract 4 times with 25 mL of ether. Add all the ether extractions and evaporate the ether on a steam bath at 35 ℃ passing through air; the melting point of the residue is between 128 and 136 ℃.

Optical rotation $[\alpha]_D^{20}$: Between -13.5° and -16.5° (after drying, 0.5 g, chloroform, 20 mL, 200 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Levomepromazine Maleate in 10 mL of methanol; the resulting solution is clear and exhibits colorless to pale yellow.

(2) ***Chloride*** —Dissolve 0.5 g of Levomepromazine Maleate in 40 mL of methanol, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 40 mL of methanol, 6 mL of dilute nitric acid and water to 0.40 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.028%).

(3) ***Heavy metals*** —Proceed with 2.0 g of Levomepromazine Maleate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

Loss on drying NMT 0.5% (2 g, 105 °C, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 1 g of Levomepromazine Maleate, previously dried, dissolve in 40 mL of acetic acid(100) and 20 mL of acetone and titrate with 0.1 mol/L perchloric acid VS (indicator: 5 drops of bromocresol green and methylrosaniline chloride TS). However, the endpoint of the titration is when the purple color of this solution turns to bluish purple and then finally to blue. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 44.45 mg of $C_{19}H_{24}N_2OS \cdot C_4H_4O_4$

Packaging and storage Preserve in light-resistant, tight containers.

Levomepromazine Maleate Tablets
레보메프로마진말레산염 정

Levomepromazine Maleate Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of levomepromazine maleate ($C_{19}H_{24}N_2OS \cdot C_4H_4O_4$: 444.55).

Method of preparation Prepare as directed under Tablets, with Levomepromazine Maleate.

Identification (1) Weigh an amount of Levomepromazine Maleate Tablets, equivalent to 40 mg of levomepromazine maleate, previously powdered, add 10 mL of water, shake vigorously to mix, and filter.

(i) Add 2 mL of the filtrate to 0.5 mL of nitric acid; the resulting solution exhibits a dark, purple color.

(ii) Add 1 drop of 2% ferric chloride TS to 2 mL of the filtrate; the solution exhibits a reddish purple color.

(2) Weigh an amount of Levomepromazine Maleate Tablets, equivalent to 25 mg of levomepromazine maleate, previously powdered, add 10 mL of ethanol, shake to dissolve, and filter. Use the filtrate as the test solution. Separately, weigh 25 mg of levomepromazine maleate RS, dissolve in 10 mL of ethanol, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of ethanol and triethylamine (95 : 5) as a developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the colors and the R_f values of the spots obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

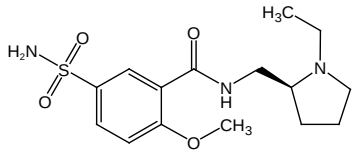
Assay Weigh accurately the mass of NLT 20 Levomepromazine Maleate Tablets, and powder them. Weigh accurately an amount, equivalent to 0.350 g of levomepromazine maleate ($C_{19}H_{24}N_2OS \cdot {}_4H_4O_4$), dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under Titrimetry). Perform a blank test in the same manner, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 4.4455 mg of $C_{19}H_{24}N_2OS \cdot C_4H_4O_4$

Indicator—Add 50 mL of 1.75 mol/L sulfuric acid to 10 mL of 0.01% methyl yellowish ethanol solution to mix.

Packaging and storage Preserve in tight containers.

Levosulpiride
레보설피리드



$C_{15}H_{23}N_3O_4S$: 341.43

5-(Aminosulfonyl)-*N*-[[(2*S*)-1-ethyl-2-pyrrolidinyl]methyl]-2-methoxy-benzamide, [*23672-07-3*]

Levosulpiride, when dried, contains NLT 98.0% and NMT 102.0% of levosulfiride ($C_{15}H_{23}N_3O_4S$: 341.43).

Description Levosulpiride occurs as a white or almost white crystalline powder. It is odorless.
It is freely soluble in dilute acetic acid or 0.5 mol/L sulfuric acid, sparingly soluble in methanol, and very slightly soluble in water.

Identification (1) Weigh 50 mg of Levosulpiride and levosulfiride RS, dissolve in methanol to make 10 mL, respectively, use these solutions as the test and standard solution, and perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and standard solution on a silica gel with fluorescent indicator for thin-layer chromatographic plate. Develop the thin-layer chromatographic plate with a mixture of isopropanol, methanol, and 30% ammonia water (8 : 1 : 1) to a distance of about 15 cm and dry at 100 ℃ for 5 minutes. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots from the test solution and the standard solution are the same in R_f value.

(2) Dry Levosulpiride and levosulfiride RS and perform the test as directed in the potassium bromide purification method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

pH The pH of the solution obtained by suspending 2.5 g of Levosulpiride in 50 mL of freshly boiled and cooled water is between 9.0 and 10.0.

Melting point Between 185 and 189 ℃.

Optical rotation $[\alpha]_D^{20}$: -69° to -66° (after drying, 1.0 g, dimethylformamide, 50 mL, 100 mm).

Purity (1) ***Chloride***—Suspend 0.4 g of Levosulpiride in 20 mL of water by stirring, and filter. Take 10 mL of the filtrate, add 6 mL of dilute nitric acid and water to make 50 mL, and use this solution as the test solution. Prepare the control solution by adding 6 mL of dilute nitric acid and water to 0.2 mL of 0.01 mol/L hydrochloric acid VS to make 50 mL (NMT 0.035%).

(2) ***Heavy metals***—Weigh 1.0 g of Levosulpiride and perform the test according to Method 2. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***N-Ethyl-2-Aminomethylpyrrolidine***—Weigh accurately about 25 mg of Levosulpiride, add 1 mL of 5% sodium hydroxide solution, and shake lightly. Then, add 2 mL of chloroform accurately, shake well for 5 minutes, and take the chloroform layer to use as the test solution. Separately, weigh accurately about 25 mg of *N*-ethyl-2-aminomethylpyrrolidine RS and dissolve in exactly 10 mL of sodium hydroxide solution. Pipet 30 μL of this solution, add 1 mL of 5% sodium hydroxide solution, and shake lightly. Then, add exactly 2 mL of chloroform, shake well for 5 minutes, and take the chloroform layer to use as the standard solution. With 2.5 μL each of the test solution and the standard solution, perform the test as directed under the Gas Chromatography according to the following operating conditions (NMT 0.3%).

Operating conditions

Detector: A flame-ionization detector

Column: A glass hollow capillary column about 0.32 mm in internal diameter and about 15 m in length, the inside coated with methyl silicone polymer for gas chromatography in 0.25 μm thickness.

Column temperature: A constant temperature of about 85 ℃.

Injector temperature: 250 ℃

Carrier gas: Helium

Flow rate: 1.4 mL/min

(4) ***Related Substances***—Weigh accurately about 25 mg of Levosulpiride, add the mobile phase, dissolve it to make exactly 10 mL. Use this solution as the test solution. Separately, weigh accurately about 25 mg each of pyroglutamic acid, 2-methoxy-5-sulfamoylbenzoic acid methyl ester, and levosulfiride RS, add the mobile phase, and dissolve to make exactly 50 mL. Pipet 1 mL of this drug and add the mobile phase to make exactly 100 mL. Use this solution as the standard solution. Perform the test with 10 μL each of the test and standard solutions according to the following operating conditions under the Liquid Chromatography; the contents of pyroglutamic acid and 2-methoxy-5-sulfamoylbenzoic acid methyl ester are NMT 0.2% respectively, the peak area of each unknown related substance relative to the total peak area is NMT 0.2%, and the total peak area of the unknown related material is NMT 0.5%.

Operating conditions

Detector: Ultraviolet absorption photometer (measurement wavelength: 220 nm).

Column: A stainless steel column with an internal diameter of about 5 mm and a length of about 30 cm is filled with 5 to 10 μm octylsilanized silica gel for liquid chromatography.

Column temperature: 45 °C

Mobile phase: A mixture of 0.05 mol/L potassium dihydrogen phosphate solution (pH 6.2), acetonitrile and methanol (6 : 3 : 1).

Flow rate: 1.0 mL/min

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Levosulpiride, previously dried, dissolve it in 30 mL of acetic acid for nonaqueous titration, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration method under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 34.143 mg of $C_{15}H_{23}N_3O_4S$

Packaging and storage Preserve in light-resistant, tight containers.

Levosulpiride Tablets
레보설피리드 정

Levosulpiride Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of levosulpiride ($C_{15}H_{23}N_3O_4S$: 341.43).

Method of preparation Prepare as directed under Tablets, with Levosulpiride.

Identification Weigh an amount of Levosulpiride Tablets, equivalent to 50 mg of levosulpiride, previously powdered, add 10 mL of methanol, shake well to mix, and filter. Use the filtrate as the test solution. Separately, weigh 50 mg of levosulpiride RS, dissolve in methanol to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and standard solution on a silica gel with fluorescent indicator for thin-layer chromatographic plate. Develop the thin-layer chromatographic plate with a mixture of isopropanol, methanol, and 30% ammonia water (8 : 1 : 1) to a distance of about 15 cm, and dry at 100 ℃ for 5 minutes. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values of the spots obtained from the test solution and the standard solution are the same.

Dissolution Take 1 tablet of Levosulpiride Tablets, and perform the test at 100 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of Solution 1 for the Disintegration as the test solution. Take 20 mL of the solution 20 minutes after starting the test to filter, and use this solution as the test solution. Separately, weigh accurately about 30 mg of levosulpiride RS, and dissolve in the test solution to make 100mL. Pipet 5 mL of this solution, add the test solution to make 50 mL, and use this solution as the standard solution. Perform the

test using the test solution and the standard solution according to the Ultraviolet-visible Spectroscopy, and determine the absorbance A_T and A_S at a wavelength of 291 nm. The acceptable dissolution criterion is NLT 80% of Levosulpiride Tablets dissolved in 20 minutes.

Dissolution rate (%) with respect to the labeled amount of levosulpiride ($C_{15}H_{23}N_3O_4S$)
$= W_S \times (A_T / A_S) / C \times 90$

W_S: Amount of levosulpiride RS (mg)
C: Labeled amount (mg) of levosulpiride in 1 tablet

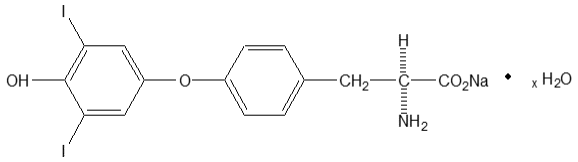
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tables of Levosulpiride Tablets, and powder them. Weigh accurately an amount equivalent to about 0.1 g of levosulpiride ($C_{15}H_{23}N_3O_4$), and add 0.05 mol/L sulfuric acid to make exactly100 mL. Sonicate for 10 minutes to filter, pipet 5 mL of the filtrate, add 0.05 mol/L sulfuric acid to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of levosulpiride RS, proceed in the same manner as in the preparation of the test solution with levosulpiride RS, and use this solution as the standard solution. Perform the test using the test solution and the standard solution according to the Ultraviolet-visible Spectroscopy, and measure the absorbance A_T and A_S at a wavelength of 291 nm.

Amount (mg) of levosulpiride ($C_{15}H_{23}N_3O_4S$)
= Amount (mg) of levosulpiride RS $\times$ (A_T / A_S)

Packaging and storage Preserve in tight containers.

Levothyroxine Sodium Hydrate
레보티록신나트륨수화물



Levothyroxine Sodium $C_{15}H_{10}I_4NNaO_4 \cdot \chi H_2O$
Sodium (2*S*)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]propanoate hydrate
[*25416-65-3*]

Levothyroxine Sodium Hydrate contains NLT 97.0% and NMT 101.0% of levothyroxine sodium hydrate ($C_{15}H_{10}I_4NNaO_4$: 798.85), calculated on the dried basis.

Description Levothyroxine Sodium Hydrate occurs as a pale yellow to pale yellowish brown powder. It is odorless.
It is slightly soluble in ethanol(95) and practically insoluble in water or ether.
It is soluble in sodium hydroxide TS.
It is gradually colored by light.

Identification (1) Heat 0.1 g of Levothyroxine Sodium Hydrate by direct firing; a violet-colored gas is produced.

(2) To 0.5 mg of Levothyroxine Sodium Hydrate, add 8 mL of a mixture of water, ethanol, hydrochloric acid and sodium hydroxide TS (6 : 5 : 2 : 2), and heat on a steam bath for 2 minutes. After cooling, add 0.1 mL of sodium nitrite TS and allow to stand in the dark for 20 minutes. Add 1.5 mL of ammonia water(28) to this solution; the resulting solution exhibits a yellowish red color.

(3) Determine the absorption spectra of the respective solutions of Levothyroxine Sodium Hydrate and Levothyroxine Sodium Hydrate RS in dilute sodium hydroxide TS (1 in 10,000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Wet Levothyroxine Sodium Hydrate with sulfuric acid and incinerate; the obtained residue responds to the Qualitative Analysis (1) and (2) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between -5° and -6° [(0.3 g, calculated on the dried basis, a mixture of ethanol(95) and sodium hydroxide TS (2 : 1), 10 mL, 100 mm].

Purity (1) ***Clarity and color of solution*—**Dissolve 0.3 g of Levothyroxine Sodium Hydrate in 10 mL of a mixture of ethanol(95) and sodium hydroxide TS (2 : 1) by warming; the resulting solution is clear and exhibits pale yellow to pale yellowish brown color.

(2) ***Soluble halide*—**Dissolve 10 mg of Levothyroxine Sodium Hydrate in 10 mL of water and 1 drop of dilute nitric acid, shake for 5 minutes to mix, and filter. Add water to the filtrate to make 10 mL and mix with 3 drops of silver nitrate TS; the resulting solution exhibits no more turbidity than the following control solution.

Control solution—Add 10 mL of water and 1 drop of dilute nitric acid to 0.20 mL of 0.01 mol/L hydrochloric acid and proceed in the same way as below.

(3) ***Related substances*—**Dissolve 20 mg of Levothyroxine Sodium Hydrate in 2 mL of a mixture of ethanol(95) and ammonia water(28) (14 : 1), and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of ethanol(95) and ammonia water(28) (14 : 1) to make exactly 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of *t*-butyl alcohol, *t*-amyl alcohol, water, ammonia water(28) and 2-butanone (59 : 32 : 17 : 15 : 7) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Spray evenly a solution of 0.3 g of ninhydrin dissolved in 100 mL of a mixture of 1-butanol and acetic acid(100) (97 : 3) on the plate, and heat the plate at 100 ℃ for 3 minutes; the spots other than the

principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying Between 7.0% and 11.0% (0.5 g, in vacuum, phosphorus pentoxide, 60 ℃, 4 hours).

Assay Weigh accurately about 25 mg of Levothyroxine Sodium Hydrate and perform the test as directed under the Assay of Liothyronine sodium.

Each mL of 0.02 mol/L sodium thiosulfate VS
= 0.6657 mg of $C_{15}H_{10}I_4NNaO_4$

Packaging and storage Preserve in light-resistant, tight containers.

Levothyroxine Sodium Tablets
레보티록신나트륨 정

Levothyroxine Sodium Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of Levothyroxine Sodium ($C_{15}H_{10}I_4NNaO_4$: 798.85).

Method of preparation Prepare Levothyroxine Sodium Tablets as directed under Tablets, with Levothyroxine Sodium Hydrate.

Identification (1) Weigh an amount of Levothyroxine Sodium Tablets, equivalent to 0.5 g of Levothyroxine Sodium, according to the labeled amount, previously powdered. Add 8 mL of a mixture of water, ethanol, hydrochloric acid and sodium hydroxide VS (6 : 5 : 2 : 2), heat in the water bath for 2 minutes, cool, and filter. To 10 mL of the filtrate, add 0.1 mL of sodium nitrate TS, and allow to stand in the dark for 20 minutes. Add 1.5 mL of ammonia water(28) to this solution; the resulting solution exhibits a yellowish red color.

(2) Weigh an amount of Levothyroxine Sodium Tablets, equivalent to 1 mg of levothyroxine sodium, previously powdered. Add 10 mL of ethanol(95), shake well to mix, filter, and use this solution as the test solution. Separately, weigh 10 mg of Levothyroxine Sodium RS, dissolve in 100 mL of ethanol (100), and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of *t*-butyl alcohol, *t*-amyl alcohol, water, ammonia water(28) and 2-butanone (59 : 32 : 17 : 15 : 7) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Spray evenly a solution of 0.3 g of ninhydrin in 100 mL of a mixture of *1*-butanol and acetic acid (97:3) on the plate, and heat the plate at 100 ℃ for 3 minutes; the spots obtained from the test solution and the standard solution exhibit a reddish purple color, and have the same R_f value.

Purity ***Soluble halides***—Weigh an amount of Levothyroxine Sodium Tablets, equivalent to 2.5 mg of Levothyroxine sodium, previously powdered. Add 25 mL of water, warm at 40 ℃, shake to mix for 5 minutes, add 3 drops of dilute nitric acid, and filter. Add 3 drops of silver nitrate TS to the filtrate; the turbidity of the resulting solution is not more intense than that of the following control solution.

Control solution—Add 25 mL of water and 3 drops of dilute nitric acid to 0.25 mL of 0.01 mol/L hydrochloric acid, and proceed in the same manner as below.

Dissolution Perform the test with 1 tablet of Levothyroxine Sodium Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 500 mL of 0.01 mol/L hydrochloric acid TS containing 0.2% sodium lauryl sulfate with the dissolution medium. Take the dissolved solution after 45 minutes from the start of the test and filter. Discard the first 10 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh an appropriate amount of Levothyroxine Sodium RS, dissolve in methanol to obtain a solution containing 0.1 mg per mL, dilute with the dissolution medium to make it the same concentration as the test solution, and use this solution as the test solution. Perform the test with 800 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of levothyroxine. It meets the requirements when the dissolution rate in 45 minutes is NLT 70% (Q).

The dissolution rate (%) of the labeled amount of Levothyroxine Sodium ($C_{15}H_{10}I_4NNaO_4$)

$$= C_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 50000$$

C_S: Concentration (mg/mL) of the standard solution
C: Labeled amount (mg) of Levothyroxine Sodium ($C_{15}H_{10}I_4NNaO_4$) in 1 tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (1.5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of methanol and 0.1% phosphoric acid (60 : 40).

Flow rate: 2 mL/min

System suitability

System performance: Proceed with 800 μL of the standard solution according to the above conditions; the symmetry factor is NMT 1.5.

System repeatability: Repeat the test 5 times with 800 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of levothyroxine is NMT 4.0%.

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following method. Take 1 tablet of Levothyroxine Sodium Tablets, transfer into a glass-stoppered centrifuge tube, add exactly 10 mL of 0.01 mol/L sodium hydroxide VS, warm at 50 ℃ for 15 minutes, and shake vigorously for 20 minutes to mix. Centrifuge this solution, pipet 5 mL of the clear supernatant, add 1 mL of the internal standard solution, and use it as the standard solution. Perform the test with 20 μL of the test solution as directed under Liquid Chromatography according to the following conditions, and calculate the ratio of the peak area of Levothyroxine Sodium to that of the internal standard.

Internal standard solution—A solution (3 in 40000) of ethinylestradiol in a mixture of acetonitrile and diluted phosphoric acid (1 in 10) (9:1).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 to 230 nm).

Column: A stainless steel column about 4 to 6 mm in internal diameter and 10 to 25 cm in length, packed with octadecyl-silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of methanol, water and phosphoric acid (6700 : 3300 : 5).

Flow rate: Adjust the flow rate so that the retention time of Levothyroxine Sodium is about 9 minutes.

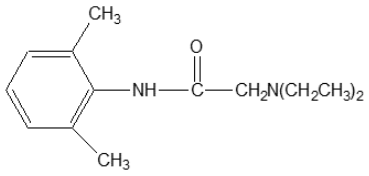
Selection of column: Add 1 mL of the internal standard solution to Levothyroxine Sodium in 5 mL of 0.01 mol/L sodium hydroxide TS (1 in 200000). Proceed with 20 μL of this solution according to the above operating conditions; levothyroxine sodium and the internal standard are eluted in this order with the resolution being NLT 2.

Assay Weigh accurately the mass of NLT 20 Levothyroxine Sodium Tablets, and powder them. Weigh accurately an amount, equivalent to about 3 mg of Levothyroxine Sodium ($C_{15}H_{10}I_4NNaO_4$), add twice the amount of potassium carbonate put and taken in a crucible, and mix well. However, the amount taken is NMT 4 g; add 8 g of potassium carbonate, and mix well. Next, compact the contents by gently tapping the crucible on a table, add 10 g of potassium carbonate to the top again, and tap again to compact it. Ignite the combined mixture in the crucible between 675 and 700 ℃ for 25 minutes and cool. Add 30 mL of water to the crucible, heat gently to boil, and filter it through a flask. Add 30 mL of water to the residue, filter through the flask above, and then wash the carbide on the crucible and funnel with boiling water until the total amount of filtrate reaches 300 mL. Slowly add 7 mL of freshly prepared bromine TS and diluted phosphoric acid (1 in 2) to this solution at a ratio of 3.5 mL per g of potassium carbonate, boil the potassium iodate-starch paper soaked with the generated gas until it doesn't change to blue, wash the inner wall of the flask with water, and boil again for 5 minutes. When boiling, replenish water from time to time to maintain NLT 250 mL of the solution. After cooling, add 5 mL of phenol, wash the inner wall of the flask with water, allow to stand for 5 minutes. and add 2 mL of diluted phosphoric acid (1 in 2) and 5 mL of potassium iodide solution. Immediately titrate the released iodine with 0.01 mol/L sodium thiosulfate VS (indicator: 3 mL of starch TS). Perform a blank test in the same manner, and make any necessary correction.

Each mL of 0.01 mol/L sodium thiosulfate VS
= 0.33286 mg of $C_{15}H_{10}I_4NNaO_4$

Packaging and storage Preserve in light-resistant, tight containers.

Lidocaine
리도카인



$C_{14}H_{22}N_2O$: 234.34

2-(Diethylamino)-*N*-(2,6-dimethylphenyl) acetamide [*137-58-6*]

Lidocaine, when dried, contains NLT 99.0% and NMT 101.0% of lidocaine ($C_{14}H_{22}N_2O$).

Description Lidocaine occurs as white to pale yellow crystals or crystalline powder.
It is very soluble in methanol or ethanol(95), freely soluble in acetic acid(100) or ether and practically insoluble in water.
It dissolves in dilute hydrochloric acid.

Identification (1) Dissolve 40 mg each of Lidocaine and lidocaine RS in 10 mL of 1 mol/L hydrochloric acid TS, add water to make 100 mL, and determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Lidocaine and lidocaine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 66 and 69 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Lidocaine in 2 mL of dilute hydrochloric acid and add water to make 10 mL; the solution is clear and colorless to pale yellow.

(2) ***Chloride*—**Dissolve 0.6 g of Lidocaine in 6 mL of dilute nitric acid and water to make 50 mL, and perform the test, using this solution as the test solution. Prepare the control solution with 0.70 mL of 0.01 mol/L hydrochloric acid (NMT 0.041%).

(3) ***Sulfate*—**Dissolve 0.5 g of Lidocaine in 5 mL of dilute hydrochloric acid and water to make 50 mL, and perform the test using this solution as the test solution. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid, 5 mL of dilute hydrochloric acid and water to make 50 mL (NMT 0.096%).

(4) ***Heavy metals*—**Carbonize 2.0 g of Lidocaine by gentle heating. After cooling, add 10 mL of a solution of magnesium nitrate in ethanol(95) (1 in 10) and burn by firing the ethanol. After cooling, add 1 mL of sulfuric acid, proceed according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Related substances*—**Dissolve 0.10 g of Lidocaine in 2 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 100 mL, and use it as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, 2-butanone, water and formic acid (5 : 3 : 1: 1) to a distance of about 10 cm, air-dry the plate. And dry the plate again at 80 ℃ for 30 minutes. After cooling, examine under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spot from the standard solution.

(6) ***2,6-dimethylaniline*—**Weigh accurately about 50.0 mg of Lidocaine, dissolve in the mobile phase to make exactly 10.0 mL, and use this solution as the test solution. Separately, weigh accurately about 50.0 mg of 2,6-dimethylaniline and dissolve in the mobile phase to make exactly 100.0 mL. Pipet 10.0 mL of this solution and add the mobile phase to make exactly 100.0 mL. Again, pipet 1.0 mL of this solution, add the mobile phase to make exactly 100.0 mL and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. The amount of 2,6-dimethylaniline with the relative retention time to Lidocaine of about 0.40 is NMT 100 ppm.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized amorphous organic silica polymer for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of phosphate buffer (pH 8.0) and acetonitrile (70 : 30).

Flow rate: 1.0 mL/min

Time span of measurement: About 3.5 times the retention time of lidocaine after the solvent peak.

Phosphate buffer (pH 8.0)—Dissolve 4.85 g of potassium dihydrogen phosphate in 1000 mL of water and adjust the pH to 8.0 with sodium hydroxide solution.

Loss on drying NMT 0.5% (1 g, in vacuum, silica gel, 24 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Lidocaine, previously dried, dissolve in 20 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 1 drop of methylrosanilinium chloride TS). The endpoint is when the solution in the purple color changes through the blue color to the bluish green color. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 23.434 mg of $C_{14}H_{22}N_2O$

Packaging and storage Preserve in tight containers.

Lidocaine Injection
리도카인 주사액

Lidocaine Injection is an aqueous solution for injection. Lidocaine Injection contains NLT 95.0% and NMT 105.0% of the labeled amount of Lidocaine Hydrochloride ($C_{14}H_{22}N_2O \cdot HCl$: 270.80).

Method of preparation Prepare as directed under Injections, with Lidocaine and an equivalent amount of Hydrochloric Acid.
No preservative is added in the case of intravenous injections.

Description Lidocaine Injection occurs as a clear, colorless liquid.

pH—Between 5.0 and 7.0.

Identification To Lidocaine Injection, equivalent to 20 mg of lidocaine hydrochloride according to the labeled amount, add 1 mL of sodium hydroxide TS, and extract with 20 mL of hexane. To 10 mL of the hexane extract, add 20 mL of 1 mol/L hydrochloric acid TS and shake vigorously to mix. Determine the absorption spectrum of the water layer as directed under Ultraviolet-visible Spectroscopy; it exhibits a maximum between 261 nm and 265 nm.

Sterility Meets the requirements.

Bacterial endotoxins Less than 1.1 EU per mg of lido-

caine hydrochloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Take exactly an amount of Lidocaine Injection, equivalent to about 0.1 g of Lidocaine Hydrochloride ($C_{14}H_{22}N_2O \cdot HCl$), add exactly 10.0 mL of the internal standard solution and 0.001 mol/L hydrochloric acid TS to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 85 mg of lidocaine RS, previously dried in a desiccator (in vacuum, silica gel) for 24 hours, dissolve in 0.5 mL of 1 mol/L hydrochloric acid TS and a suitable volume of 0.001 mol/L hydrochloric acid TS and add exactly 10.0 mL of the internal standard solution. Then, add 0.001 mol/L hydrochloric acid TS to make exactly 50 mL and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and calculate the ratios, Q_T and Q_S, of the peak area of lidocaine to that of the internal standard for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of Lidocine Hydrochloride } (C_{14}H_{22}N_2O \cdot HCl) = \text{Amount (mg) of lidocaine RS} \times \frac{Q_T}{Q_S} \times 1.1556$$

Internal standard solution—A solution of benzophenone in methanol (1 in 4000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless-steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 2.88 g of sodium lauryl sulfate in 1000 mL of a mixture of 0.02 mol/L phosphate buffer solution, pH 3.0, and acetonitrile (11 : 9).

Flow rate: Adjust the flow rate so that the retention time of lidocaine is about 6 minutes.

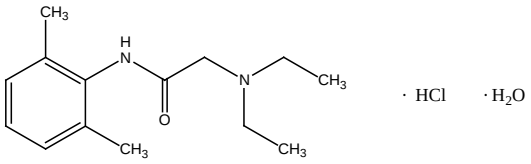
System suitability

System performance: Proceed with 5 μL of the standard solution under the above operating conditions; Lidocaine and the internal standard are eluted in this order with the resolution being NLT 6.0.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution under the above operating conditions; the relative standard deviation of the ratios of peak area of Lidocaine to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in hermetic containers.

Lidocaine Hydrochloride Hydrate
리도카인염산염수화물



Lidocaine Hydrochloride $C_{14}H_{22}N_2O \cdot HCl \cdot H2O$: 288.81
2-(Diethylamino)-*N*-(2,6-dimethylphenyl)
acetamide hydrate hydrochloride [*6108-05-0*]

Lidocaine Hydrochloride Hydrate contains NLT 97.5% and NMT 102.5% of lidocaine hydrochloride ($C_{14}H_{22}N_2O \cdot HCl$: 270.80), calculated on the anhydrous basis.

Description Lidocaine Hydrochloride Hydrate occurs as a white crystalline powder. It is odorless and has a slightly bitter taste.
It is very soluble in water or ethanol(95), freely soluble in chloroform, and practically insoluble in ether.

Identification (1) Put 0.3 g of Lidocaine Hydrochloride Hydrate in a separatory funnel, dissolve in 5 to 10 mL of water, add 4 mL of 6 mol/L ammonium hydroxide TS, and extract 4 times with 15 mL each of chloroform. Combine the extracts, evaporate to concentration, and dry the residue in a silica gel desiccator in vacuum for 24 hours. Determine the infrared spectra of the obtained crystalline precipitate and Lidocaine Hydrochloride Hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak obtained from the test solution corresponds to that from the standard solution, as obtained in the Assay.

(3) An aqueous solution of Lidocaine Hydrochloride Hydrate responds to the Qualitative Analysis (2) for chloride.

Melting point Between 74 and 79 °C.

Purity (1) ***Sulfate***—Dissolve 0.1 g of Lidocaine Hydrochloride Hydrate in 10 mL of water, and use this solution as the test solution. Add 0.10 mL of 0.020 mol/L sulfuric acid to 10 mL of water, and use this solution as the control solution. To each of the test solution and control solution, add 1 mL of 3 mol/L hydrochloric acid and 1 mL of barium chloride TS. The turbidity of the test solution is not more turbid than that of the control solution (NMT 0.1%).

(2) ***Heavy metals***—Proceed with 1.0 g of Lidocaine Hydrochloride Hydrate according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (20 ppm).

Water Between 5.0% and 7.0% (0.2 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1%.

Assay Weigh accurately about 0.1 of Lidocaine Hydrochloride Hydrate, dissolve in the mobile phase to make 50 mL, and use the solution as the test solution. Separately, weigh accurately about 85 mg of Lidocaine RS, dissolve in 0.5 mL of 1 mol/L hydrochloric acid by warming, if necessary, add the mobile phase to make 50 mL, and use this solution as the standard solution. Perform the test with 20 µL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas from the solutions, A_T and A_S, according to the automatic integration method.

$$\text{Amount (mg) of LidicaineHydrochloride } (C_{14}H_{22}N_2O\cdot HCl) = \text{Amount (mg) of lidocaine RS} \times \frac{A_T}{A_S} \times \frac{270.80}{234.34}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 3.9 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 µm in particle diameter).

Column temperature: Between 20 and 25 ℃.

Mobile phase: Mix 50 mL of acetic acid(100) and 930 mL of water, and adjust the pH to 3.4 with 1 mol/L sodium hydroxide solution. Mix about 4 volumes of this solution with 1 part of acetonitrile so that the retention time of Lidocaine is about 4 to 6 minutes.

Flow rate: 1.5 mL/min

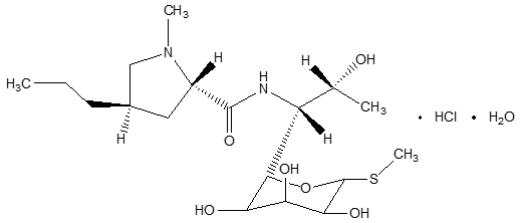
System suitability

System performance: Dissolve 22 mg of methyl *p*-hydroxybenzoate in 100 mL of the mobile phase. Mix 2 mL of this solution with 20 mL of the standard solution. Proceed with 20 µL of this solution under the above operating conditions; the resolution between the peaks of lidocaine and methyl *p*-hydroxybenzoate is NLT 3.

System repeatability: Repeat the test 5 times with 20 µL of the standard solution under the above operating conditions; the relative standard deviation of the peak area of lidocaine is NMT 1.5%.

Packaging and storage Preserve in well-closed containers.

Lincomycin Hydrochloride Hydrate
린코마이신염산염수화물



Lincomycin Hydrochloride

$C_{18}H_{34}N_2O_6S\cdot HCl\cdot H_2O$: 461.01

(2*S*,4*R*)-*N*-[(1*R*,2*R*)-2-Hydroxy-1-[(2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-trihydroxy-6-methylsulfanyloxan-2-yl]propyl]-1-methyl-4-propylpyrrolidine-2-carboxamide hydrate hydrochloride [*7179-49-9*]

Lincomycin Hydrochloride Hydrate is the hydrochloride of a substance having antibacterial activity produced by the growth of *Streptomyces lincolnensis var. lincolnensis*.

Lincomycin Hydrochloride Hydrate contains NLT 825 µg (potency) of lincomycin ($C_{18}H_{34}N_2O_6S$: 406.54) per mg, calculated on the anhydrous basis.

Description Lincomycin Hydrochloride Hydrate occurs as white crystals or a crystalline powder.
It is freely soluble in water or methanol, sparingly soluble in ethanol(95), and very slightly soluble in acetonitrile.

Identification (1) Determine the infrared spectra of Lincomycin Hydrochloride Hydrate and lincomycin hydrochloride hydrate RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Lincomycin Hydrochloride Hydrate (1 in 100) responds to the Qualitative Analysis (2) for chloride.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{25}$: Between +135° and +150° (0.5 g calculated on the anhydrous basis, water, 25 mL, 100 mm).

pH Dissolve 0.1 g of Lincomycin Hydrochloride Hydrate in 1 mL of water; the pH of the solution is between 3.0 and 5.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Lincomycin Hydrochloride Hydrate in 10 mL of water; the solution is colorless and clear.

(2) ***Heavy metal***—Proceed with 2.0 g of Lincomycin Hydrochloride Hydrate according to Method 4 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 5 ppm).

(3) ***Lincomycin B content***—Perform the test with 20 µL each of the test solution, the standard solution (1) and the standard solution (2) as directed under the Liquid

Chromatography according to the following conditions, and determine the peak area of lincomycin and lincomycin B with a relative retention time of about 0.5 with respect to lincomycin; the peak area of lincomycin B is NMT 5.0% of the sum of the peak areas of lincomycin and lincomycin B.

Operating conditions

Proceed as directed under the operating conditions under the Assay.

System suitability

System performance and repeatability: Proceed as directed under the system suitability under the Assay.

Test for required detectability: Pipet 1 mL of the test solution and add the mobile phase to make exactly 20 mL. Confirm that the peak area of lincomycin obtained from 20 μL of this solution is between 3.5% and 6.5% of the peak area of lincomycin obtained from 20 μL of the test solution.

Water Between 3.0% and 6.0% (0.5 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in sterile preparations. However, it is exempt from the requirements where there is a final sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins Less than 0.5 EU per mg (potency) of lincomycin hydrochloride when used for the manufacturing of sterile preparations.

Histamine It meets the requirements when used in sterile preparations. Weigh an appropriate amount of Lincomycin Hydrochloride Hydrate, dissolve in isotonic sodium chloride injection to prepare a solution containing 3.0 mg (potency) per mL, and use the solution as the test solution.

Assay Weigh accurately about 10 mg (potency) each of Lincomycin Hydrochloride Hydrate and lincomycin hydrochloride RS, dissolve each in the mobile phase, add the mobile phase to make exactly 10 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of lincomycin.

$$\text{Potency (μg) of lincomycin } (C_{18}H_{34}N_2O_6S) = \text{Potency of lincomycin hydrochloride RS (μg)} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 46 °C.

Mobile phase: Add 13.5 mL of phosphoric acid in water to make 1000 mL, and adjust the pH to 6.0 with ammonia TS. To 780 mL of this solution, add 150 mL of acetonitrile and 150 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of lincomycin is about 9 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the number of theoretical plates of lincomycin is NLT 4000, and the symmetry factor is NMT 1.3.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas for lincomycin is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Lincomycin Hydrochloride Capsules
린코마이신염산염 캡슐

Lincomycin Hydrochloride Capsules contain NLT 90.0% and NMT 120.0% the labeled amount of lincomycin ($C_{18}H_{34}N_2O_6S$: 406.54).

Method of preparation Prepare as directed under Capsules, with Lincomycin Hydrochloride Hydrate.

Identification (1) Weigh an amount equivalent to 50 mg (potency) of lincomycin hydrochloride and 50 mg (potency) of lincomycin hydrochloride RS according to the labeled amount, and dissolve in 10 mL of methanol, and use this solution as the test solution and the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of 2-butanone, acetone, and water (8 : 4 : 1) to a distance of about 10 cm and air-dry the plate. Spray 0.5% potassium permanganate, and spray 0.2% bromophenol blue solution after 10 minutes; the R_f values and colors of the blue spots from the test solution and the standard solution are the same.

(2) In the chromatogram obtained by performing the test as directed under the Assay, the ratio of the retention time of the internal standard from the test solution and the standard solution to that of lincomycin are the same.

Water NMT 7.0% (0.2 g, volumetric titration, direct titration).

Dissolution Perform the test with 1 capsule of Lincomycin Hydrochloride Capsules at 100 revolutions per minute according to Method 1, using 500 mL of water as the dissolution medium. Take the dissolved solution after 45

minutes from the start of the test and filter. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add the dissolution medium to make exactly *V′* mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of lincomycin RS, dissolve it in the dissolution medium to make it the same concentration as the test solution, and use this solution as the standard solution. Perform the test as directed under the Assay under Lincomycin Hydrochloride Hydrate with the test solution and the standard solution. It meets the requirements if the dissolution rate in 45 minutes is NLT 75% (Q).

Dissolution rate (%) with respect to the labeled amount of lincomycin ($C_{18}H_{34}N_2O_6S$)

$$= C_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 50000$$

Cs: Concentration [mg (potency)/mL] of the standard solution

C: Labeled amount [mg (potency)] of lincomycin ($C_{18}H_{34}N_2O_6$) in 1 capsule

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately an amount equivalent to about 0.1 g (potency) according to the marked potency of Lincomycin Hydrochloride Capsules, and use the mobile phase to make exactly 100 mL, and perform the test in the Assay under Lincomycin Hydrochloride Hydrate.

Potency (μg) of lincomycin ($C_{18}H_{34}N_2O_6S$)
= Potency (μg) of lincomycin hydrochloride hydrate RS

$$\times \frac{A_T}{A_S} \times 10$$

Packaging and storage Preserve in tight containers.

Lincomycin Hydrochloride Injection
린코마이신염산염 주사액

Lincomycin Hydrochloride Injection is an aqueous injection and contains NLT 93.0% and NMT 107.0% of the labeled amount of lincomycin ($C_{18}H_{34}N_2O_6S$: 406.54).

Method of preparation Prepare as directed under Injections, with Lincomycin Hydrochloride Hydrate.

Description Lincomycin Hydrochloride Injection occurs as a colorless and clear liquid.

Identification (1) Weigh an amount equivalent to 30 mg (potency) of Lincomycin Hydrochloride Hydrate according to the labeled amount of Lincomycin Hydrochloride Injection, add 30 mL of water, and use this solution as the test solution. Separately, dissolve 10 mg (potency) of lincomycin hydrochloride RS in 10 mL of water, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, dissolve 150 g of ammonium acetate in 800 mL of water, adjust the pH to 9.6 with ammonia water(28), and add water to make 1000 mL. To 80 mL of this solution, add 40 mL of 2-propanol and 90 mL of ethyl acetate, shake to mix, develop the plate with the upper layer as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray evenly potassium permanganate solution (1 in 1000) on the plate; the R_f values of the principal spot obtained from the test solution and the spot obtained from the standard solution are the same.

(2) Both the test solution and the standard solution exhibit the same retention times in the chromatograms obtained by the test under the Assay.

pH Between 3.0 and 5.5.

Sterility Meets the requirements.

Bacterial endotoxins Lincomycin Hydrochloride Injection is NMT 0.5 EU per mg (potency) of lincomycin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

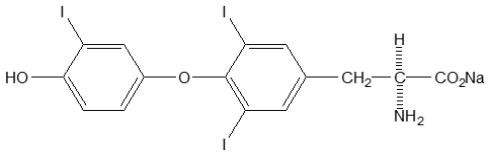
Extractable volume of injections Meets the requirements.

Assay Take exactly an amount of Lincomycin Hydrochloride Injection, equivalent to about 0.1 g (potency) according to the labeled potency, dilute it with the mobile phase to make exactly 100 mL, and perform the test as directed under the Assay of Lincomycin Hydrochloride Hydrate.

Potency (μg) of lincomycin ($C_{18}H_{34}N_2O_6S$)
= Potency (μg) of lincomycin hydrochloride RS $\times \frac{A_T}{A_S} \times 10$

Packaging and storage Preserve in hermetic containers.

Liothyronine Sodium
리오티로닌나트륨



$C_{15}H_{11}I_3NNaO_4$: 672.96

Sodium (2*S*)-2-amino-3-[4-(4-hydroxy-3-iodophenoxy)-

3,5-diiodophenyl]propanoate [*55-06-1*]

Liothyronine Sodium contains NLT 95.0% and NMT 101.0% of Liothyronine Sodium ($C_{15}H_{11}I_3NNaO_4$), calculated on the dried basis.

Description Liothyronine Sodium occurs as a white to pale brown powder, which is odorless.
It is slightly soluble in ethanol(95) and practically insoluble in water or ether.
It dissolves in sodium hydroxide TS or ammonia TS.

Identification (1) To 5 mL of a solution of Liothyronine Sodium in ethanol(95) (1 in 1000), add 1 mL of ninhydrin TS and warm on a steam bath for 5 minutes; the resulting solution exhibits a violet color.

(2) Weigh 20 mg of Liothryonine Sodium, add 2 to 3 drops of sulfuric acid, heat over a flame; it produces violet gas.

(3) Determine the absorption spectra of Liothyronine Sodium and a solution of Liothyronine Sodium RS in ethanol(95) (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Ignite 20 mg of Liothyronine Sodium to carbonize. After cooling, add 5 mL of water to the residue, shake to mix, and filter; the filtrate responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between +18° and +22° (0.2 g, calculated on the dried basis, a mixture of ethanol(95) and 1 mol/L hydrochloric acid TS (4 : 1), 10 mL, 100 mm).

Purity (1) ***Chloride***—Transfer 0.1 g of Liothyronine Sodium, previously dried, to a platinum dish and incinerate while preventing the dish from the contact of air currents. When carbonized, allow it to cool, coat with 2 drops of water, and break up with a glass rod. Add 10 mL of water and 5 mL of ammonia water(28) to mix and transfer to a 50-mL flask. Wash the residue on the platinum dish with water and transfer to the flask to make a total volume of 25 mL. Add 10 mL of silver chloride solution (1 in 20), shake, then filter, and transfer to a Nessler cylinder. Wash the flask and filter paper with 10 mL of water and add the washings to the Nessler cylinder to combine. Put nitric acid to oxidize and dilute with 50 mL of water. Separately, mix 5 mL of ammonia water(28), 20 mL of water and 10 mL of silver nitrate solution (1 in 20), filter the mixture, and transfer the filtrate to a Nessler cylinder. Wash the filter paper with 10 mL of water and add the washings to the Nessler cylinder to combine. Oxidize with nitric acid, dilute with water to make 50 mL, and use this solution as the control solution. Add sodium chloride solution (1 in 1000) to the control solution until the turbidity of the control solution becomes identical to that of the test solution; the volume consumed is NMT 2.0 mL (NMT 1.2%).

(2) ***Soluble halide***—To 10 mg of Liothyronine Sodium, add 10 mL of water and 1 drop of dilute nitric acid, shake for 5 minutes, and filter. Add water to the filtrate to make 10 mL and add 3 drops of silver nitrate TS to mix; the resulting solution is not more turbid than the following control solution.

Control solution—To 0.35 mL of 0.01 mol/L hydrochloric acid, add 1 drop of dilute nitric acid and water to make 10 mL and add 3 drops of silver nitrate TS.

(3) ***Iodine and iodide***—Dissolve 0.1 g of Liothryonine Sodium in 10 mL of dilute sodium hydroxide TS and 15 mL of water, add 5 mL of dilute sulfuric acid, shake occasionally to mix, and allow to stand for 10 minutes. Next, filter the mixture, transfer the filtrate into a Nessler cylinder, and add 10 mL of chloroform and 3 drops of potassium iodide solution (1 in 100). After shaking to mix for 30 seconds, allow to stand; the color of the chloroform solution is not more intense than that of the following control solution.

Control solution—Weigh exactly 0.111 g of potassium iodide and dissolve in water to make 1000 mL. Pipet 1 mL of this solution and add 10 mL of dilute sodium hydroxide TS, 14 mL of water and 5 mL of dilute sulfuric acid. After shaking to mix, filter the mixture, transfer the filtrate into a Nessler cylinder, and perform the test in the same manner as below.

(4) ***Related substances***—Dissolve 0.15 g of Liothyronine Sodium in 5 mL of diluted ammonia TS (1 in 3) and use this solution as the test solution. Pipet 1 mL of this solution, add diluted ammonia TS (1 in 3) to make exactly 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 1 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of t-butyl alcohol, t-amyl alcohol, water, ammonia water(28) and 2-butanone (59 : 32 : 17 : 15 : 7) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Spray evenly a solution, made by dissolving 0.3 g of ninhydrin in 100 mL of a mixture of *1*-butanol and acetic acid(100) (97 : 3), on the plate and heat at 100 °C for 3 minutes; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 4.0% (0.2 g, 105 °C, 2 hours).

Assay Weigh accurately about 25 mg of Liothyronine Sodium and prepare the test solution as directed under the Oxygen Flask Combustion, using a mixture of 10 mL of sodium hydroxide (1 in 100) and 1 mL of a freshly prepared solution of sodium bisulfate (1 in 100) as the absorbent. Put a small amount of water in the upper part of apparatus A, take out C with caution, and wash C, B and the inner wall of A with 40 mL of water. To this solution, add 1 mL of bromine-acetic acid TS, insert the stopper C, and shake vigorously for 1 minute, and wash C, B and the inner wall of A with 40 mL of water and add 0.5 mL of

formic acid. Stopper the flask with C again, shake vigorously for 1 minute, and wash C, B and the inner wall of A with 40 mL of water. Bubble the solution with enough nitrogen gas in the flask to remove the oxygen and excess bromine, and dissolve in 0.5 g of potassium iodide. Add 3 mL of dilute sulfuric acid immediately, shake to mix, allow to stand for 2 minutes, and titrate with 0.02 mol/L sodium thiosulfate VS (indicator: 3 mL of starch TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.02 mol/L sodium thiosulfate VS
= 0.7477 mg of $C_{15}H_{11}I_3NNaO_4$

Packaging and storage Preserve in light-resistant, tight containers.

Liothyronine Sodium Tablets
리오티로닌나트륨 정

Liothyronine Sodium Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of liothyronine sodium ($C_{15}H_{11}I_3NNaO_4$: 672.96).

Method of preparation Prepare Levothyroxine Sodium Tablets as directed under Tablets, with Levothyroxine Sodium.

Identification (1) To a glass-stoppered centrifuge tube, add a portion of finely powdered Liothyronine Sodium Tablets, equivalent to 0.1 mg of Liothyronine Sodium, according to the labeled amount, add 30 mL of dilute sodium hydroxide TS, shake vigorously, and centrifuge. Put the clear supernatant in a separatory funnel, add 10 mL of diluted hydrochloric acid, and extract twice with 20 mL of ethyl acetate. Filter sequentially each extract using cotton wool with 8 g of anhydrous sodium sulfate placed on the funnel. Evaporate the filtrate on a steam bath to dryness with the aid of a current of nitrogen. Dissolve the residue in 0.5 mL of methanol, and use this solution as the test solution. Separately, weigh 10 mg of liothyronine sodium for thin-layer chromatography, dissolve in methanol to make 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of t-butyl alcohol, t-amyl alcohol, water, ammonia water(28) and 2-butanone (59 : 32 : 17 : 15 : 7) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Spray evenly a solution of 0.3 g of ninhydrin in 100 mL of a mixture of *1*-butanol and acetic acid (97:3) on the plate, and heat the plate at 100 ℃ for 3 minutes; the spots obtained from the test solution and the standard solution exhibit a reddish purple color, and have the same R_f value.

(2) The colored solution obtained in the Assay exhibits a blue color.

Disintegration Meets the requirements.

Uniformity of dosage units It meets the requirements when tested according to the following procedure. Put 1 tablet of Liothyronine Sodium Tablets in a glass-stoppered centrifuge tube, add exactly 10 mL of 0.01 mol/L sodium hydroxide TS, warm at 50 ℃ for 15 minutes, and shake vigorously to mix for 20 minutes. Centrifuge Liothyronine Sodium Tablets for 5 minutes, and filter the clear supernatant, if necessary. Take exactly an appropriate amount of this solution, and add 0.01 mol/L sodium hydroxide VS to make a solution containing about 0.5 μg of Liothyronine Sodium ($C_{15}H_{11}I_3NNaO_4$) per mL. Pipet 5 mL of this solution, add exactly 1 mL of the internal standard solution, and use this solution as the test solution. Perform the test with 200 μL of the test solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak area of the liothyronine to that of the internal standard.

Internal standard solution—A solution of propylparahydroxybenzoate in a mixture of methanol and diluted phosphoric acid (9 : 1) (1 in 250000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of methanol and water (57 : 43).

Flow rate: Adjust the flow rate so that the retention time of liothyronine is about 9 minutes.

System suitability

System performance: Add 1 mL of the internal standard solution to liothyronine sodium in 5 mL of 0.01 mol/L sodium hydroxide TS (1 in 200000), and use this solution as the system suitability solution. Proceed with 200 μL of this solution as directed under the above operating conditions; the internal standard and liothyronine are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 200 μL each of the system suitability solution according to the above conditions; the relative standard deviation of the ratios of the peak area of liothyronine to that of the internal standard is NMT 1.0%.

Assay Weigh accurately NLT 20 Losartan Potassium Tablets, and powder them. Put a portion of the powder accurately weighed, equivalent to about 50 mg of liothyronine sodium ($C_{15}H_{11}I_3NNaO_4$), in an agate mortar, add 1 g of powdered potassium carbonate, and mix well. Transfer the mixture cautiously to a porcelain crucible,

and compact the contents by gently tapping the crucible on a table. Add an additional 1.5 g of powdered potassium carbonate to the same agate mortar, mix well with any content adhering to the mortar, cautiously overlay the mixture on the top of the same porcelain crucible, and compact the contents again in the same manner. Ignite the combined mixture between 675 and 700 ℃ for 30 minutes. Add water after cooling, heat gently to boil, and filter the contents through a glass filter (G4) into a 20-mL volumetric flask. Wash the residue with water and combine the washings with the filtrate. Add water after cooling to make 20 mL, and use this solution as the test solution. Separately, weigh accurately about 75 mg of potassium Iodide RS, previously dried at 105 ℃ for 4 hours, and dissolve in water to make exactly 200 mL. Take exactly 5 mL of the solution, add a solution of potassium carbonate (1 in 8) to make exactly 100 mL, pipet 2 mL of this solution, add a solution of potassium carbonate (1 in 8) to make exactly 20 mL, and use this solution as the standard solution. Pipet 5 mL each of the test solution and the standard solution into glass-stoppered test tubes, add 3.0 mL of diluted sulfuric acid (4 in 25) and 2.0 mL of potassium permanganate TS, and heat on a steam bath for 15 minutes. Add 1.0 mL of diluted sodium nitrite TS (1 in 10) after cooling, shake to mix, and add 1.0 mL of a solution of ammonium sulfate (1 in 10). Allow to stand at room temperature for 10 minutes with occasional shaking. Next, add 1.0 mL of potato starch TS and 1.0 mL of a freshly prepared diluted potassium iodide TS (1 in 40), shake to mix, and transfer each solution to a 20-mL volumetric flask. Wash the glass-stoppered test tube with water, combine the washings, add water to make 20 mL, and allow to stand for 10 minutes. Perform the test with these solutions as directed under the Ultraviolet-visible Spectroscopy, using a solution prepared with 5 mL of potassium carbonate (1 in 8) in the same manner as the test solution as a control solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution at the absorbance maximum wavelength of about 600 nm, respectively.

$$\text{Amount (mg) of Liothyronine Sodium } (C_{15}H_{11}I_3NNaO_4) = \text{Amount (mg) of potassium iodide RS} \times \frac{A_T}{A_S} \times \frac{1}{2000} \times 1.3513$$

Packaging and storage Preserve in light-resistant, tight containers.

Lipase
리파제

Lipase is an enzyme with fat digestion activity, prepared from a useful strain in *Rhizopus japonicus* or Aspergillus; and contains NLT 90.0% of the digestive power unit.

Description Lipase occurs as a white to grayish white or pale yellowish brown powder and has a characteristic odor.

Identification Lipase shows positive when tested according to the Assay.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Lipase according to Method 2 under the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Lipase according to Method 3 under the Arsenic and perform the test (NMT 2 ppm).

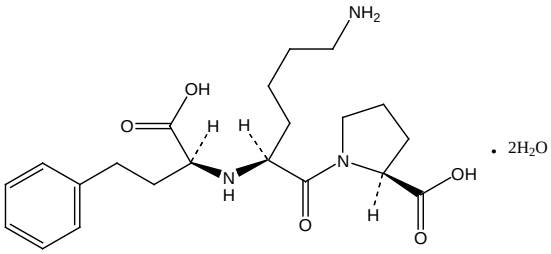
Loss on drying NMT 8.0% (1 g, 105 ℃, 4 hours).

Residue on ignition NMT 20.0% (1 g, constant weight).

Assay Dissolve Lipase in water to make 1 to 5 fat digestion activity unit/mL, and use this solution as the test solution. Weigh 20 g of polyvinyl alcohol (average degree of polymerization 1725 ± 25, content 95.0 ± 1.0%) to prepare the emulsifier according to the Fat digestion activity under the Digestive Power. Prepare the substrate solution according to the Fat digestion activity under the Digestive Power. Prepare the buffer using phosphate buffer of pH 6.0 and perform the test according to the Fat digestion activity under the Digestive Power.

Packaging and storage Preserve in tight containers.

Lisinopril Hydrate
리시노프릴수화물



$C_{21}H_{31}N_3O_5 \cdot 2H_2O$: 441.52

(2*S*)-1-[(2*S*)-6-Amino-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]hexanoyl]pyrrolidine-2-carboxylic acid dihydrate [*83915-83-7*]

Lisinopril Hydrate contains NLT 98.0% and NMT 101.0% of lisinopril ($C_{21}H_{31}N_3O_5$: 405.49), calculated on the anhydrous basis.

Description Lisinopril Hydrate occurs as a white crystalline powder and has a slightly distinctive odor.
It is soluble in water, sparingly soluble in methanol and practically insoluble in ethanol(95).

Melting point—About 160℃ (with decomposition).

Identification (1) Determine the absorption spectra of

solutions of Lisinopril Hydrate and Lisinopril Hydrate RS in methanol (1 in 1000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Lisinopril Hydrate and Lisinopril Hydrate RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -43.0° and -47.0° (0.25 g calculated on the anhydrous basis, zinc acetate buffer solution, 0.25 mol/L, pH 6.4, 25 mL, 100 mm).

0.25 mol/L zinc acetate buffer solution—To 600 mL of water, add 150 mL of acetic acid(100) and 54.9 g of zinc acetate dihydrate, mix to dissolve, and add 150 mL of ammonia water(28) while stirring. After cooling at room temperature, add ammonia water(28) to adjust the pH to 6.4, and add water to make 1000 mL.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Lisinopril Hydrate as directed under Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Dissolve 0.10 g of Lisinopril Hydrate in 50 mL of water and use this solution as the test solution. Pipet 3 mL of the test solution, add water to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 15 μL of the test solution and the standard solution as directed under Liquid Chromatography according to the following conditions, and determine each peak area of each solution by the automatic integration method; the peak area with a relative retention time of about 1.2 to Lisinopril in the test solution is not greater than 1/5 of the peak area of Lisinopril in the standard solution, and the peak areas other than those of Lisinopril and the peaks mentioned above are not greater than 2/15 of the peak area of Lisinopril in the standard solution. The total area of related substances other than Lisinopril is not greater than the peak area of Lisinopril from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 20 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (7 μm in particle diameter).

Column temperature: A constant temperature of about 60 °C.

Mobile phase: Control the stepwise or gradient elution by mixing the mobile phases A and B as follows.

Mobile phase A: Diluted 0.05 mol/L sodium dihydrogen phosphate TS (1 in 2).

Mobile phase B: A mixture of diluted 0.05 mol/L sodium dihydrogen phosphate TS (1 in 2) and acetonitrile (3 : 2).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 10	90 → 50	10 → 50
10 - 25	50	50

Flow rate: 1.5 mL/min

System suitability

Test for required detectability: Take 2.5 mL of the standard solution and add water to make 50 mL. Confirm that the peak area of Lisinopril obtained from 15 μL of this solution is within the range of 3.5% to 6.5% of that of Lisinopril obtained from the standard solution.

System performance: Take 10 mg of Lisinopril Hydrate and 2 mL of a solution of anhydrous caffeine (1 in 1000) and add water to make 200 mL. Proceed with 15 μL of this solution according to the conditions; lisinopril and caffeine are eluted in this order with the resolution being NLT 6.

System repeatability: Repeat the test 6 times with 15 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of Lisinopril is NMT 2.0%.

Time span of measurement: About 2.5 times the retention time of Lisinopril after the solvent peak.

Water Between 8.0% and 9.5% (0.3 g, volumetric titration, back titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.66 g of Lisinopril Hydrate, dissolve in 80 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 40.55 mg of $C_{21}H_{31}N_3O_5$

Packaging and storage Preserve in well-closed containers.

Lithium Carbonate
탄산리튬

Li_2CO_3: 73.89

Dilithium carbonate [*554-13-2*]

Lithium Carbonate, when dried, contains NLT 99.5% and NMT 101.0% of lithium carbonate (Li_2CO_3).

Description Lithium Carbonate occurs as a white crystalline powder and is odorless.

It is sparingly soluble in water, slightly soluble in hot water, and practically insoluble in ethanol(95) or in ether. It dissolves in dilute acetic acid.

Dissolve 1.0 g of Lithium Carbonate in 100 mL of water; the pH of the solution is between 10.9 and 11.5.

Identification (1) Dissolve 0.2 g of Lithium Carbonate in 3 mL of dilute hydrochloric acid, add 4 mL of sodium hydroxide TS and 2 mL of sodium monohydrogen phosphate TS; a white precipitate is formed. Add another 2 mL of dilute hydrochloric acid; this precipitate dissolves.

(2) An aqueous solution of Lithium Carbonate (1 in 100) responds to the Qualitative Analysis for carbonate.

(3) Perform the test with Lithium Carbonate as directed under the Flame Coloration (1); the resulting solution exhibits a persistent red color.

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Lithium Carbonate in 10 mL of water by warming; the solution is clear and colorless.

(2) ***Acetic acid-insoluble substances***—Dissolve 1.0 g of Lithium Carbonate in 40 mL of dilute acetic acid, filter the insoluble substances using filter paper for quantitative analysis, wash 5 times each with 10 mL of water, and ignite with the filter paper to incinerate; the amount is NMT 1.5 mg.

(3) ***Chloride***—Weigh 0.40 g of Lithium Carbonate, add 10 mL of water and 7 mL of dilute nitric acid, and dissolve by heating to boiling. After cooling, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.022%).

(4) ***Sulfate***—Weigh 0.40g of Lithium Carbonate, add 10 mL of water and 4 mL of dilute hydrochloric acid, and dissolve by heating to boiling. After cooling, add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid VS (NMT 0.048%).

(5) ***Heavy metals***—Weigh 4.0 g of Lithium Carbonate, add 5 mL of water, dissolve by slowly adding 10 mL of hydrochloric acid while stirring, and evaporate to dryness on a steam bath. To the residue, add 10 mL of water, transfer into the Nessler tube, add 1 drop of phenolphthalein TS, and add ammonia TS until the color of the solution turns slightly red. To this solution, add 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. When preparing the control solution, evaporate 10 mL of hydrochloric acid to dryness, dissolve the residue in 10 mL of water, transfer into the Nessler tube, and add 1 drop of phenolphthalein TS. Add ammonia TS until the solution exhibits a slightly red color, and add 2.0 mL of lead standard solution, 2 mL of dilute acetic acid, and water to make 50 mL (NMT 5 ppm).

(6) ***Sodium***—Weigh accurately about 0.8 g of Lithium Carbonate, dissolve in water to make exactly 100 mL, and use this solution as the sample stock solution. Pipet 25 mL of the sample stock solution, add water to make exactly 100 mL, and use this solution as the test solution. Separately, weigh exactly 25.4 mg of sodium chloride, dissolve in water to make exactly 1000 mL, and use this solution as the standard solution. Pipet 25 mL of the sample stock solution, add exactly 20 mL of the standard solution, add water to make exactly 100 mL, and use this solution as the standard addition solution. Determine the sodium emission intensity under the following conditions using a flame photometer with the test solution and the standard addition solution. Set the wavelength scale to 589 nm, spray the standard addition solution into the flame while it is burning, adjust the sensitivity to make the emission intensity L_S read around 100 on the scale, and determine the emission intensity L_T of the test solution. Next, under the same conditions as before, change the wavelength to 580 nm, determine the emission intensity L_B of the test solution, and calculate the amount of sodium using the following equation; the amount is NMT 0.05%.

$$\text{Content (\%) of sodium (Na)} = \frac{L_T - L_B}{L_S - L_T} \times \frac{W'}{W} \times 100$$

W: Amount (mg) of the sample in 25 mL of the sample stock solution

W': Amount (mg) of the sample in 20 mL of the standard solution

(7) ***Magnesium***—Weigh 5.0 g of Lithium Carbonate, add 20 mL of water, dissolve by slowly adding 15 mL of hydrochloric acid while stirring, and evaporate to dryness on a steam bath. Dissolve the residue in 50 mL of water, filter it if necessary, and use the filtrate as solution A. Separately, evaporate 15 mL of hydrochloric acid to dryness on a steam bath. Proceed in the same manner to obtain the solution, and use this solution as solution B. To 3.0 mL of solution A, add 0.2 mL of titan yellow solution (1 in 1000) and water to make 20 mL, add 5 mL of sodium hydroxide solution (3 in 20), and allow to stand for 10 minutes; the color of the solution is not more intense than the following control solution.

Control solution—Dry magnesium sulfate heptahydrate at 105 ℃ for 2 hours, heat at 450 ℃ for 3 hours, and dissolve 49.5 mg of this substance in water to make 1000 mL. To 6 mL of this solution, add 3 mL of solution B and 0.2 mL of titan yellow solution (1 in 1000) and water to make 20 mL, and proceed in the same manner.

(8) ***Valium***—To 20 mL of solution A of (7), add 6 mL of water, 0.5 mL of dilute hydrochloric acid, 3 mL of ethanol(95), and 2 mL of potassium sulfate TS, and allow to stand for 1 hour; the turbidity of the solution is not more intense than the following control solution.

Control solution—Dissolve 17.8 mg of barium chloride dihydrate in water to make 1000 mL. To 6 mL of this solution, add 20 mL of solution B of (7) and 0.5 mL of dilute hydrochloric acid, and proceed in the same manner.

(9) ***Aluminum***—To 10 mL of solution A of (7), add 10 mL of water and 5 mL of pH 4.5 acetic acid-sodium acetate buffer solution, shake to mix, add 1 mL of L-

ascorbic acid solution (1 in 100), 2 mL of aluminon TS, and water to make 50 mL, and shake well to mix. Allow to stand for 10 minutes; the color of the solution is not more intense than the following control solution.

Control solution—Dissolve 0.1758 g of aluminum potassium sulfate hydrate in water to make 1000 mL. To 1.0 mL of this solution, add 10 mL of solution B of (7) and water to make 20 mL, add 5 mL of pH 4.5 acetic acid-sodium acetate buffer solution, and proceed in the same manner.

(10) ***Iron***—Proceed with 1.0 g of Lithium Carbonate according to Method 2 and perform the test under Method B. However, use 11 mL of dilute hydrochloric acid to make the test solution. Prepare the control solution with 1.0 mL of iron standard solution (NMT 10 ppm).

(11) ***Potassium***—Dissolve 1.0 g of Lithium Carbonate in water to make 100 mL, and use this solution as the test solution. To 5 mL of the test solution, add 1.0 mL of dilute acetic acid, shake well to mix, add 5 mL of sodium tetraphenylborate solution (1 in 30), and shake immediately to mix. Allow to stand for 10 minutes; the turbidity of the solution is not more intense than the following control solution.

Control solution—Dissolve 9.5 mg of potassium chloride in water to make 1000 mL. To 5 mL of this solution, add 1.0 mL of dilute acetic acid, shake well to mix, and proceed in the same manner.

(12) ***Calcium***—Weigh accurately about 5 g of Lithium Carbonate, add 50 mL of water and 15 mL of hydrochloric acid, remove carbon dioxide by boiling, and add 5 mL of ammonium oxalate TS. Add ammonia TS to alkalify the solution. Allow to stand for 4 hours. Filter the precipitate using the glass filter, wash with hot water until the washings is no longer turbid within 1 minute when adding calcium chloride TS, transfer the precipitate with the glass filter into a beaker, and add water to submerge the glass filter. Add 3 mL of sulfuric acid, warm at 70 to 80 ℃, and titrate with 0.02 mol/L potassium permanganate VS until a pale red color persists for 30 seconds; the amount of calcium (Ca: 40.08) is NMT 0.05%.

Each mL of 0.02 mol/L potassium permanganate VS
= 2.0039 mg of Ca

(13) ***Arsenic***—Dissolve 1.0 g of Lithium Carbonate in 2 mL of water and 3 mL of hydrochloric acid, use this solution as the test solution, and perform the test (NMT 2 ppm).

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

Assay Weigh accurately 1 g of Lithium Carbonate, previously dried, add exactly 100 mL of water and 50 mL of 0.5 mol/L sulfuric acid, and remove carbon dioxide by gently boiling. After cooling, titrate excess sulfuric acid with 0.5 mol/L sodium hydroxide VS. However, the endpoint of the titration is when the red color of this solution turns yellow (indicator: 3 drops of methyl red TS). Perform a blank test in the same manner.

Each mL of 0.5 mol/L sulfuric acid VS
= 36.945 mg of Li_2CO_3

Packaging and storage Preserve in well-closed containers.

Lithium Carbonate Capsules
탄산리튬 캡슐

Lithium Carbonate Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of lithium carbonate (Li_2CO_3 : 73.89).

Method of preparation Prepare as directed under Capsules, with Lithium Carbonate.

Identification Weigh the contents of Lithium Carbonate Capsules as directed under the Identification (2) of Lithium Carbonate.

Dissolution Perform the test with 1 capsule of Pentobarbital Sodium Capsules at 100 revolutions per minute according to Method 1, using 900 mL of water as the dissolution medium. Take 900 mL of the dissolved solution 30 minutes after starting the test, add water to make 1000 mL, and filter. Transfer 20 mL of the filtrates to a volumetric flask, add 500 mL of water, 1 drop of hydrochlroric acid and 20 mL of a suitable surfactant solution and mix. Add water to this solution to make exactly 1000 mL and use this solution as the test solution. Perform the test as directed under the Assay.

It meets the requirements if the dissolution rate of Lithium Carbonate Capsules in 30 minutes is NLT 80%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the contents in NLT 20 capsules of Lithium Carbonate Capsules. Weigh accurately a portion of the content, equivalent to about 0.6 g of lithium carbonate (Li_2CO_3) in a volumetric flask, add 40 mL of water and 5 mL of hydrochloric acid and shake until the solid is well disintegrated. Dilute with water to make exactly 1000 mL and filter. Pipet 10 mL of the filtrates, add 800 mL of water, 20 mL of the surfactant solution, and water to make exactly 1000 mL, and use this solution as the test solution. Perform the test as directed under the Assay of Lithium Carbonate Tablets.

$$\text{Amount (mg) of lithium carbonate } (Li_2CO_3) = \text{Amount (mg) of lithium carbonate RS} \times \frac{P_T}{P_S} \times 20$$

Packaging and storage Preserve in well-closed containers.

Lithium Carbonate Tablets
탄산리튬 정

Lithium Carbonate Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of lithium carbonate (Li_2CO_3 : 73.89).

Method of preparation Prepare as directed under Tablets, with Lithium Carbonate.

Identification Perform the test according to the Identification of Lithium Carbonate.

Dissolution Perform the test with 1 tablet of Lithium Carbonate Tablets at 100 revolutions per minute according to Method 1 under the Dissolution, using 900 mL of water as the dissolution medium. Take 900 mL of the dissolved solution 30 minutes after starting the test, add water to make 1000 mL, and filter. Pipet 10 mL of the filtrate, add 500 mL of water, 1 drop of hydrochloric acid and 20 mL of an appropriate surfactant solution, mix, and add water to make exactly 1000 mL. Use this solution as the test solution. Perform the test as directed under the Assay below.
Meets the requirements if the dissolution rate of Lithium Carbonate Tablets in 30 minutes is NLT 80%.

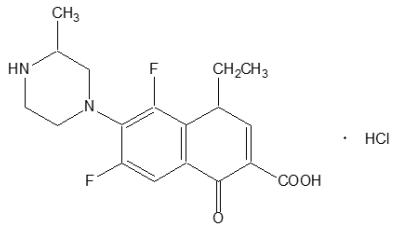
Uniformity of dosage units It has to Meets the requirements.

Assay Weigh accurately NLT 20 Lithium Carbonate Tablets and powder them. Weigh accurately an amount, equivalent to about 0.6 g of lithium carbonate (Li_2CO_3), add 40 mL of water and 5 mL of hydrochloric acid, shake to dissolve, and add water to make exactly 1000 mL. Filter, pipet 10 mL of the filtrate, add 800 mL of water and 20 mL of an appropriate surfactant solution, add water to make exactly 1000 mL, and use this solution as the test solution. Separately, weigh accurately 30 mg of lithium carbonate RS, previously dried at 200 ℃ for 4 hour, add 20 mL of water and 0.5 mL of hydrochloric acid, shake to dissolve, and add water to make exactly 100 mL. Pipet 20 mL of this solution, add 800 mL of water and 20 mL of an appropriate surfactant solution, add water to make exactly 1000 mL and use this solution as the standard solution. Determine the luminescence intensities, P_T and P_S, of the test solution and the standard solution, respectively, at the wavelength of 671 nm, using a flame photometer.

$$\text{Amount (mg) of lithium carbonate } (Li_2CO_3) = \text{Amount (mg) of lithium carbonate RS} \times \frac{P_T}{P_S} \times 20$$

Packaging and storage Preserve in well-closed containers.

Lomefloxacin Hydrochloride
로메플록사신염산염



$C_{17}H_{19}F_2N_3O_3 \cdot HCl$: 387.81
1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid hydrochloride (1:1), [*98079-52-8*]

Lomefloxacin Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of lomefloxacin hydrochloride ($C_{17}H_{19}F_2N_3O_3 \cdot HCl$).

Description Lomefloxacin Hydrochloride occurs as a white to light yellowish white crystalline powder.
It is slightly soluble in water or ethylene glycol, very slightly soluble in methanol and practically insoluble in ethanol(95).
It dissolves in sodium hydroxide TS.
A solution of sodium hydroxide TS of Lomefloxacin Hydrochloride (1 in 40) shows no optical rotation.

Melting point—About 310 ℃ (with decomposition, after drying)

Identification (1) Add 20 mg of Lomefloxacin Hydrochloride in 2 mL of water, heat on a steam bath to dissolve, cool, and add 1 drop of ferric chloride TS; the resulting solution exhibits a red color.

(2) Take 5 mL of an aqueous solution of Lomefloxacin Hydrochloride (1 in 500) and add 1 mL of reinecke salt TS; a pale red precipitate is formed.

(3) Weigh 10 mg of Lomefloxacin Hydrochloride, decompose as directed under the Oxygen Flask Combustion using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as an absorbent, shake well to mix, and absorb the combustion gas; the resulting solution responds to the Qualitative Analysis for fluoride.

(4) Dissolve 10 mg of Lomefloxacin Hydrochloride in 10 mL of sodium hydroxide TS and add water to make 100 mL. Pipet 2.0 mL of this solution and add water to make 20 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 281 nm and 285 nm and between 325 nm and 329 nm, a minimum between 305 nm and 309 nm and absorption at the wavelengths between 330 nm and 340 nm.

(5) Determine the infrared spectra of Lomefloxacin Hydrochloride, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; it exhibits absorption at the wavenumbers of about 3060 cm^{-1}, 2700 cm^{-1}, 2460 cm^{-1}, 1725 cm^{-1}, 1615 cm^{-1} and 808 cm^{-1}.

(6) Dissolve 1 g of Lomefloxacin Hydrochloride in 10 mL of sodium hydroxide TS, add dilute nitric acid to make it acidic, and filter. The filtrate responds to the Qualitative Analysis for chloride.

pH Dissolve 50 mg of Lomefloxacin Hydrochloride in 10 mL of water; the pH of this solution is between 3.0 and 5.0.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Lomefloxacin Hydrochloride under Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Lomefloxacin Hydrochloride under Method 4 and perform the test. However, dissolve the residue after incineration in 10 mL of dilute hydrochloric acid and use this solution as the test solution (NMT 2 ppm).

(3) ***Related substances***—Dissolve 10 mg of Lomefloxacin Hydrochloride in 50 mL of a mixture of phosphate buffer solution, pH 2.5 and methanol (3 : 2), and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of phosphate buffer solution, pH 2.5 and methanol (3 : 2) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 7 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution as directed in the automatic integration; the sum of peak area other than lomefloxacin obtained from the test solution is not greater than 1/10 times of the peak area of lomefloxacin from the standard solution.

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 280 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: Add the phosphate buffer solution, pH 2.5 to a certain amount of methanol to make 1000 mL, add 0.87 g of sodium 1-pentanesulfonate, and shake to mix. However, select the amount of methanol between 370 mL and 420 mL.

Flow rate: Adjust the flow rate so that the retention time of lomefloxacin is about 6 minutes.

Time span of measurement: About 2 times the retention time of lomefloxacin after the solvent peak.

System suitability

System performance: Dissolve 50 mg of Lomefloxacin Hydrochloride, previously dried, in 0.01 mol/L sodium hydroxide TS to make 50 mL. Pipet 5 mL of this solution and add a mixture of phosphate buffer solution, pH 2.5 and methanol (3 : 2) to make 50 mL. Pipet 10 mL of this solution, add 10 mL of a mixture of theophylline phosphate buffer solution, pH 2.5 and methanol (3 : 2) (3 in 20,000), and add the mixture of phosphate buffer solution, pH 2.5 and methanol (3 : 2) to make exactly 50 mL. Proceed with 7 μL of this solution under the above operating conditions; theophylline and lomefloxacin are eluted in this order with the resolution between these peaks being NLT 9.

Detection sensitivity: Adjust so that the peak height of lomefloxacin obtained from 7 μL of the standard solution is between 5 mm and 15 mm.

Loss on drying NMT 0.3% (0.5 g, 105 ℃, 2 hours).

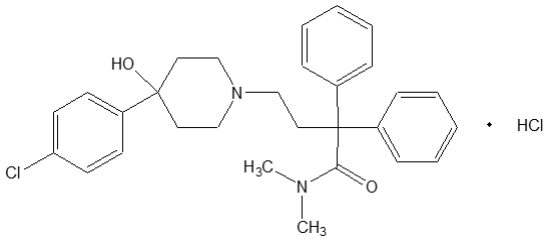
Residue on ignition NMT 0.2% (1 g, platinum crucible).

Assay Weigh accurately about 0.3 g of Lomefloxacin Hydrochloride, previously dried, add 20 mL of a mixture of methanol and ethylene glycol (1 : 1), shake well to mix, add exactly 15 mL of 0.1 mol/L perchloric acid, and heat at 100 ℃ in an oil bath for 90 minutes. After cooling, add 10 mL of methanol and 50 mL of acetonitrile, and titrate with excess perchloric acid with 0.1 mol/L sodium acetate VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 38.781 mg of $C_{17}H_{19}F_2N_3O_3 \cdot HCl$

Packaging and storage Preserve in tight containers.

Loperamide Hydrochloride
로페라미드염산염



$C_{29}H_{33}ClN_2O_2 \cdot HCl$: 513.50

4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]-*N*,*N*-dimethyl-2,2-diphenylbutanamide hydrochloride [*34552-83-5*]

Loperamide Hydrochloride contains NLT 98.0% and NMT 102.0% of loperamide hydrochloride ($C_{29}H_{33}ClN_2O_2 \cdot HCl$), calculated on the dried basis.

Description Loperamide Hydrochloride occurs as a white to pale yellow powder.
It is freely soluble in methanol, 2-propanol and chloroform, and slightly soluble in water or dilute acid.

Melting point—About 225 °C (with decomposition).

Identification (1) Weigh accurately about 40 mg each of Loperamide Hydrochloride and Loperamide Hydrochlo-

ride RS, put each into 100-mL volumetric flasks, dissolve in about 50 mL of 2-propanol, and add 0.1 mol/L hydrochloric acid. And then add 2-propanol to fill to the height of the gauge line. Determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Loperamide Hydrochloride and Loperamide Hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy: both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Chloride content***—Weigh accurately about 13 mg of Loperamide Hydrochloride and perform the test as directed under the Oxygen Flask Combustion. Use a mixture of 10 mL of 0.02 mol/L sodium hydroxide and 2 drops of 30% hydrogen peroxide as an absorbent. When the combustion is complete, wash the inner wall etc. with 50 mL of 2-propanol. Add 4 mL of 0.1 mol/L nitric acid and titrate with 0.01 mol/L mercuric nitrate VS (indicator: diphenylcarbazone TS). The chloride content is NLT 13.52% and NMT 14.20%.

Each mL of 0.01 mol/L mercuric nitrate VS
= 0.3545 mg of Cl

(2) ***Related Substances***—Dissolve Loperamide Hydrochloride and Loperamide Hydrochloride RS in chloroform to make solutions containing 10 mg per mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 10 μL each of these solutions to the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of chloroform, methanol and formic acid (85 : 10 : 5) to a distance of about 15 cm, and air-dry the plate. Examine the plate under iodine steam; R_f value, color and intensity of the principal spot obtained from the test solution are the same as those from the standard solution and no other spots are observed.

(3) ***Heavy metals***—Proceed with 1.0 g of Loperamide Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Loss on drying NMT 0.5% (1 g, in vacuum, 80 ℃, 4 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.4 g of Loperamide Hydrochloride, previously dried, dissolve in 50 mL of ethanol, add 5.0 mL of hydrochloric acid TS, and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Read the consumption between the equivalence point I and the equivalence point 2.

Each mL of 0.1 mol/L sodium hydroxide VS
= 51.35 mg of $C_{29}H_{33}ClN_2O_2 \cdot HCl$

Packaging and storage Preserve in tight containers.

Loperamide Hydrochloride Capsules
로페라미드염산염 캡슐

Loperamide Hydrochloride Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of Loperamide Hydrochloride ($C_{29}H_{33}ClN_2O_2 \cdot HCl$: 513.51).

Method of preparation Prepare as directed under Capsules, with Loperamide Hydrochloride.

Identification (1) Weigh an amount of Loperamide Hydrochloride Capsules equivalent to about 10 mg of Loperamide Hydrochloride according to the labeled amount, dissolve in 10 mL of methanol, shake for 5 minutes, and filter. Use this solution as the test solution Separately, dissolve Loperamide Hydrochloride RS in methanol to obtain a solution having known concentration of 10 mg per mL and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL of the test solution and 1 μL of the standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate using a mixture of chloroform, methanol and formic acid (85 : 10 : 5) as the developing solvent to a distance of about 15 cm, dry at 40 to 60 ℃ and expose to fumes of iodine. Examine the plate under the iodine fume; the R_f values of the spots obtained from the test solution and the standard solution are the same.

(2) The retention times of the major peaks obtained from the test solution and the standard solution obtained under the Assay are the same.

Dissolution Perform the test with 1 capsule of Loperamide Hydrochloride Capsules at 100 revolutions per minute according to Method 1 under the Dissolution test. Mix 200 mL of 1 mol/L acetic acid TS and 600 mL of water, adjust the pH to 4.70 ± 0.05 with 1 mol/L sodium hydroxide TS and dilute with water to make 1000 mL. Take the dissolved solution after 30 minutes from the start of the dissolution test and use the filtrate as the test solution. Separately, weigh Loperamide Hydrochloride RS, previously dried at 80 ℃ for 4 hours in vacuum and dissolve at the same concentration as the test solution and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Assay.
It meets the requirements if the dissolution rate of Loperamide Hydrochloride Capsules in 30 minutes is NLT 80%.

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed as directed under the Assay.

Assay Weigh accurately the contents of NLT 20 capsules of Loperamide Hydrochloride Capsules. Weigh accurately an amount equivalent to about 10 mg of Loperamide Hydrochloride in diluted methanol (7 in 10) to make exactly 50 mL and treat under the supersonic wave for 15 minutes and filter. Discard the first 10 mL of the filtrate and pipet 10.0 mL of the filtrate, add 4.0 mL of the internal standard solution and diluted methanol (7 in 10) to make exactly 50 mL and use this solution as the test solution. Separately, take accurately about 10 mg of Loperamide Hydrochloride RS, previously dried for 4 hours at 80 ℃ in vacuum and dissolve in diluted methanol (7 in 10) to make exactly 50 mL. Pipet 10.0 mL of this solution, add 4.0 mL of the internal standard solution and diluted methanol (7 in 10) to make exactly 50 mL and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography.

$$\text{Amount (mg) of Loperamide Hydrochloride } (C_{29}H_{33}ClN_2O_2 \cdot HCl) = \text{Amount (mg) of loperamide Hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh 15 mg of propyl p-hydroxybenzoate, add the diluted methanol (7 in 10), and dissolve to make 50 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column about 4 mm internal diameter and 15 to 30 cm length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

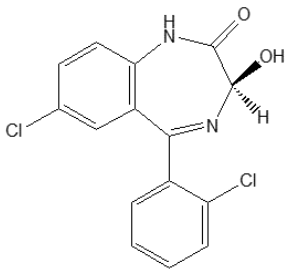
Mobile phase: Dissolve about 1.8 g of anhydrous monosodium phosphate in 300 mL of water, add 700 mL of methanol and adjust the pH to 7.0 by adding phosphoric acid (1 in 100).

Flow rate: Adjust the flow rate so that the retention time of loperamide is about 9 minutes.

Column selection: Proceed with 10 μL of the standard solution according to the above conditions; the internal standard and loperamide are eluted in this order with the resolution being NLT 3.0.

Packaging and storage Preserve in tight containers.

Lorazepam
로라제팜



and enantiomer

$C_{15}H_{10}Cl_2N_2O_2$: 321.16

(*RS*)-7-Chloro-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-1,4-benzodiazepin-2-one [*846-49-1*]

Lorazepam, when dried, contains NLT 98.5% and NMT 101.0% of lorazepam ($C_{15}H_{10}Cl_2N_2O_2$).

Description Lorazepam occurs as a white crystalline powder and is odorless.
It is sparingly soluble in ethanol(95) or in acetone, slightly soluble in ether and practically insoluble in water.
It is gradually colored by light.

Identification (1) Take 20 mg of Lorazepam, add 15 mL of dilute hydrochloric acid, boil for 5 minutes and cool; the resulting solution responds to the Qualitative Analysis for primary aromatic amines.

(2) Determine the absorption spectra of ethanol(95) solutions of Lorazepam and Lorazepam RS (1 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Lorazepam and Lorazepam RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) Perform the Flame Coloration 2) with Lorazepam; it exhibits a green color.

Absorbance $E_{1cm}^{1\%}$ (229 nm): Between 1080 and 1126 (1 mg after drying, ethanol(95), 200 mL).

Purity (1) ***Chloride***—Take 1.0 g of Lorazepam, add 50 mL of water, and allow to stand for 1 hour with occasional shaking, and filter. Pipet 25 mL of the filtrate, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.20 mL of 0.01 mol/L hydrochloric acid (NMT 0.014%).

(2) ***Heavy metals***—Proceed with about 1.0 g of Lorazepam as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Lorazepam as directed under Method 3 and perform the test (NMT 2

ppm).

(4) ***Related substances***—Dissolve about 0.10 g of Lorazepam in 20 mL of ethanol(95) and use this solution as the test solution. Pipet 1 mL of this solution, add ethanol(95) to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, 1,4-Dioxane and acetic acid(100) (91 : 51 : 4) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Observe the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, 105 ℃, 3 hours).

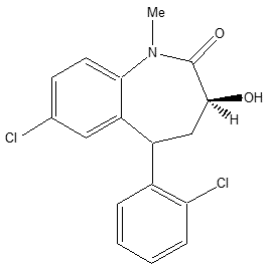
Residue on ignition NMT 0.3% (1 g).

Assay Weigh accurately about 0.4 g of Lorazepam, previously dried, dissolve in 50 mL of acetone, and titrate with 0.1 mol/L tetrabutylammonium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L tetrabutylammonium hydroxide VS
= 32.116 mg of $C_{15}H_{10}Cl_2N_2O_2$

Packaging and storage Preserve in light-resistant, tight containers.

Lormetazepam
로르메타제팜



and enantiomer

$C_{16}H_{12}Cl_2N_2O_2$: 335.19

7-Chloro-5-(2-chlorophenyl)-3-hydroxy-1-methyl-1*H*-benzo[1,4]diazepin-2(3*H*)-one [*848-75-9*]

Lormetazepam contains NLT 99.0% and NMT 101.0% of lometrazepam ($C_{16}H_{12}Cl_2N_2O_2$: 335.19), calculated on the dried basis.

Description Lormetazepam occurs as a white crystalline powder.

It is soluble in methanol or in ethanol and practically insoluble in water.

Identification (1) Determine the infrared spectra of Lormetazepam and Lormetazepam RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the peak obtained from the test solution (2) corresponds to that from the standard solution in the test for related substances.

Purity ***Related substances***—Weigh accurately about 0.250 g of Lormetazepam, add 70% methanol to make exactly 100 mL, and use this solution as the test solution (1). Pipet 1 mL of this solution, add 70% methanol to make exactly 100 mL, pipet 10 mL of this solution again to make 50 mL, and use this solution as the test solution (2). Pipet 25 mL of the test solution (2), add 70% methanol to make exactly 50 mL, and use this solution as the test solution (3). Separately, weigh exactly 5 mg of Lormetazepam RS and dissolve in 70% methanol to make exactly 100 mL. Pipet 5 mL of this solution, add 70% methanol to make 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the area of the peaks from these solutions by the automatic integration method; the peak area other than the major peak obtained from the test solution (1) is not greater than the area of the major peak obtained from the test solution (2) (0.2%), the number of peaks having the area greater than the area of the major peak from the test solution (3) is NMT 2. The total area of these peaks is not greater than 2.5 times the area of the major peak area from the test solution (2) (0.5%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 20 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of phosphate buffer solution and methanol (52 : 48).

Flow rate: 2 mL/min

System suitability

System performance: Weigh 5 mg of Lormetazepam RS, dissolve in 70% methanol to make 100 mL, pipet 5 mL of this solution and add 70% methanol to make 50 mL. Dissolve 25 mL of this solution and lorazepam in 70% methanol, take 25 mL of a solution containing 5 μg per mL, and mix. Proceed with 10 μL of this solution according to the above conditions; the resolution between two major peaks is NLT 4.

Phosphate buffer solution—Weigh 4.91 g of sodium

dihydrogen phosphate and 0.633 g of sodium monohydrogen phosphate in water to make 1000 mL.

Loss on drying NMT 1.0% (1 g, 105 ℃, 3 hours).

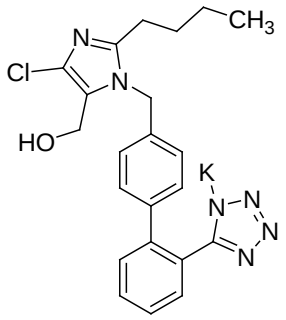
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Lormetazepam, dissolve in 50 mL of nitroethane and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 33.52 mg of $C_{16}H_{12}Cl_2N_2O_2$

Packaging and storage Preserve in light-resistant, tight containers.

Losartan Potassium
로사르탄칼륨



$C_{22}H_{22}ClKN_6O$: 461.00
Potassium [2-butyl-5-chloro-3-[[4-[2-(1,2,3-triaza-4-azanidacyclopenta-2,5-dien-5-yl) phenyl]phenyl]methyl]imidazol-4-yl]methanol [*124750-99-8*]

Losartan Potassium contains NLT 98.5% and NMT 101.0% of losartan potassium ($C_{22}H_{22}ClKN_6O$), calculated on the anhydrous basis.

Description Losartan Potassium occurs as a white crystalline powder.
It is very soluble in water and freely soluble in methanol or ethanol(99.5).

Identification (1) Determine the infrared spectra of Losartan Potassium and Losartan Potassium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the two spectra, dissolve each solution in methanol, evaporate to dryness, and perform the test in the same manner.
Losartan Potassium responds to the Qualitative Analysis (1) for potassium salt.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Losartan Potassium according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Dissolve 30 mg of Losartan Potassium in 100 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution as directed in the automatic integration; the peak area other than the solvent peak and losartan in the test solution is not greater than 1/10 of the peak area of losartan in the standard solution. Also, the total area of the peaks other than losartan in the test solution is not greater than 3/ 10 of the peak area of losartan in the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column 4.0 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: Diluted phosphoric acid (1 in 1000)

Mobile phase B: Acetonitrile

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 25	75 → 10	25 → 90
25 - 35	10	90

Flow rate: 1.0 mL/min

System suitability

Test for required detectability: Pipet 1 mL of the standard solution and add methanol to make exactly 10 mL. Confirm that the peak area of losartan obtained from 10 μL of this solution is equivalent to 7% to 13% of peak area of losartan in the standard solution.

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; the number of theoretical plate of losartan peak are NLT 10000 plates with the symmetry factor being NMT 1.3.

System repeatability: Perform the test six times with 10 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of losartan is NMT 2.0%.

Time span of measurement: For 35 minutes after injecting the test solution.

Water NMT 0.5% (0.25 g, volumetric titration, direct titration).

Assay Weigh accurately about 25 mg each of Losartan Potassium and Losartan Potassium RS (water previously measured), dissolve in methanol to make exactly 100 mL, and use these solutions as the test solution and the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, determine the peak areas, A_T and A_S, of losartan in the test solution and the standard solution, respectively.

Amount (mg) of losartan potassium ($C_{22}H_{22}ClKN_6O$)
= Amount (mg) of losartan Potassium RS, calculated on the anhydrous basis $\times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4.0 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of diluted phosphoric acid (1 in 1000) and acetonitrile (3 : 2).

Flow rate: Adjust the flow rate so that the retention time of losartan is about 6 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; the number of theoretical plates of losartan peak is NLT 5500 plates with the symmetry factor being NMT 1.4.

System repeatability: Repeat the test six times with 10 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of losartan is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Losartan Potassium Tablets
로사르탄칼륨 정

Losartan Potassium Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of losartan potassium ($C_{22}H_{22}ClKN_6O$: 461.01).

Method of preparation Prepare as directed under Tablets, with Losartan Potassium.

Identification Proceed as directed under the Assay described; the test solution shows the peak at the same retention time as the standard solution.

Dissolution Perform the test with 1 tablet of Losartan Potassium Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take the dissolved solution after 45 minutes from the start of the test, and filter. Discard the first 10 mL of the filtrate, take exactly V mL of the next filtrate, add water so that 1 mL contains about 25 μg of losartan potassium according to the labeled amount to make exactly V' mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of losartan potassium RS, dissolve in water to make 100 mL, and pipet 5 mL of this solution. Add water to make 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 256 nm as directed under the Ultraviolet-visible Spectroscopy. Meets the requirements if the dissolution rate of Losartan Potassium Tablets in 45 minutes is NLT 85%.

Dissolution rate (%) with respect to the labeled amount of losartan potassium ($C_{22}H_{22}ClKN_6O$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 45$$

W_S: Amount of losartan potassium RS (mg)

C: Labeled amount (mg) of losartan potassium ($C_{22}H_{22}ClKN_6O$) in 1 tablet

Purity ***Related substances*—**Weigh accurately the mass of NLT 20 tablets of Losartan Potassium Tablets, and powder them. Weigh an amount equivalent to 10 tablets of Losartan Potassium Tablets, transfer to a 2000-mL volumetric flask, and add 0.01 mol/L phosphate buffer solution, pH 8.0. Shake until completely dispersed, fill 0.01 mol/L phosphate buffer solution, pH 8.0, to the gauge line, and filter. Pipet 25.0 mL of this solution, add 0.01 mol/L phosphate buffer solution, pH 8.0, to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 40 mg of losartan potassium RS, and add 0.01 mol/L phosphate buffer solution, pH 8.0, to make exactly 100 mL; pipet 25.0 mL of this solution, and add 0.01 mol/L phosphate buffer solution, pH 8.0, to make exactly 200 mL; pipet 5.0 mL of this solution, and add 0.01 mol/L phosphate buffer solution, pH 8.0, to make exactly 100 mL. Perform the test with exactly 20 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas A_T and A_S of the related substances and the standard solution from the test solution; the amount of each related substance is NMT 0.2%, and the total amount of related substances is NMT 1.0%.

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 230 nm).

Column: A stainless steel column of about 4 mm in internal diameter and 15 cm in length, packed with octa-

decylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: Flow solution B from 0% to 100% from the beginning to 35 minutes, flow solution B at 0% for 5 minutes, and maintain solution B at 0% for at least 10 minutes before injection.

Solution A: A mixture of acetonitrile, water and phosphoric acid (50 : 950 : 1).

Solution B: A mixture of acetonitrile, water and phosphoric acid (900 : 100 : 1).

Flow rate: 1.0 mL/min

Time span of measurement: About 3 times the retention time of losartan potassium after the solvent peak.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tables of Losartan Potassium Tablets, and powder them. Weigh accurately an amount equivalent to about 25 mg of losartan potassium, transfer to a 500-mL volumetric flask, and dissolve in 0.01 mol/L phosphate buffer solution, pH 8.0 to make 500 mL. Centrifuge this solution, and use the clear supernatant as the test solution. Separately, weigh accurately about 25 mg of losartan potassium RS, dissolve in 0.01 mol/L phosphate buffer solution, pH 8.0 to make 500 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of losartan potassium from each solution, A_T and A_S, respectively.

$$\text{Amount (mg) of losartan potassium } (C_{22}H_{22}ClKN_6O) = \text{Amount (mg) of losartan potassium RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 230 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of acetonitrile and 0.01 mol/L phosphate buffer solution, pH 2.5 (40 : 60).

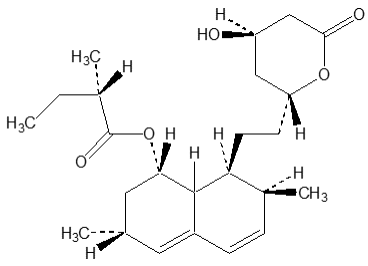
Flow rate: 1.0 mL/min

0.01 mol/L phosphate buffer solution, pH 8.0—Dilute phosphate buffer solution, pH 8.0, 5 times, and add 0.2 mol/L sodium hydroxide to adjust pH to 8.0.

0.01 mol/L phosphate buffer solution, pH 2.5—Dissolve 1.65 g of sodium dihydrogen phosphate dihydrate in 1000 mL of water, and add diluted phosphoric acid (1 in 10) to adjust the pH to 2.5.

Packaging and storage Preserve in tight containers.

Lovastatin
로바스타틴



$C_{24}H_{36}O_5$: 404.54

[(1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-Hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl](2*S*)-2-methyl butanoate [*75330-75-5*]

Lovastatin contains NLT 98.5% and NMT 101.0% of lovastatin ($C_{24}H_{36}O_5$), calculated on the dried basis.

Description Lovastatin occurs as a white crystalline powder.
It is soluble in acetone, sparingly soluble in ethanol(95) and practically insoluble in water.

Identification (1) Dissolve 10 mg each of Lovastatin and Lovastatin RS in acetonitrile to make 100 mL. Pipet 5 mL of these solutions, add acetonitrile to make exactly 50 mL, and use these solutions as the test solution and the standard solution. Determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Lovastatin and Lovastatin RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{25}$: Between +324° and +338° (0.125 g, after drying, acetonitrile, 25 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Lovastatin and perform the test according to Method 2. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Lovastatin related substance I***—Weigh accurately about 25 mg of Lovastatin, dissolve in acetonitrile to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately about 10.0 mg of Lovastatin RS and dissolve in acetonitrile to make 100 mL. Pipet 2.0 mL of this solution, add acetonitrile to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, determine the peak area of Lovastatin and lovastatin related substance I (dihydrolovastatin), and calculate the amount of lovastatin related substances I (NMT

1.0%).

$$\text{Content (\%) of lovastatin related substance I} = 2.5 \times F \times \frac{C}{W} \times \frac{A_T}{A_S}$$

F: Correction factor for lovastatin related substance I (1.6).

C: Concentration (μg/mL) of lovastatin RS in the standard solution

W: Amount (mg) of lovastatin in the test solution

A_T: Peak area of lovastatin related substance I obtained from the test solution

A_S: Peak area of lovastatin obtained from the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 200 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octylsilane silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Flow rate: 1.5 mL/min

Mobile phase: A mixture of acetonitrile and 0.01 mol/L phosphoric acid (13 : 7).

System suitability

System performance: Dissolve 10 mg each of Lovastatin RS and lovastatin related substance I RS in acetonitrile to make 100 mL. Pipet 2.0 mL of this solution and add acetonitrile to make 100 mL. Proceed with 10 μL of this solution according to the above operating conditions; the relative retention times are about 1.0 for lovastatin and 1.3 for lovastatin related substance I with the resolution between these peaks being NLT 6.0.

System repeatability: Perform the test six times with 10 μL each of the standard solution according to the above operating conditions, the relative standard deviation of the peak area for lovastatin is NMT 5.0%.

(3) ***Other related substances***—Weigh accurately about 25 mg of Lovastatin, dissolve in acetonitrile to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of Lovastatin RS and dissolve in acetonitrile to make exactly 100 mL. Pipet 2 mL of this solution, add acetonitrile to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, determine all the peak areas by automatic integration method, and calculate the amount of related substances;. The amount of each related substance is NMT 0.2%, and the total amount of related substances is NMT 1.0%. Exclude any related substances with the amount NMT 0.04%.

$$\text{Content (\%) of related substances} = 2.5 \times F \times \frac{C}{W} \times \frac{A_T}{A_S}$$

F: Correction factor for each related substance (1.4 for related substances with the relative retention time of 0.73; 1.0 for any other related substances)

C: Concentration (μg/mL) of lovastatin RS in the standard solution

W: Amount (mg) of lovastatin in the test solution

A_T: Peak area of each related substance obtained from the test solution

A_S: Peak area of lovastatin obtained from the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 238 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (4 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Flow rate: 1.5 mL/min

Mobile phase: Use mobile phases A and B to control the step or gradient elution as follows.

Mobile phase A: Adjust the pH to 4.0 by adding 1 mol/L sodium hydroxide TS to 0.001 mol/L phosphoric acid.

Mobile phase B: Acetonitrile

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 2	60	40
2 - 5	60 → 45	40 → 55
5 - 8	45	55
8 - 16	45 → 10	55 → 90
16 - 25	10	90
25 - 27	10 → 60	90 → 40
27 - 35	60	40

System suitability

System performance: Weigh 10.0 mg each of Lovastatin RS and compactin, dissolve in acetonitrile to make 100 mL, take 2.0 mL of this solution, and add acetonitrile to make 100 mL. Proceed with 10 μL of this solution according to the above operating conditions; the relative retention times are about 1.0 for lovastatin and 0.85 for compactin with the resolution between these peaks being NLT 3.5.

System repeatability: Repeat the test six times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area for lovastatin is NMT 5.0%

Loss on drying NMT 0.3% (1 g, vacuum, 60 ℃, 6 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 30 mg each of Lovastatin and lovastatin RS, dissolve in acetonitrile to make exactly 100 mL, and use these solutions as the test solution and the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the major peak areas A_T and A_S, from the test solution and the standard solution.

$$\text{Amount (mg) of lovastatin } (C_{24}H_{36}O_5) = \text{Amount (mg) of lovastatin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 238 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octylsilane silica gel for liquid chromatography (5 μm in particle diameter).

Flow rate: 1.5 mL/min

Mobile phase: A mixture of acetonitrile and 0.1% phosphoric acid (65 : 35).

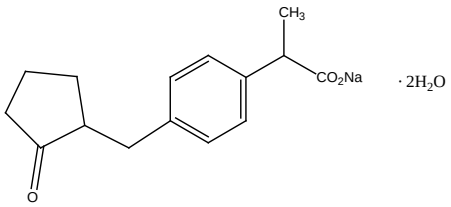
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; the number of theoretical plate is NLT 3000 with the symmetry factor being NMT 1.4.

System repeatability: Repeat the test five times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas is NMT 1.0%.

Packaging and storage Preserve in tight containers under nitrogen in a cold place.

Loxoprofen Sodium Hydrate
록소프로펜나트륨수화물



$C_{15}H_{17}NaO_3 \cdot 2H_2O$: 304.31

Sodium (*RS*)-2-[4-[(2-oxocyclopentyl)methyl]phenyl] propanoate dihydrate [*80382-23-6*]

Loxoprofen Sodium Hydrate contains NLT 98.5% and NMT 101.0% of loxoprofen sodium ($C_{15}H_{17}NaO_3$: 268.28), calculated on the anhydrous basis.

Description Loxoprofen Sodium Hydrate occurs as white to yellow crystals or a crystalline powder.

It is very soluble in water or methanol, soluble in ethanol(95) and practically insoluble in ether.

An aqueous solution of Loxoprofen Sodium Hydrate (1 in 20) shows no optical rotation.

Dissolve 1.0 g of Loxoprofen Sodium Hydrate in 20 mL of freshly boiled and cooled water; the pH of this solution is between 6.5 and 8.5.

Identification (1) Determine the absorption spectra of Loxoprofen Sodium Hydrate and Loxoprofen Sodium Hydrate RS (1 in 55000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Loxoprofen Sodium Hydrate and Loxoprofen Sodium Hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Loxoprofen Sodium Hydrate (1 in 10) responds to the Qualitative Analysis for sodium salt.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Loxoprofen Sodium Hydrate in 10 mL of water; the solution is clear and is colorless to pale yellow color. The color is not more intense than that of the diluted Matching Fluids A (1 in 2).

(2) ***Heavy metals***—Proceed with about 2.0 g of Loxoprofen Sodium Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve about 1.0 g of Loxoprofen Sodium Hydrate in 10 mL of methanol and use this solution as the test solution. Pipet1 mL of this solution, add methanol to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of 1,2-dichloroethane and acetic acid(100) (9 : 1) to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spot from the standard solution.

Water Between 11.0% and 13.0% (0.2 g, volumetric titration, direct titration).

Assay Weigh accurately about 60 mg of Loxoprofen Sodium Hydrate and dissolve in diluted methanol (3 in 5) to make exactly 100 mL. Pipet 5 mL of this solution, add exactly 10 mL of the internal standard solution, add again diluted methanol (3 in 5) to make 100 mL, and use this solution as the standard solution. Separately, weigh accurately about 50 mg of Loxoprofen RS, previously dried in a desiccator (in vacuum, 60 ℃) for 3 hours, and dissolve in diluted methanol (3 in 5) to make exactly 100 mL. Pipet 5 mL of this solution, proceed in the same manner

as in the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of the peak area of loxoprofen to that of the internal standard.

$$\text{Amount (mg) of loxoprofen } (C_{15}H_{17}NaO_3) = \text{Amount (mg) of loxoprofen RS (mg)} \times \frac{Q_T}{Q_S} \times 1.0892$$

Internal standard solution—A solution of ethyl benzoate in diluted methanol (3 in 5) (1 in 50000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 222 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of methanol, water, acetic acid(100) and triethylamine (600 : 400 : 1 : 1).

Flow rate: Adjust the flow rate so that the retention time of loxoprofen is about 7 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; loxoprofen and the internal standard are eluted in this order with the resolution being NLT 10.

System repeatability: Perform the test five times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the ratio of the peak area of loxoprofen to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Loxoprofen Sodium Tablets
록소프로펜나트륨 정

Loxoprofen Sodium Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of loxoprofen sodium ($C_{15}H_{17}NaO_3$: 268.29).

Method of preparation Prepare as directed under Tablets, with Loxoprofen Sodium Hydrate.

Identification Proceed as directed under the Assay described; the test solution shows the peak at the same retention time as the standard solution.

Dissolution Perform the test with 1 tablet of Loxoprofen Sodium Tablets at 100 revolutions per minute according to Method 2 under the Dissolution Test, using 900 mL of water as the dissolution solution. Take the dissolved solution 30 minutes after the start of the Dissolution and filter it. Discard the first 10 mL of the filtrate, take exactly V mL of the next filtrate, add the first solution in the Dissolution so that 1 mL contains about 60 μg of loxoprofen sodium according to the labeled amount to make exactly V' mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of loxoprofen sodium RS, and dissolve in water to make 200 mL. Perform the test with 20 μL each of the test and standard solutions as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas A_T and A_S of loxoprofen sodium ($C_{15}H_{17}NaO_3$) for each solution. Meets the requirements if the dissolution rate of Loxoprofen Sodium Tablets in 30 minutes is NLT 75%.

$$\text{Dissolution rate (\%) of the labeled amount of loxoprofen sodium } (C_{15}H_{17}NaO_3) = W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 450$$

W_S: Amount (mg) of loxoprofen sodium RS

C: Labeled amount (mg) of loxoprofen sodium ($C_{15}H_{17}NaO_3$) in 1 tablet

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 220 nm).

Column: A stainless-steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of 0.02 mol/L potassium dihydrogen phosphate TS, pH 3.0, and acetonitrile (65 : 35).

Flow rate: 1.0 mL/min

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Loxoprofen Sodium Tablets, and powder them. Weigh accurately an amount equivalent to about 30 mg of loxoprofen sodium, dissolve in 60% methanol to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 30 mg of loxoprofen sodium RS, dissolve in 60% methanol to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of loxoprofen from each solution, A_T and A_S, respectively.

$$\text{Amount (mg) of loxoprofen } (C_{15}H_{17}NaO_3) = \text{Amount (mg) of loxoprofen RS (mg)} \times \frac{A_T}{A_S} \times 1.089$$

1.089: Molecular weight of loxoprofen sodium / Molecular weight of loxoprofen.

Operating conditions

Detector: An ultraviolet absorption spectrophotome-

ter (wavelength: 220 nm).

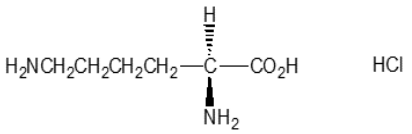
Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of 0.02 mol/L potassium dihydrogen phosphate TS, pH 3.0, and acetonitrile (13 : 7).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

L-Lysine Hydrochloride
L-리신염산염



Lysine Hydrochloride $C_6H_{14}N_2O_2 \cdot HCl$: 182.65
(2*S*)-2,6-Diaminohexanoic acid hydrochloride [*657-27-2*]

L-Lysine Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of L-Lysine Hydrochloride ($C_6H_{14}N_2O_2 \cdot HCl$).

Description L-Lysine Hydrochloride occurs as a white powder, which is odorless but has a slightly distinctive taste.
It is freely soluble in water or formic acid and very slightly soluble in ethanol(95).

Optical rotation $[\alpha]_D^{20}$: Between +19.0° and +21.5° (2 g after drying, 6 mol/L hydrochloric acid TS, 25 mL, 100 mm).

Identification (1) Determine the infrared spectra of L-Lysine Hydrochloride and L-Lysine Hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the spectra, dissolve L-Lysine Hydrochloride in water, evaporate the water to dryness at 60 °C, and repeat the test with the residue.

(2) An aqueous solution of L-Lysine Hydrochloride (1 in 10) responds to the Qualitative Analysis for chloride.

pH Dissolve 1.0 g of L-Lysine Hydrochloride in 10 mL of water; the pH is between 5.0 and 6.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of L-Lysine Hydrochloride in 10 mL of water; the solution is clear and colorless.

(2) ***Sulfate***—Weigh 0.6 g of L-Lysine Hydrochloride and perform the test. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid (NMT 0.028%).

(3) ***Ammonium***—Weigh 0.25 g of L-Lysine Hydrochloride and perform the test. Prepare the control solution with 5.0 mL of ammonium standard solution (NMT 0.02%).

(4) ***Heavy metals***—Proceed with 2.0 g of L-Lysine Hydrochloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Iron***—Dissolve 0.333 g of L-Lysine Hydrochloride in water to make 45 mL, add 2 mL of hydrochloric acid, and use this solution as the test solution. To 1.0 mL of iron standard solution, add water to make 45 mL, add 2 mL of hydrochloric acid, and use this solution as the standard solution. Add 50 mg of ammonium peroxydisulfate and 3 mL of 30% ammonium thiocyanate to the test solution and the standard solution and mix; the color obtained from the test solution is not more intense than that from the standard solution (NMT 30 ppm).

(6) ***Arsenic***—Proceed with 1.0 g of L-Lysine Hydrochloride according to Method 1 and perform the test (NMT 2 ppm).

(7) ***Related substances***—Weigh 0.10 g of L-Lysine Hydrochloride, dissolve in 25 mL of water, and use this solution as the test solution. Pipet 1 mL of this solution and add water to make exactly 50 mL. Pipet 5 mL of this solution, add water to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of 1-propanol and ammonia water(28) (67 : 33) as the developing solvent to a distance of about 10 cm, and dry the plate at 100 °C for 30 minutes. Spray evenly the plate with a solution of ninhydrin in acetone (1 in 50) and heat at 80 °C for 5 minutes; the spots other than the principal spot from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 1.0% (1 g, 105 °C, 3 hours).

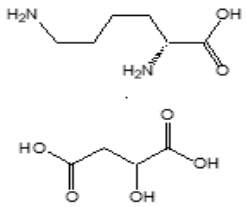
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately 0.1 g of L-Lysine Hydrochloride, previously dried, dissolve in 2 mL of formic acid, add exactly 15 mL of 0.1 mol/L perchloric acid, and heat on a steam bath for 30 minutes. After cooling, add 45 mL of acetic acid(100) and titrate the excess perchloric acid with 0.1 mol/L sodium acetate VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner.

Each mL of 0.1 mol/L perchloric acid VS
= 9.132 mg of $C_6H_{14}N_2O_2 \cdot HCl$

Packaging and storage Preserve in tight containers.

L-Lysine Malate
L-리신말산염



$C_{10}H_{20}N_2O_7$: 280.28
L-Lysine (2*S*)-2-hydroxybutanedioate, [*71555-10-7*]

L-Lysine Malate, when dried, contains NLT 98.5% and NMT 101.0% of L-lysine malate ($C_{10}H_{20}N_2O_7$: 280.28).

Description L-Lysine Malate occurs as a white crystalline powder.

Identification (1) Take 20 mL of an aqueous solution of L-Lysine Malate (1 in 20), transfer into a test tube, add 1 mL of acetone, 0.2 mL of 2.5% sodium pentacyanonitrosylferrate(III) solution and 1 g of borax, and shake for a few minutes; the resulting solution exhibits a reddish purple color.

(2) To 2 drops of an aqueous solution of L-Lysine Malate (1 in 10), add 2 mL of 0.1% α-naphthol TS and heat on a steam bath for 4 minutes. Add 5 mL of water and 7 mL of 10 mol/L sodium hydroxide TS while cooling; the resulting solution exhibits a yellowish dark red color.

Optical rotation $[\alpha]_D^{20}$: Between +2.5° and +4.5° (after drying, 10 g, 100 mL).

Purity (1) ***Chloride***—Weigh 0.5 g of L-Lysine Malate and perform the test as directed under the Chloride. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.021%).

(2) ***Sulfate***—Weigh 0.6 g of L-Lysine Malate and perform the test as directed under the Sulfate. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid (NMT 0.028%).

(3) ***Ammonium***—Weigh 1.0 g of L-Lysine Malate and perform the test as directed under the Ammonium. Prepare the control solution with 2.0 mL of ammonium standard solution (NMT 0.002%).

(4) ***Heavy metals***—Proceed with 2.0 g of L-Lysine Malate according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Iron***—Weigh 1.0 g of L-Lysine Malate, incinerate, then add 1 mL of hydrochloric acid (2 in 3) and 0.6 mL of nitric acid (1 in 3), and evaporate to dryness on a steam bath. Dissolve the residue in 2 mL of hydrochloric acid and 10 mL of water, transfer the solution to a Nessler cylinder, and use this solution as the test solution. Prepare the control solution with 1.0 mL of the iron standard solution. To the test and standard solutions, put 30 mg of ammonium persulfate to mix and add 2 mL of 10% ammonium thiocyanate TS, respectively. Add water to make 25 mL and compare the test solution with the standard solution; the color of the test solution is not more intense than that of the standard solution (NMT 10 ppm).

(6) ***Arsenic***—Proceed with 2.0 g of L-Lysine Malate according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of arsenic standard solution (NMT 1 ppm).

Pyrogens Weigh accurately 20.0 g of L-Lysine Malate, dissolve in 0.9% isotonic sodium chloride injection to make 1000 mL, and inject 10 mL per kilogram.

Other amino acids Weigh 0.1 g of L-Lysine Malate, add water, dissolve to make 10 mL, and use this solution as the test solution. Perform the test with this solution as directed under the Paper Chromatography. Spot 5 μL of the test solution on a filter paper, develop the filter paper with a mixture of n-butanol, water and acetic acid(100) (5 : 2 : 1) as the developing solvent to a distance of about 30 cm, and air-dry the filter paper. Spray evenly a solution of ninhydrin in acetone (1 in 50) on the filter paper and heat at 90 °C for 10 minutes; no purple spots appear other than the principal spot.

Loss on drying NMT 0.05% (1 g, 105 °C, 3 hours).

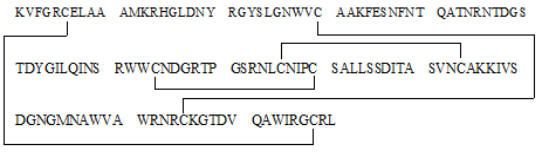
Residue on ignition NMT 0.10% (2 g).

Assay Weigh accurately about 0.2 g of L-Lysine Malate, previously dried, dissolve in 3 mL of formic acid, add 50 mL of acetic acid(100) for non-aqueous titration, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 14.014 mg of $C_{10}H_{20}N_2O_7$

Packaging and storage Preserve in tight containers.

Lysozyme Hydrochloride
리소짐염산염



$C_{616}H_{963}N_{193}O_{182}S_{10}\cdot xHCl$
[12650-88-3, egg white lysozyme]

Lysozyme Hydrochloride is an alkaline polypeptide obtained from the albumen of a hen and has a decomposi-

tion reaction of mucopolysaccharides.

Lysozyme Hydrochloride contains NLT 0.8 mg (potency) of lysozyme per mg, calculated on the dried basis.

Description Lysozyme Hydrochloride occurs as a white crystal, or crystalline or amorphous powder, which is odorless. It is soluble in water or normal saline solution and practically insoluble in ethanol or ether. The pH of an aqueous solution of Lysozyme Hydrochloride (3 in 200) is between 3.0 and 5.0.

Identification (1) Dissolve 0.2 g of Lysozyme Hydrochloride in 100 mL of acetate buffer solution, pH 5.4. To 5 mL of this solution, add 1 mL of ninhydrin TS and heat for 10 minutes; the resulting solution exhibits a bluish purple color.

(2) Determine the absorption spectrum of a solution, prepared by dissolving Lysozyme Hydrochloride in acetate buffer solution, pH 5.4 (1 in 10000); it exhibits a maximum at between 279 nm and 281 nm.

Purity (1) ***Clarity and color of solution***—To 5 mL of an aqueous solution of Lysozyme Hydrochloride (3 in 200), add dilute hydrochloric acid, if necessary, to adjust the pH to 3; the resulting solution is clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Lysozyme Hydrochloride as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Lysozyme Hydrochloride according to Method 3 under the Arsenic and perform the test (NMT 2 ppm).

(4) ***Nitrogen***—Perform the test with Lysozyme Hydrochloride as directed under the Nitrogen Determination; the amount of nitrogen (N : 14.007) is 16.5% to 19.0%, calculated on the dried basis.

Loss on drying NMT 8.0% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 2.0% (0.5 g).

Assay Weigh accurately about 50 mg (potency) each of Lysozyme Hydrochloride and lysozyme RS (previously determined for loss on drying in the same manner as Lysozyme Hydrochloride). Add phosphate buffer solution, pH 6.2 to each to make exactly 100.0 mL. Take 2.0 mL of these solutions and add phosphate buffer solution, pH 6.2 to make 100.0 mL. Take again 2.0 mL of the resulting solutions, add phosphate buffer solution, pH 6.2 to make 50.0 mL, and use these solutions as the test solution and the standard solution, respectively. Take 3.0 mL each of substrate solutions, transfer into 3 test tubes, and warm at 35℃ for 3 minutes. Separately, warm the standard solution, the test solution and phosphate buffer solution, pH 6.2 at 35 ℃ for 3 minutes, take 3.0 mL, and transfer into the previous test tubes. After allowing to stand at 35 ℃ for 10 ± 0.1 minutes, determine each absorbance, A_S, A_T, and A_0, at 640 nm, using water as the control solution. Repeat the test 3 times and calculate according to the following equation with the mean value obtained.

$$\begin{aligned}&\text{Amount [mg (potency)] of lysozyme per mg,}\\&\text{calculated on the dried basis of lysozyme Hydrochloride}\\&=\frac{\text{Amount [mg (potency)]of lysozyme RS per mg,}\\\text{calculated on the dried basis)}}{\text{Amount (mg)of Lysozyme Hydrochloride,}\\\text{calculated on the dried basis}}-\frac{A_0-A_T}{A_0-A_S}\end{aligned}$$

Substrate solution—To about 50 mg of dried mycelium of *Micrococcus lysodeikticus*, put 60 mL of phosphate buffer solution, pH 6.2 to make the solution turbid. Using phosphate buffer solution, pH 6.2 as the control solution, adjust the solution by adding phosphate buffer solution, pH 6.2 so that the transmittance becomes 10% at the layer length of 10 mm and the wavelength of 640 nm.

Packaging and storage Preserve in tight containers.

Magnesium Aluminometasilicate
메타규산알루민산마그네슘

Magnesium Aluminometasilicate contains NLT 29.1% and NMT 35.5% of aluminum oxide (Al_2O_3 : 101.96) and NLT 11.4% and NMT 14.0% of magnesium oxide (MgO : 40.30), calculated on the dried basis.

Description Magnesium Aluminometasilicate occurs as a white powder or grains.
It is odorless and tasteless.
It is practically insoluble in water or ethanol(95).
To 1 g of Magnesium Aluminometasilicate, add 10 mL of dilute hydrochloric acid, and heat; most of Magnesium Aluminometasilicate is soluble.

Identification (1) To 0.5 g of Magnesium Aluminometasilicate, add 5 mL of dilute sulfuric acid (1 in 3), heat until white fumes are evolved, cool, add 20 mL of water, and filter. Use the residue in the Identification (3). Neutralize the filtrate with ammonia TS, and filter the produced precipitate. Use the filtrate in the Identification (2). Dissolve the residue in dilute hydrochloric acid; the solution responds to the Qualitative Analysis for aluminum salt.

(2) The filtrate obtained in (1) responds to the Qualitative Analysis for magnesium salt.

(3) Wash the residue obtained in (1) with 30 mL of water, add 2 mL of methylene blue solution (1 in 10000), and wash again with 30 mL of water; the precipitate exhibits a blue color.

Purity (1) ***Soluble salts***—To 10 g of Magnesium Aluminometasilicate, add 150 mL of water, and boil gently for 15 minutes while shaking well to mix. After cooling, add water to make 150 mL, centrifuge, and take 75 mL of the clear supernatant. To this liquid, add water to make 100 mL, and use this solution as the test solution. Take

25 mL of the test solution, evaporate it to dryness on a steam bath, and ignite at 700 ℃ for 2 hours; the amount of the residue is NMT 20 mg.

(2) ***Alkali***—Take 20 mL of the test solution obtained in (1), and add 2 drops of phenolphthalein TS and 0.5 mL of 0.1 mol/L hydrochloric acid; the solution is colorless.

(3) ***Chloride***—Take 10 mL of the test solution obtained in (1), add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.75 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.053%).

(4) ***Sulfate***—Take 1 mL of the test solution obtained in (1), add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid VS (NMT 0.480%).

(5) ***Heavy metals***—To 1.0 g of Magnesium Aluminometasilicate, add 20 mL of water and 3 mL of hydrochloric acid, evaporate it to dryness on a steam bath. To the residue, add 2 mL of dilute acetic acid and 20 mL of water, boil for 2 minutes, filter, and wash the residue with two 5 mL portions of water. Combine the filtrate and washings, add 0.15 g of hydroxylamine hydrochloride, and heat to boiling. After cooling, add 0.15 g of sodium acetate and water to make 50 mL. Use this solution as the test solution and perform the test as directed under the Heavy Metals. Evaporate 3 mL of hydrochloric acid to dryness on a steam bath, add 3.0 mL of lead standard solution, 0.15 g of hydroxylamine hydrochloride, 0.15 g of sodium acetate, 2 mL of dilute acetic acid and water to make 50 mL, and use this solution as the control solution (NMT 30 ppm).

(6) ***Iron***—Weigh 0.2 g of Magnesium Aluminometasilicate, add 8 mL of dilute hydrochloric acid, and boil for 1 minute. After cooling, add acetate-sodium acetate buffer solution, pH 4.5, for Iron to make 50 mL, and centrifuge. Take 25 mL of the clear supernatant, add acetate-sodium acetate buffer solution, pH 4.5, for Iron to make 30 mL, and use this solution as the test solution. Perform the test as directed in Method A under the Iron.

Control solution—Add 4 mL of dilute hydrochloric acid to 3.0 mL of the iron standard solution, and add acetate-sodium acetate buffer solution, pH 4.5, for Iron to make 30 mL. Use this solution as the standard solution and proceed in the same manner as the test solution.

(7) ***Arsenic***—To 0.4 g of Magnesium Aluminometasilicate, add 10 mL of water and 1 mL of sulfuric acid, and shake well to mix. After cooling, use this solution as the test solution and perform the test (NMT 5 ppm).

Loss on drying NMT 20.0% (1 g, 110 ℃, 7 hours).

Acid-neutralizing capacity Weigh accurately about 0.2 g of Magnesium Aluminometasilicate, transfer to a stoppered flask, add 100.0 mL of 0.1 mol/L hydrochloric acid, close the flask with a stopper, shake to mix for 1 hour at 37 ± 2 ℃, and then filter. Take 50.0 mL of the filtrate, and titrate the excess of hydrochloric acid with 0.1 mol/L sodium hydroxide VS while shaking well to mix until the pH becomes 3.5. Each g of Magnesium Aluminometasilicate, calculated on the dried basis, should consume NLT 210 mL of 0.1 mol/L hydrochloric acid.

Assay (1) ***Aluminum oxide***—Weigh accurately about 0.5 g of Magnesium Aluminometasilicate, transfer to an Erlenmeyer flask, add 3.5 mL of dilute hydrochloric acid and 30 mL of water, and heat on a steam bath for 15 minutes. Then, add 3.5 mL of hydrochloric acid and heat on a steam bath for 10 minutes. After cooling, transfer to a 250-mL volumetric flask. Wash the Erlenmeyer flask with water, and combine the washings with water to make 250.0 mL. Centrifuge this solution and use the clear supernatant as the test solution. Pipet 20.0 mL of the test solution, add 20.0 mL of 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS, and add 8 mL of acetate-sodium acetate buffer solution, pH 4.8 and 20 mL of water. Boil for 5 minutes, cool, add 50 mL of ethanol(95), and titrate with 0.02 mol/L zinc sulfate VS until a pale dark green color changes to a pale red color (indicator: dithizone TS 2 mL). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 1.0196 mg of Al_2O_3

(2) ***Magnesium oxide***—Take 50.0 mL of the test solution obtained in Assay (1), add 50 mL of water and 10 mL of triethanolamine (1 in 2), and shake well to mix. Add 5 mL of ammonia-ammonium chloride buffer solution, pH 10.7, and titrate with 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 40 mg of eryochrome black T-sodium chloride indicator). The endpoint of the titration is when the reddish purple color of the solution changes to a blue color lasting for 30 seconds. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 0.8060 mg of MgO

Packaging and storage Preserve in tight containers.

Magnesium Aluminosilicate Suspension
규산알루민산마그네슘 현탁액

Magnesium Aluminosilicate Suspension contains aluminum oxide (Al_2O_3 : 101.96) equivalent to NLT 27.0% and NMT 34.3% of the labeled amount of magnesium aluminosilicate, calculated on the dried basis, and NLT 20.5% and NMT 27.7% of magnesium oxide

(MgO : 40.30).

Method of preparation Prepare as directed under Suspension, with Magnesium Aluminosilicate.

Identification (1) ***Aluminum oxide in magnesium aluminosilicate***—Weigh an amount of Magnesium Aluminosilicate Suspension, equivalent to about 0.5 g of magnesium aluminosilicate, according to the labeled amount, add 5 mL of diluted sulfuric acid (1 in 3), and heat until white smoke generates. After cooling, add 20 mL of water to filter. Neutralize the filtrate with strong ammonia water, filter again, and dissolve the precipitate with dilute hydrochloric acid; the weakly acidic solution responds to the Qualitative Analysis for aluminum.

(2) ***Magnesium oxide in magnesium silicate***—Weigh an amount of Magnesium Aluminosilicate Suspension, equivalent to 0.5 g of magnesium aluminosilicate, according to the labeled amount, add 5 mL of diluted sulfuric acid (1 in 3), and heat until white smoke generates. After cooling, add 20 mL of water to filter. Neutralize the filtrate with strong ammonia water and filter again. The filtrate responds to the Qualitative Analysis for magnesium salt.

pH Between 7.5 and 9.5.

Acid-neutralizing capacity Take exactly an amount of Magnesium Aluminosilicate Suspension, equivalent to 0.1 g of magnesium aluminosilicate (83 mg of magnesium aluminosilicate, Previously dried), according to the labeled amount, transfer to a flask with a glass stopper, add exactly 50 mL of 0.1 mol/L hydrochloric acid VS, and shake to mix at about 37 ± 2 ℃ for 1 hour. If necessary, filter and wash with water. Combine the filtrate and the washings and titrate excess hydrochloric acid with 0.1 mol/L sodium hydroxide VS (indicator: 5 drops of bromophenol blue TS).
1 g of magnesium aluminosilicate of Magnesium Aluminosilicate Suspension (previously dried) is NLT 250 mL of 0.1 mol/L hydrochloric acid.

Assay (1) ***Aluminum oxide***—Pipet an amount of Magnesium Aluminosilicate Suspension, equivalent to 1 g of magnesium aluminosilicate (830 mg of magnesium aluminosilicate, previously dried), according to the labeled amount, add 40 mL of dilute hydrochloric acid, and evaporate to dryness on a steam bath. Dry the residue on evaporation in the dryer at a 110 ℃ for 1 hour, add 80 mL of hydrochloric acid TS to the residue, shake well to mix, and extract in hot water by shaking. Wash the residue with hot water and combine with the washings. Repeat the same procedure twice. Add water to the filtrate and washings to make exactly 250 mL, and use this solution as the test solution. Pipet 10 mL of the test solution and adjust the pH to 3.0 by adding 30 mL of water, 5 mL of acetic acid-ammonium acetate buffer solution, pH 3.0, and 2 to 3 drops of strong ammonia water. Add 0.5 mL of Cu-PAN TS and heat. While boiling titrate with 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS. The endpoint is when the color of the solution changes from red to yellow persisting for NLT 1 minute. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 0.5098 mg of Al_2O_3

(2) ***Magnesium oxide***—Take exactly an amount of Magnesium Aluminosilicate Suspension, equivalent to 1 g of magnesium aluminosilicate, according to the labeled amount (830 mg of magnesium aluminosilicate on the dried basis), add 40 mL of dilute hydrochloric acid, and evaporate to dryness on a steam bath. Dry the residue on evaporation in the dryer at a 110 ℃ for 1 hour, add 80 mL of hydrochloric acid TS to the residue, shake well to mix, and extract in hot water by shaking. Wash the residue with hot water and combine with the washings. Repeat the same procedure twice. Add water to the filtrate and washings to make exactly 250 mL, and use this solution as the test solution. Pipet 10 mL of the test solution, add 20 mL of water, and add 2 g of ammonium chloride and 1 drop of methyl red TS. Heat until it boils, add ammonia TS carefully until the color of the solution turns yellow, boil for 2 minutes, and filter. Wash well the precipitate with hot ammonium chloride solution (1 in 50), and combine the filtrate and the washings. Add 3 mL of triethanolamine, 1 mL of potassium cyanide TS, and 5 mL of strong ammonia water to adjust the pH to 10.0, and titrate with 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 4 drops of eriochrome black T TS). The endpoint is when the red color of the solution disappears completely and appears light bluish green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 0.4030 mg of MgO

Packaging and storage Preserve in tight containers.

Magnesium Aluminosilicate Tablets
규산알루민산마그네슘 정

Magnesium Aluminosilicate Tablets contain aluminum oxide (Al_2O_3 : 101.96) equivalent to NLT 27.0% and NMT 34.3% of the labeled amount of magnesium aluminosilicate and NLT 20.5% and NMT 27.7% of magnesium oxide (MgO : 40.30).

Method of preparation Prepare as directed under Tablets, with Magnesium Aluminosilicate.

Identification (1) Weigh an amount of Magnesium Aluminosilicate Tablets, equivalent to 0.5 g of magnesi-

um aluminosilicate according to the labeled amount, add 5 mL of dilute sulfuric acid (1 in 3), and heat until white smoke generates. After cooling, add 20 mL of water to filter. Use the residue in Identification (3). Add ammonia TS to the filtrate to neutralize, and filter the obtained precipitate. Use the filtrate in Identification (2). The solution obtained by adding dilute hydrochloric acid to the residue responds to the Qualitative Analysis for aluminum salt.

(2) The filtrate obtained in Identification (1) responds to the Qualitative Analysis for magnesium salt.

(3) Wash the residue obtained in Identification (1) with 30 mL of water, add 2 mL of methylene blue solution (1 in 10,000), and wash with 30 mL of water again; the blue precipitate is produced.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Acid-neutralizing capacity Weigh accurately the mass of NLT 20 Magnesium Aluminosilicate Tablets, and powder. Weigh accurately an amount, equivalent to about 20 mg of magnesium aluminosilicate, transfer into a volumetric flask with a stopper, add exactly 100 mL of 0.1 mol/L hydrochloric acid VS. With the stopper closed, mix by shaking at 37 ± 2 ℃ for 1 hour and then filter. Pipet 50 mL of the filtrate, and titrate the excess hydrochloric acid while stirring well, with 0.1 mol/L sodium hydroxide VS until the pH becomes 3.5. Perform a blank test in the same manner and make any necessary correction. The volume of 0.1 mol/L hydrochloric acid VS consumed for 1 g of magnesium aluminosilicate, calculated on the dried basis, is NLT 250 mL.

Assay (1) ***Aluminum oxide***—Weigh accurately the mass of NLT 20 Magnesium Aluminosilicate Tablets, and power. Weigh accurately an amount, equivalent to about 0.5 g of magnesium aluminosilicate, transfer into a 100-mL Erlenmeyer flask, add 3.5 mL of dilute hydrochloric acid, and heat on a steam bath for 15 minutes. After cooling, transfer to a 250-mL volumetric flask, wash the Erlenmeyer flask with water, and add the washings and water to make exactly 250 mL. Centrifuge the solution and use the supernatant clear solution as the test solution. Pipet 20 mL of the test solution, add exactly 20 mL of 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS, add 8 mL of acetic acid-ammonium acetate buffer solution, pH 4.8 and 20 mL of water, and then boil for 5 minutes. After cooling, add 50 mL of ethanol(95) and titrate with 0.02 mol/L zinc sulfate VS (indicator: 2 mL of dithizone TS). The endpoint is when the solution changes from the light dark green to light red. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 1.020 mg of Al_2O_3

(2) ***Magnesium oxide***—Pipet 50 mL of the test solution obtained in Assay (1), add 50 mL of water and 10 mL of triethanolamine solution (1 in 2), and shake well to mix, and then add 5 mL of ammonia-ammonium chloride buffer solution, pH 10.7. Titrate with 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 0.04 g of eriochrome black T-sodium chloride indicator). The endpoint is when the reddish purple color of the solution appears with the blue color persisting for 30 seconds. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 0.8061 mg of MgO

Packaging and storage Preserve in tight containers.

Magnesium Aluminum Hydrate
수산화알루민산마그네슘

AlH_5MgO_5 : 136.32

[*39366-43-3*]

Magnesium Aluminum Hydrate contains NLT 25.0% and NMT 35.0% of aluminum oxide (Al_2O_3: 101.96) and NLT 25.0% and NMT 35.0% of magnesium oxide (MgO: 40.30).

Description Magnesium Aluminum Hydrate occurs as a white powder and is odorless and tasteless.

Identification Dissolve 0.5 g of Magnesium Aluminum Hydrate in 10 mL of dilute hydrochloric acid by warming; the resulting solution responds to the Qualitative Analysis for aluminum salt and magnesium salt.

Purity (1) ***Chloride***—Weigh 1.0 g of Magnesium Aluminum Hydrate, add 30 mL of dilute nitric acid, heat slowly to boiling while shaking well to mix, cool, add water to make 100 mL, and centrifuge. To 5 mL of the clear supernatant, add 6 mL of dilute nitric acid and water to make 50 mL, and perform the test. Prepare the control solution with 0.4 mL of 0.01 mol/L hydrochloric acid (NMT 0.284%).

(2) ***Sulfate***—Weigh 1.0 g of Magnesium Aluminum Hydrate, add 15 mL of dilute hydrochloric acid, heat gently while shaking well to, cool, add water to make 250 mL, and centrifuge. To 25 mL of the clear supernatant, add 1 mL of dilute nitric acid and water to make 50 mL, and perform the test. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.480%).

(3) ***Heavy metals***—Weigh 0.5 g of Magnesium Aluminum Hydrate, add 8 mL of hydrochloric acid and 5 mL of water, heat gently to boiling while shaking well to mix, and evaporate to dryness on a steam bath. To the residue, add 30 mL of water, warm while shaking well to mix, and filter. To the filtrate, add 2 mL of dilute acetic acid and 5 drops of ammonia TS, warm with shaking to mix until the solution is clear. After cooling, add water to

make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution by adding 2 mL of dilute acetic acid and water to 2.0 mL of lead standard solution to make 50 mL (NMT 40 ppm).

(4) ***Arsenic***—To 0.8 g of Magnesium Aluminum Hydrate, add 10 mL of dilute sulfuric acid, heat slowly to boiling while shaking well to mix, cool, and filter. To 2.5 mL of the filtrate, add water to make 5 mL (NMT 10 ppm), and perform the test.

Acid-neutralizing capacity Weigh accurately 20 mg of Magnesium Aluminum Hydrate, transfer to a stoppered Erlenmeyer flask, add exactly 100 mL of 0.1 mol/L hydrochloric acid, stopper, shake to mix at 37 ± 2 ℃ for 1 hour, and filter. Take exactly 50 mL of the filtrate, and titrate the excess hydrochloric acid with 0.1 mol/L sodium hydroxide VS (indicator: 5 drops of bromophenol blue TS). 1.0 g of Magnesium Aluminum Hydrate consumes NLT 250 mL of 0.1 mol/L hydrochloric acid.

Loss on ignition Between 35% and 45% (1 g, 800 ℃, constant mass).

Assay (1) ***Aluminum oxide***—Weigh accurately about 1.0 g of Magnesium Aluminum Hydrate, dissolve in 30 mL of dilute hydrochloric acid by heating, add water to make exactly 250 mL, and use this solution as the test solution. Pipet 15 mL of the test solution, add exactly 25 mL of 0.05 mol./L ethylenediaminetetraacetic acid disodium salt and 20 mL of acetic acid-ammonium acetate buffer solution, pH 4.8, and boil for five minutes. After cooling, add 55 mL of ethanol(95), and titrate with 0.05 mol/L zinc sulfate VS (indicator: 2 mL of dithizone TS). The endpoint of titration is when the solution changes from the pale dark green to pale violet. Perform a blank test in the same manner and make any necessary correction.

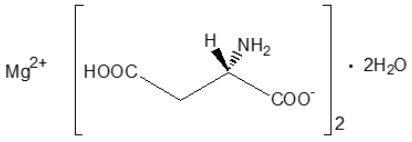
Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.549 mg of Al_2O_3

(2) ***Magnesium oxide***—Pipet 10 mL of the test solution obtained in (1), add a small amount of water, and add 5 mL of diluted triethanolamine solution (1 in 2), shake to mix, adjust the pH to 10.0 with ammonia water, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 40 mg of eriochrome black T-sodium chloride indicator). The endpoint of titration is when the reddish purple color of the solution turns into the blue color. Perform a blank test in the same manner and make any necessary correction.

Each mL of ethylenediaminetetraacetic acid disodium salt VS
= 2.015 mg of MgO

Packaging and storage Preserve in well-closed containers.

Magnesium Aspartate Hydrate
아스파르트산마그네슘수화물



$C_8H_{12}O_8N_2Mg \cdot 2H2O$: 324.53
Magnesium (2S)-2-amino-4-hydroxy-4-oxo-butanoate dihydrate

Magnesium Aspartate Hydrate contains NLT 98.0% and NMT 102.0% of magnesium aspartate ($C_8H_{12}O_8N_2Mg$: 288.49), calculated on the anhydrous basis.

Description Magnesium Aspartate Hydrate occurs as a white crystalline powder or colorless crystals.
It is freely soluble in water.

Identification (1) Incinerate 15 mg of Magnesium Aspartate Hydrate until white residue is obtained. Dissolve the residue in 1 mL of dilute hydrochloric acid, neutralize with dilute sodium hydroxide TS using a litmus paper, and if necessary, filter. To this solution, add 6 mol/L ammonia water; a white precipitate is formed. To the precipitate, add 10.7 w/v% ammonium chloride solution; the precipitate dissolves. To this, add 9 w/v% dibasic sodium phosphate solution; a white crystalline precipitate is formed.

(2) Dissolve 0.10 g of Magnesium Aspartate Hydrate in water to make 10 mL. To 1 mL of this solution, add water to make 50 mL, and use the resulting solution as the test solution. Separately, dissolve 10 mg of magnesium aspartate hydrate RS in water to make 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, water and acetic acid(100) (60 : 20 : 20) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray evenly ninhydrin TS on the plate, and dry the plate at 105 ℃ for 15 minutes; the colors and R_f values of the principal spots obtained from the test solution and the standard solution are the same.

Optical rotation $[\alpha]_D^{20}$: Between +20.5° and +23.0° (0.5 g, calculated on the anhydrous basis, a solution prepared by mixing 51.5 g of hydrochloric acid with water to make 100 mL, 25 mL, 100 mm).

pH Dissolve 2.5 g of Magnesium Aspartate Hydrate in water to make 100 mL. The pH of this solution is between 6.0 and 8.0.

Purity (1) ***Clarity and color of solution*—**Dissolve 2.5 g of Magnesium Aspartate Hydrate in water to make 100 mL. The solution is colorless and clear.

(2) ***Chloride*—**Perform the test with 1.0 g of Magnesium Aspartate Hydrate. Prepare the control solution with 0.564 mL of 0.01 mol/L hydrochloric acid (NMT 0.02%).

(3) ***Sulfate*—**Perform the test with 0.5 g of Magnesium Aspartate Hydrate. Prepare the control solution with 0.52 mL of 0.005 mol/L sulfuric acid (NMT 0.05%).

(4) ***Ammonium*—**Perform the test with 0.25 g of Magnesium Aspartate Hydrate. Prepare the control solution with 5 mL of ammonium standard solution (NMT 0.02%).

(5) ***Heavy metals*—**Proceed with 2.0 g of Magnesium Aspartate Hydrate as directed under Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(6) ***Iron*—**Place 0.20 g of Magnesium Aspartate Hydrate in a separatory funnel, and dissolve in 10 mL of dilute hydrochloric acid. To this, add 10 mL of 4-methyl-2-pentanone each and shake to mix for 3 minutes three times. Combine the obtained organic layers. To the organic solvent layer, add 10 mL of water, and shake to mix for 3 minutes. Place the water layer in a Nessler tube, add 2 mL of 20 w/v% citric acid and 0.1 mL of mercaptoacetic acid to mix, and add 10 mol/L of ammonia water to alkalify. To this, add water to make 20 mL, and allow to stand for 5 minutes; the color of the resulting solution is not more intense than the color of the control solution prepared by proceeding 10 mL of diluted iron standard solution (1 in 10) in the same manner (NMT 50 ppm).

(7) ***Ninhydrin-positive substances*—**Dissolve 0.10 g of Magnesium Aspartate Hydrate in water to make 10 mL. To 1 mL of this solution, add water to make 50 mL, and use the resulting solution as the test solution (1). To 1 mL of the test solution (1), add water to make 50 mL, and use this solution as the test solution (2). To 5 mL of the test solution (2), add water to make 20 mL, and use this solution as the standard solution (1). Separately, dissolve 10 mg of magnesium aspartate dihydrate RS and 10 mg of glutamic acid RS together in water to make 25 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution (1), the standard solution (1) and the standard solution (2) on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, water and acetic acid(100) (60 : 20 : 20) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray evenly ninhydrin TS on the plate, and dry the plate at 105 ℃ for 15 minutes; the spots other than the principal spot obtained from the test solution (1) are not more intense than the spots from the standard solution (1) (0.5%). This test is valid when the two principal spots obtained from the standard solution (2) are clearly separated.

Water Between 10.0% and 14.0% (0.1 g, volumetric titration, direct titration).

Assay Weigh accurately about 0.26 g of Magnesium Aspartate Hydrate, dissolve in 10 mL of water, add 10 mL of ammonia-ammonium chloride buffer solution (pH 10.0), and titrate with 0.1 mol/L ethylenediaminetetraacetic acid disodium salt VS until the violet color of the resulting solution turns to a blue color (indicator: about 50 mg of eryochrome black T-sodium chloride indicator).

Each mL of 0.1 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 28.853 mg of $C_8H_{12}O_8N_2Mg$

Packaging and storage Preserve in well-closed container.

Magnesium Carbonate
탄산마그네슘

[*546-93-0*]

Magnesium Carbonate is salt water-alkali magnesium carbonate. Magnesium Carbonate contains NLT 40.0% and NMT 44.0% of magnesium oxide (MgO: 40.30).

Perform the sedimentation test; substances with volumes NMT 12.0 mL scale can be labeled informally as heavy magnesium carbonate.

Description Magnesium Carbonate occurs as easily breakable white masses or a powder and is odorless.
It is practically insoluble in water, ethanol(95), ether, or 1-propanol.
It dissolves in dilute hydrochloric acid with effervescence.
A saturated solution of Magnesium Carbonate is alkaline.

Identification (1) Dissolve 1 g of Magnesium Carbonate in 10 mL of dilute hydrochloric acid, and boil. After cooling, add sodium hydroxide TS to neutralize, and filter if necessary. Magnesium Carbonate responds to the Qualitative Analysis for magnesium salt.

(2) Magnesium Carbonate responds to the Qualitative Analysis (1) for carbonate.

Purity (1) ***Soluble salts***—Weigh 2.0 g of Magnesium Carbonate, add 40 mL of 1-propanol and 40 mL of water, and heat to boiling while stirring continuously. After cooling and filtering, wash with water, combine filtrate and washings, and add water to make exactly 100 mL. Pipet 50 mL of this solution, evaporate on a steam bath to dryness, and dry the residue at 105 ℃ for 1 hour; the amount of the residue is NMT 10.0 mg.

(2) ***Heavy metals***—Moisten 1.0 g of Magnesium Carbonate with 4 mL of water, dissolve in 10 mL of dilute hydrochloric acid, evaporate to dryness on a steam bath, and dissolve the residue in 35 mL of water, 2 mL of

dilute acetic acid, and 1 drop of ammonia TS. Filter if necessary, wash the filter paper, combine washings with the filtrate, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by evaporating 10 mL of dilute hydrochloric acid to dryness on a steam bath and adding 2 mL of dilute acetic acid, 3.0 mL of lead standard solution, and water to make 50 mL (NMT 30 ppm).

(3) ***Iron***—Proceed with 0.10 g of Magnesium Carbonate according to Method 1 and perform the test as directed under Method A. Prepare the control solution with 2.0 mL of iron standard solution (NMT 200 ppm).

(4) ***Arsenic***—Moisten 0.40 g of Magnesium Carbonate with 1.5 mL of water, dissolve in 3.5 mL of dilute hydrochloric acid, use this solution as the test solution, and perform the test (NMT 5 ppm).

(5) ***Calcium oxide***—Weigh accurately about 0.6 g of Magnesium Carbonate, and dissolve in 35 mL of water and 6 mL of dilute hydrochloric acid. Add 250 mL of water and 5 mL of L-tartaric acid solution (1 in 5), add 10 mL of 2,2',2″-nitrilotriethanol (3 in 10) and 10 mL of 8 mol/L potassium hydroxide TS, allow to stand for 5 minutes, and titrate with 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 0.1 g of NN indicator). The endpoint of titration is reached when the purple color of the solution turns blue. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 0.5608 mg of CaO

The amount of calcium oxide (CaO: 56.08) is NMT 0.6%.

(6) ***Acid-insoluble substances***—Weigh 5.0 g of Magnesium Carbonate, add 75 mL of water, add 10 mL of hydrochloric acid in small portions while stirring for mixing, and boil for 5 minutes. After cooling, filter insoluble substances using a filter paper for qualitative analysis, and wash the insoluble substances. Wash the washings until no turbidity forms when silver nitrate TS is added, and ignite the residue with the filter paper to incinerate; the amount of the residue is NMT 2.5 mg.

Sedimentation test Weigh 1.0 g of Magnesium Carbonate that has passed through a No. 100 sieve, transfer into the measuring cylinder with a stopper and a scale of 50 mL at a place where it is 15 cm from the bottom, add water to make 50 mL, and mix exactly for 1 minute by shaking vigorously. Allow to stand for 15 minutes, and determine the height of the sediment (mL scale).

Microbiological examination of non-sterile products The total aerobic microbial count is NMT 1000 CFU, and the total combined yeasts/molds count is NMT 100 CFU per g of Magnesium Carbonate. Also, *Escherichia coli*, *Salmonella*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* are not detected.

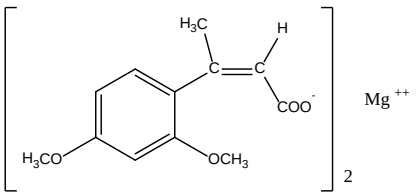
Assay Weigh accurately about 0.4 g of Magnesium Carbonate, dissolve in 10 mL of water and 3.5 mL of dilute hydrochloric acid, and add water to make exactly 100 mL. Pipet 25 mL of this solution, add 50 mL of water and 5 mL of pH 10.7 ammonia-ammonium chloride buffer solution, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 40 mg of eryochrome black T-sodium chloride indicator). Perform a blank test in the same manner and make any necessary correction. From the consumed amount of the 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS, subtract the amount of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS that is equivalent to calcium oxide (CaO) obtained as directed in Purity (5).

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.0152 mg of MgO

Each mg of calcium oxide (CaO)
= 0.36 mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS

Packaging and storage Preserve in well-closed containers.

Magnesium Dimecrotate
디메크로트산마그네슘



$C_{24}H_{26}O_8Mg$: 466.75

(2*Z*)-3-(2,4-Dimethoxyphenyl)-2-butenoic acid, magnesium salt (2:1), [*54283-65-7*]

Magnesium Dimecrotate contains NLT 97.0% and NMT 103.0% of magnesium dimecrotate ($C_{24}H_{26}O_8Mg$) and NLT 4.95% and NMT 5.47% of magnesium (Mg), calculated on the anhydrous basis.

Description Magnesium Dimecrotate occurs as a white powder with no odor and has a salty taste of magnesium salt. It is soluble in methanol and hot acetic acid, sparingly soluble in ethanol, water, chloroform, and practically insoluble in ether.

Identification (1) Dissolve an appropriate amount of Magnesium Dimecrotate in water and add 2 drops of bromine water; the resulting solution exhibits a pink color and then is decolorized.

(2) Dissolve 1 g of Magnesium Dimecrotate in 100 mL of ethanol, and use this solution as the test solution. Separately, weigh 1 g of dimecrotic acid RS, dissolve in

ethanol to make 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 50 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Develop the plate with a mixture of toluene, ethyl formate and anhydrous formic acid (5 : 4 : 1) to a distance of about 13 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values of the spots obtained from the test solution and the standard solution are the same.

(3) Weigh 1 mg of Magnesium Dimecrotate and dissolve in 100 mL of methanolic hydrochloric acid. Pipet 1 mL of this solution, add methanolic hydrochloric acid to make 100 mL, and determine absorption spectrum of the solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at 216 nm and 283 nm.

(4) Dissolve 0.1 g of Magnesium Dimecrotate in 4 mL of ethanol, and use this solution as the test solution. Separately, weigh 0.84 g of magnesium chloride, dissolve in water to make 100 mL, and use this solution as the standard solution (0.1% as magnesium). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the test solution and the standard solution on the thin-layer chromatographic plate of cellulose with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of methanol, water and hydrochloric acid (8 : 1 : 1) to a distance of about 12 cm, and air-dry the plate. Spray evenly a solution of 8-hydroxyquinoline in methanol (1 in 100) on the plate, expose the plate to ammonia, and examine under ultraviolet light (wavelength 365 nm); the R_f values of the spots obtained from the test solution and the standard solution are the same.

Melting point Between 120 and 135 ℃.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Magnesium Dimecrotate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 0.25 g of Magnesium Dimecrotate according to Method 3 and perform the test. Prepare the control solution with 1 mL of the arsenic standard solution (NMT 4 ppm).

(3) ***Related substances*** —Weigh accurately about 10 mg of Magnesium Dimecrotate, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately 1 g of dimecrotic acid RS, 10 mg of resorcinol RS, 10 mg of 4-methyl-7-methoxycoumarin RS and 10 mg of 4-methyl-7-hydroxycoumarin RS, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the standard solution (1). Weigh accurately 15 mg of dimecrotic acid E-isomer RS, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the standard solution (2). Pipet 10 mL each of the standard solution (1) and the standard solution (2), add the mobile phase to make exactly 50 mL, and use these solutions as the standard solution (3). Perform the test with 20 μL each of the test solution and the standard solution (3) as directed under the Liquid Chromatography according to the following conditions, and determine the amount of each related substance according to the following equation; resorcinol, 4-methyl-7-methoxycoumarin and 4-methyl-7-hydroxycoumarin are NMT 0.15% respectively, each related substance is NMT 0.10%, dimecrotate E-isomer is NMT 1.5%, and the total amount of related substances is NMT 2.0%.

$$\text{Content (\%) of each related substance} = 100 \times \frac{C_S}{C_T} \times \frac{A_T}{A_S}$$

*C*s: Concentration (mg/mL) of each related substance in the standard solution

C_T: Concentration (mg/mL) of dimecrotic acid in the test solution

A_T: Peak area of each related substance in the test solution

*A*s: Peak area of each related substance in the standard solution

$$\text{Content (\%) of each related substance} = 100 \times \frac{C_S}{C_T} \times \frac{A_T}{A_S} \times \frac{100}{94.79}$$

*C*s: Concentration (mg/mL) of dimecrotic acid in the standard solution

C_T: Concentration (mg/mL) of dimecrotic in the test solution

A_T: Peak area of each related substance in the test solution

*A*s: Peak area of each related substance in the standard solution

Operating conditions

Detector: An UV-vis spectrophotometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 ℃.

Mobile phase: A mixture of pH 3.0 sodium phosphate monobasic buffer and acetonitrile (7 : 3).

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution (3) according to the above conditions; the resolution between the peaks of resorcinol, 4-methyl-7-methoxycoumarin, 4-methyl-7-hydroxycoumarin, dimecrotic acid and dimecrotic acid E-isomer is NLT 2.0.

Water NMT 15.0% (0.05 g, volumetric titration, direct titration).

Assay (1) ***Dimecrotic acid***—Weigh accurately about 10 mg of Magnesium Dimecrotate, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately 10 mg of dimecrotic acid RS, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the test solution. Proceed with 20 μL each of the test solution and the standard solution, and perform the test as directed under the Liquid Chromatography according to the operating conditions for related substances to determine the peak areas of dimecrotic acid in each solution, A_T and A_S.

$$\text{Content (\%) of magnesium dimecrotate } (C_{24}H_{26}O_8Mg) = 100 \times \frac{C_S}{C_T} \times \frac{A_T}{A_S} \times \frac{100}{94.79}$$

C_S: Concentration (mg/mL) of dimecrotic acid in the standard solution

C_T: Concentration (mg/mL) of dimecrotic acid in the test solution.

(2) ***Magnesium***—Weigh accurately about 0.15 g of Magnesium Dimecrotate, dissolve in 50 mL of water, and heat at 80 ℃. After cooling, add 15 mL of ammonia buffer solution and 2 mL of strong ammonia water, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS until reddish purple changes to bluish purple (Indicator: 40 mg of eriochrome black T-sodium chloride indicator).

Each of 0.05 mol/L Ethylenediaminetetraacetic acid disodium salt VS
= 1.21 mg of Mg

Packaging and storage Preserve in well-closed containers.

Magnesium Dimecrotate Tablets
디메크로트산마그네슘 정

Magnesium Dimecrotate Tablets contains NLT 90.0% and NMT 110.0% of the labeled amount of magnesium dimecrotate ($C_{24}H_{26}O_8Mg$: 466.75).

Method of preparation Prepare Magnesium Dimecrotate Tablets as directed under Tablets, with Magnesium Dimecrotate.

Identification (1) Powder 5 Magnesium Dimecrotate Tablets, add 25 mL of water, and dissolve until fully disintegrated; the pH of the resulting solution is between 6.0 and 8.5.

(2) Powder 1 tablet of Magnesium Dimecrotate Tablets, dissolve in water, and add 2 drops of bromine water; the resulting solution exhibits a pink color and then is decolorized. In the case of sugar-coated tablets, remove the sugar coating by previously washing the coated sugar with water.

(3) Powder 2 tablets of Magnesium Dimecrotate Tablets, extract with ethanol(95), and evaporate ethanol(95). Dissolve the residue in 10 mL of ethanol(95) and use this solution as the test solution. In the case of sugar-coated tablets, remove the sugar coating by previously washing the coated sugar with water. Separately, weigh 1 g of dimecrotic acid RS, add ethanol(95) to make 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 50 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of toluene, ethyl formate and anhydrous formic acid (5 : 4 : 1) as the developing solvent to a distance of about 13 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values of the spots obtained from the test solution and the standard solution are the same.

(4) Powder 2 Magnesium Dimecrotate Tablets, extract with ethanol(95), and evaporate ethanol(95). Dissolve the residue in 4 mL of ethanol(95) and use this solution as the test solution. In the case of sugar-coated tablets, remove the sugar coating by previously washing the coated sugar with water. Separately, weigh 6 g of magnesium chloride, dissolve in water to make 100 mL, and use this solution as the standard solution (0.5% as magnesium). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of cellulose with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of water, hydrochloric acid and methanol (1 : 1 : 1) to a distance of about 12 cm, and air-dry the plate. Spray evenly a solution of 8-hydroxyquinoline in methanol (1 in 100) on the plate, expose the plate to ammonia, and examine under ultraviolet light (wavelength 365 nm); the R_f values of the spots obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 tablet of Magnesium Dimecrotate Tablets at 100 revolutions per minute according to Method 1 under the Dissolution, using 900 mL of water as the dissolution medium. Take 20 mL of the dissolved solution 60 minutes after starting the Dissolution, filter through a membrane filter with a pore size not exceeding 0.45 μm, discard the first 10 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately about 75 mg of dimecrotic acid RS and add methanolic hydrochloric acid solution to make exactly 50 mL. Pipet 1 mL of this solution, add methanolic hydrochloric acid solution to make exactly 100 mL, and use this solution as the standard solution. Perform the test using the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, and measure the absorbance A_T and A_S at a wavelength of 280 nm. Meets the requirements if the dissolution rate in 60 minutes is NLT 60%.

Dissolution rate (%) of the labeled amount of Magnesium dimecrotate ($C_{24}H_{26}O_8Mg$)
$= W_S \times (A_T / A_S) \times (1 / C) \times 18 \times (100 / 94.79)$

W_S: Amount (mg) of dimecrotic acid RS
C: Labeled amount (mg) of magnesium dimecrotate ($C_{24}H_{26}O_8Mg$) in 1 tablet

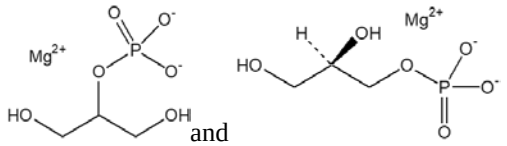
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tables of Magnesium Dimecrotate Tablets and powder. In the case of sugar-coated tablets, remove the sugar coating by previously washing the coated sugar with water. Weigh accurately an amount, equivalent to 75 mg of magnesium dimecrotate ($C_{24}H_{26}O_8Mg$), add 20 mL of methanolic hydrochloric acid solution, shake carefully to mix with a glass rod, and decant in a volumetric flask. Add the methanolic hydrochloric acid solution in the residue, repeat the procedure, and add methanolic hydrochloric acid solution to make exactly 50 mL. Filter this solution, discard the first filtrate, pipet 1 mL of the subsequent filtrate, add the methanolic hydrochloric acid solution to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 75 mg of dimecrotic acid RS and add methanolic hydrochloric acid solution to make exactly 50 mL. Pipet 1 mL of this solution, add methanolic hydrochloric acid solution to make 100 mL, and use this solution as the standard solution. Perform the test using the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, and measure the absorbance, A_T and A_S at a wavelength of 280 nm.

Amount (mg) of magnesium dimecrotate($C_{24}H_{26}O_8Mg$)
= Amount (mg) of dimecrotic acid RS × (A_T / A_S) × 1.055

Packaging and storage Preserve in light-resistant, well-closed containers.

Magnesium Glycerophosphate
글리세로인산마그네슘



and
and enantiomer

$C_3H_7MgO_6P$: 194.36
Magnesium 2,3-dihydroxypropyl phosphate

Magnesium Glycerophosphate contains NLT 11.0% and NMT 12.5% of Mg, calculated on the dried basis.

Description Magnesium Glycerophosphate occurs as a white powder.
It is practically insoluble in ethanol(95).
It dissolves in dilute solutions of acids.
It is hygroscopic.

Identification (1) Weigh 1 g of Magnesium Glycerophosphate into a test tube connected to a glass column, add 1 g of potassium hydrogen sulfate, mix, and then heat strongly to produce white vapors. Pass the vapors into a newly prepared 1% w/v solution of pentacyanonitrosyl iron(III) acid sodium dihydrate, and drop piperidine onto the filter paper; the filter paper develops a blue color in contact with piperidine.

(2) Incinerate 0.1 g of Magnesium Glycerophosphate in a crucible, add 5 mL of nitric acid to the residue, and heat it for 1 min on a steam bath and filter it. The filtrate responds to the Qualitative test 2) for phosphate.

(3) Magnesium Glycerophosphate responds to the Qualitative tests for magnesium.

Purity (1) ***Clarity and color of solution***—Dissolve 2.5 g of Magnesium Glycerophosphate in water and make 50 mL; the resulting solution is not more turbid than the reference turbidity solution.

Reference turbidity solution—Add 70 mL of water to 30 mL of standard turbidity solution. Prepare when use and shake well for use.

Prepare as directed under the Reagents of Pharmaceutical plastic container test.

(2) ***Acid***—Dissolve 1.0 g of Magnesium Glycerophosphate in 100 mL of water and titrate with 0.1 mol/L sodium hydroxide solution (indicator: 2 drops of phenolphthalein TS); the consumption is NMT 1.5 mL.

(3) ***Chloride***—Proceed with 0.20 g of Magnesium Glycerophosphate and perform the test. Prepare the control solution with 0.84 mL of 0.01 mol/L hydrochloric acid solution (NMT 0.15%).

(4) ***Sulfate***—Proceed with 0.20 g of Magnesium Glycerophosphate and perform the test. Prepare the control solution with 0.42 mL of 0.005 mol/L sulfuric acid VS (NMT 0.1%).

(5) ***Phosphate***—Dissolve 2.5 g of Magnesium Glycerophosphate in water to make 50mL. To 4.0 mL of this solution, add water to make 100 mL. And, to 1.0 mL of this solution, add water to make 100 mL and use this solution as the test solution. Add 4 mL of sulfomolybdic acid TS and 0.1 mL of tin(II) chloride solution to the test solution and allow to stand for 10 minutes; the color obtained is not darker than the color obtained by preparing the mixture of 2 mL of phosphate standard solution and 98 mL of water as described above (NMT 0.5%).

(6) ***Heavy metals***—Dissolve 1.0 g of Magnesium Glycerophosphate in 20 mL of water, add 15 mL of hydrochloric acid, and then add 25 mL of 4-methyl-2-pentanone. Shake the mixture for 1 minute. After standing, take the aqueous layer and evaporate to dryness. Dissolve the residue in 2 mL of dilute acetic acid, add 50 mL of water, and use this solution as the test solution. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 20 ppm).

(7) ***Iron*—**Put 67 mg of Magnesium Glycerophosphate into a Nestler tube and dissolve it in water to make 10 mL, add 2 mL of 20% w/v citric acid solution and 0.1 mL of mercaptoacetic acid, and mix, and then, make the solution alkaline by adding 10 mol/L ammonia water and make 20 mL with water. Allow it to stand for 5 minutes; the color of this solution is less intense than that obtained by taking 1.0 mL of the iron standard solution and adjusting the volume to 10 mL with water, using the same procedure described above (NMT 150 ppm).

(8) ***Glycerin and ethanol solution*—**Dissolve 1.0 g of Magnesium Glycerophosphate in 25 mL of ethanol(95) and shake for 2 minutes, filter the mixture and wash the residue with 5 mL of ethanol(95). Combine the filtrate and the washed liquid, then evaporate it to dryness. Next, dry the residue at 70 ℃ for 1 hour and weigh the mass (NMT 1.5%).

Loss on drying NMT 12.0% (1 g, 150 ℃, 4 h.).

Assay Weigh accurately about 0.2 g of Magnesium Glycerophosphate, dissolve it in 40 mL of water, and then add 10 mL of ammonia-ammonium chloride buffer solution (pH 10.0). Titrate the solution with 0.1 mol/L ethylenediaminetetraacetic acid disodium salt solution. The endpoint of the titration is when the purple color turns blue (indicator: Eriochrome Black T-sodium chloride indicator, 50 mg).

Each mL of 0.1 mol/L
ethylenediaminetetraacetic acid disodium salt VS
= 2.431 of mg

Packaging and storage Preserve in tight containers.

Magnesium Hydroxide
수산화마그네슘

$Mg(OH)_2$: 58.32

[*1309-42-8*]

Magnesium Hydroxide, when dried, contains NLT 95.0% and NMT 100.5% magnesium hydroxide [$Mg(OH)_2$].

Description Magnesium Hydroxide occurs as a white, massive powder.
It is practically insoluble in water or ethanol(95).
It dissolves in dilute hydrochloric acid.

Identification A solution of Magnesium Hydroxide in 3 mol/L hydrochloric acid TS (1 in 20) responds to the Qualitative Analysis (1) for magnesium.

Purity (1) ***Soluble salts*—**Weigh accurately 2.0 g of Magnesium Hydroxide, place in a beaker, add 100 mL of water, and cover with a watch glass. Heat on a steam bath for 5 minutes, and filter while it is still hot. After cooling, add water to the filtrate to make 100 mL. To 50 mL of this solution, add 2 drops of methyl red TS, and titrate with 0.1 mol/L sulfuric acid VS until the resulting solution exhibits a red color; the consumed amount is NMT 2.0 mL. Also, from the solution made to 100 mL above, evaporate 25 mL to dryness, and dry the residue at 105 ℃ for 3 hours; the amount is NMT 10 mg.

(2) ***Carbonate*—**To 0.10 g of Magnesium Hydroxide, add 5 mL of water and boil. After cooling, add 5 mL of 6 mol/L acetic acid; the resulting solution hardly exhibits bubbles.

(3) ***Calcium*—**Place 0.25 g of Magnesium Hydroxide, previously dried, in a beaker, add 30 mL of diluted hydrochloric acid (1 in 10), and stir to dissolve, with heating if necessary, Place 200 mL of this solution in a volumetric flask, add 4 mL of lanthanum TS, add water to make 200 mL, and use this solution as the test solution. Separately, weigh accurately 249.7 mg of calcium carbonate, previously dried at 300 ℃ for 3 hours and cooled in a silica gel desiccator for 2 hours, dissolve in a small amount of hydrochloric acid, and add water to make exactly 100 mL. Place 5.0, 10.0 and 15.0 mL each of this solution in respective 1000-mL volumetric flasks, add 20 mL of lanthanum TS and 40 mL of diluted hydrochloric acid (1 in 10) to each, fill each flask to the gauge line, and use each of these solutions as the standard solution. Each of these standard solutions contains 5.0, 10.0 and 15.0 μg of calcium per mL, respectively. Place 4 mL of lanthanum TS and 10 mL of diluted hydrochloric acid (1 in 10) in a 200-mL volumetric flask, add water to the gauge line, and use this solution as the blank test solution. Perform the test with the blank test solution, the test solution, and the standard solutions as directed under the calibration curve under the Atomic Absorption Spectroscopy, and determine the amount of calcium; the amount is NMT 1.5%.

Gas: Air–acetylene
Lamp: Calcium hollow cathode lamp
Wavelength: 422.7 nm

(4) ***Heavy metals*—**Dissolve 1.0 g of Magnesium Hydroxide in 15 mL of 3 mol/L hydrochloric acid TS, and evaporate to dryness on a steam bath. Dissolve the residue in 20 mL of water, and filter. To the filtrate, add 2 mL of 1 mol/L acetic acid, neutralize with a Litmus paper, add water to make 50 mL, and use this solution as the test solution. Separately, proceed with 15 mL of 3 mol/L hydrochloric acid TS in the same manner as the preparation of test solution, and use the resulting solution as the control solution. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(5) ***Lead*—**Dissolve 1.0 g of Magnesium Hydroxide in 20 mL of 3 mol/L hydrochloric acid TS, and use this solution as the test solution. Place the test solution in a separatory funnel and wash it with 10 mL of water. Add 6 mL of diammonium hydrogen citrate solution, 2 mL of hydroxylamine hydrochloride TS and 2 drops of phenol red TS, and add strong ammonia water until the solution becomes alkaline. If necessary, cool the solution, add 2 mL of potassium cyanide solution, and perform extrac-

tion with every 5 mL of extracting dithizone solution until the extract exhibits a green color. Combine the resulting extracts in another separatory funnel. To the combined extracts, add 20 mL of diluted nitric acid (1 in 100), shake to mix for 30 seconds, and discard the chloroform layer. To the nitric acid layer, add 5.0 mL of standard dithizone solution and 4 mL of ammonia-cyanide TS, and shake to mix for 30 seconds; the violet color of the chloroform layer is not more intense than the color of a solution prepared by proceeding with 1.5 mL of diluted lead standard solution (1 in 10) in the same manner as the preparation of the test solution (NMT 1.5 ppm).

Ammonia-cyanide TS—Dissolve 2 g of potassium cyanide in 15 mL of ammonia water(28), and dilute with water to make 100 mL.

(6) ***Arsenic***—To 0.5 g of Magnesium Hydroxide, add 10 mL of dilute hydrochloric acid, and warm to dissolve. After cooling, use this solution as the test solution and perform the test (NMT 4 ppm).

Loss on drying NMT 2.0% (1 g, 105 ℃, 2 hours).

Loss on ignition Between 30.0% and 33.0% 1 g, 800 ℃).

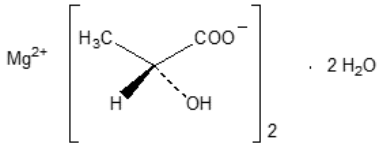
Microbiological examination of non-sterile products No colon bacterium is detected when tested.

Assay Weigh accurately about 75 mg of Magnesium Hydroxide, previously dried, place in an Erlenmeyer flask, add 2 mL of 3 mol/L hydrochloric acid TS, and stir to dissolve. To this solution, add 100 mL of water, and add 1 mol/L sodium hydroxide TS to adjust the pH to 7. To this, add 5 mL of pH 10.7 ammonia-ammonium chloride buffer solution, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS until the resulting solution exhibits a blue color (indicator: 0.15 mL of eriochrome black T TS).

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.916 mg of $Mg(OH)_2$

Packaging and storage Preserve in tight containers.

Magnesium Lactate Hydrate
락트산마그네슘수화물



and enantiomer

$C_6H_{10}MgO_6 \cdot 2H_2O$: 238.48

Magnesium bis(2-hydroxypropanoate); Mixtures of magnesium (2*R*)-,(2*S*)-and (2*RS*)-2-hydroxy propanoate dihydrate

Magnesium Lactate Hydrate, when dried, contains NLT 98.0% and NMT 102.0% of magnesium lactate ($C_6H_{10}MgO_6$: 202.44).

Description Magnesium Lactate Hydrate occurs as a white powder and is odorless.
It is soluble in hot water and slightly soluble in cold water.

Identification Weigh about 1 g of Magnesium Lactate Hydrate, add 10 mL of dilute hydrochloric acid, dissolve by heating the solution on a steam bath, and filter. The filtrate responds to the Qualitative Analysis for magnesium salt and lactate.

pH Dissolve about 4.0 g of Magnesium Lactate Hydrate in 100 mL of water by heating, and cool; the pH of this solution is between 4.5 and 6.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Magnesium Lactate Hydrate in 50 mL of water by heating on a steam bath; the resulting solution is colorless and clear.

(2) ***Heavy metals***—Proceed with 2.0 g of Magnesium Lactate Hydrate according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Chloride***—Dissolve 0.35 g of Magnesium Lactate Hydrate in 30 mL of water by heating on a steam bath and add 6 mL of nitric acid (1 in 10) and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 1.0 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.1%).

Loss on drying Between 11.9% and 18.2% (1 g, 130 ℃, 3 hours).

Assay Weigh accurately about 1.0 g of Magnesium Lactate Hydrate, previously dried, add water, and dissolve by heating on a steam bath. Add water to make 200.0 mL and filter. Add 90 mL of water to 10.0 mL of the filtrate, put 10 mL of triethanolamine (1 in 2) and 5 mL of ammonia-ammonium chloride buffer solution (pH 10.7), and titrate with 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 1 drop of eriochrome black T TS).

Each mL of 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.0244 mg of $C_6H_{10}MgO_6$

Packaging and storage Preserve in tight containers.

Magnesium Lactate and Pyridoxine Hydrochloride Tablets
락트산마그네슘·피리독신염산염 정

Magnesium Lactate and Pyridoxine Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of magnesium lactate hydrate ($C_6H_{10}MgO_6 \cdot 2H_2O$: 238.48) and NLT 90.0% and NMT 150.0% of the labeled amount of pyridoxine hydrochloride.

Method of preparation Prepare as directed under Tablets, with Magnesium Lactate Hydrate and Pyridoxine Hydrochloride.

Identification (1) ***Magnesium lactate hydrate***—(i) Magnesium: Weigh an amount of Magnesium Lactate and Pyridoxine Hydrochloride Tablets, equivalent to 1 g of magnesium lactate hydrate, add 10 mL of dilute hydrochloric acid and dissolve it by warming on a steam bath and filter. Use this filtrate as the test solution. This test solution responds to the Qualitative Analysis for magnesium.

(ii) Lactic acid: Add potassium permanganate TS to the test solution and heat it; the odor of acetaldehyde is evolved.

(2) ***Pyridoxine hydrochloride***—Take Magnesium Lactate and Pyridoxine Hydrochloride Tablets and perform the test as directed under the Identification of pyridoxine hydrochloride under Analysis for Vitamins

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Magnesium lactate hydrate***—Weigh accurately the mass of NLT 20 tablets of Magnesium Lactate and Pyridoxine Hydrochloride Tablets, and powder. Weigh accurately about 1.0 g of magnesium lactate hydrate ($C_6H_{10}MgO_6 \cdot 2H_2O$), add water, and dissolve by heating on a steam bath. After cooling, add water to make 200 mL, and filter. Add 90 mL of water to 10.0 mL of the filtrate, put 10 mL of triethanolamine (1 in 2) and 5 mL of ammonia-ammonium chloride buffer solution (pH 10.7), and titrate with 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 1 drop of eriochrome black T TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.3848 mg of $C_6H_{10}MgO_6 \cdot 2H_2O$

(2) ***Pyridoxine hydrochloride***—Weigh accurately the mass of over 20 tablets of Magnesium Lactate and Pyridoxine Hydrochloride Tablets and powder. Perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in tight containers.

Magnesium Oxide
산화마그네슘

MgO : 40.30

[*1309-48-4*]

Magnesium Oxide, when ignited, contains NLT 96.0% and NMT 101.0% of magnesium oxide (MgO).

5 g of Magnesium Oxide of which the volume is NMT 30 mL can be referred to as heavy magnesium oxide by the nickname.

Description Magnesium Oxide occurs as white powder or grains. It is odorless.
It is practically insoluble in water, ethanol(95) or ether.
It dissolves in dilute hydrochloric acid.
It absorbs moisture and carbon dioxide in the air.

Identification A solution of Magnesium Oxide in dilute hydrochloric acid (1 in 50) responds to the Qualitative Analysis for magnesium salt.

Purity (1) ***Alkali and soluble salts***—Place 2.0 g of Magnesium Oxide in a beaker, add 100 mL of water, cover with a watch glass, and heat on a steam bath for 5 minutes. Immediately filter, cool, take 50 mL of the filtrate, and add 2 drops of methyl red TS and 2.0 mL of 0.05 mol/L sulfuric acid VS. The solution exhibits a red color. Also, evaporate 25 mL of the filtrate to dryness and dry the residue at 105 ℃ for 1 hour. The obtained amount is NMT 10 mg.

(2) ***Carbonate***—To 0.10 g of Magnesium Oxide, add 5 mL of water and boil. After cooling, add 5 mL of acetic acid(31). The solution hardly exhibits bubbles.

(3) ***Heavy metals***—Dissolve 1.0 g of Magnesium Oxide in 20 mL of dilute hydrochloric acid, evaporate to dryness on a steam bath, and dissolve the residue in 35 mL of water. Add 1 drop of phenolphthalein TS, neutralize with ammonia TS, and add 2 mL of dilute hydrochloric acid. If necessary, filter, wash the filter paper, combine the washings with the filtrate, and add water to make 50 mL. Use this as the test solution and perform the test. Prepare the control solution by adding 1 drop of phenolphthalein TS to 20 mL of dilute hydrochloric acid, neutralizing with ammonia TS, and adding 2 mL of dilute hydrochloric acid, 2.0 mL of lead standard solution, and water to make 50 mL (NMT 20 ppm).

(4) ***Iron***—Prepare the test solution with 40 mg of Magnesium Oxide according to Method 1 and perform the test according to Method A. Prepare the control solution with 2.0 mL of iron standard solution (NMT 500 ppm).

(5) ***Calcium oxide***—Weigh accurately 0.25 g of Magnesium Oxide, previously ignited, add 6 mL of dilute hydrochloric acid and heat to dissolve. After cooling, add 300 mL of water, 3 mL of L-tartaric acid solution (1 in 5), 10 mL of 2,2',2″-nitrilotriethanol solution (3 in 10), and 10 mL of 8 mol/L potassium hydroxide TS, allow to

stand for 5 minutes, and titrate with 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 0.1 g of NN indicator). However, the endpoint of titration is when the purple color of the solution turns to the blue color. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 0.5608 mg of CaO

The amount of calcium oxide (CaO : 56.08) is NMT 1.5%.

(6) ***Arsenic*—**Dissolve 0.5 g of Magnesium Oxide in 5 mL of dilute hydrochloric acid. Use this as the test solution and perform the test (NMT 4 ppm).

(7) ***Acid insolubles*—**To 2.0 g of Magnesium Oxide, add 75 mL of water. While shaking for mixing, add 12 mL of hydrochloric acid dropwise, and boil for 5 minutes. Filter with a filter paper for qualitative analysis and take the insolubles. Wash the insolubles with water until no turbidity is observed even after adding silver nitrate TS to the washings. Ignite the residue together with the filter paper to ash. The obtained amount is NMT 2.0 mg.

(8) ***Fluoride*—**Perform the test as directed in Purity (7) under Natural Aluminum Silicate. The amount of fluorine (F : 19.00) is NMT 0.08%.

Loss on ignition NMT 10% (0.25 g, 900 ℃, constant mass).

Assay Weigh accurately about 0.2 g of Magnesium Oxide, previously ignited at 900 ℃ to a constant mass, dissolve in 10 mL of water and 4.0 mL of dilute hydrochloric acid, and add water to make exactly 100 mL. Pipet 25 mL of this solution, add 50 mL of water and 5 mL of pH 10.7 ammonia-ammonium chloride buffer solution, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 40 mg of eryochrome black T-sodium chloride indicator). Perform a blank test in the same manner and make any necessary correction.
From the consumed amount of the 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS, subtract the amount of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS that is equivalent to calcium oxide (CaO) obtained as directed in Purity (5).

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.0152 mg of MgO

Each mg of calcium oxide (CaO)
= 0.36 mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS

Packaging and storage Preserve in tight containers.

Magnesium Silicate
규산마그네슘

Magnesium Silicate contains NLT 45.0% of silicon dioxide (SiO_2: 60.08) and NLT 20.0% of magnesium oxide (MgO: 40.30) and the ratio of percentages (%) of silicon dioxide to magnesium oxide is NLT 2.2 and NMT 2.5.

Description Magnesium Silicate occurs as a white fine powder. It is odorless and tasteless.
It is practically insoluble in water, ethanol(95) or ether.

Identification (1) Weigh about 0.5 g of Magnesium Silicate and dissolve in 10 mL of dilute hydrochloric acid, and shake to mix and filter the solution. Add ammonia TS to the filtrate to neutralize. The resulting solution responds to the Qualitative Analysis for magnesium salt.

(2) Prepare the bead by fusing sodium ammonium hydrogen phosphate tetrahydrate and place the bead on a platinum loop. Coast Magnesium Silicate to fuse again: infusible masses appear in the bead, which changes to an opaque bead with clear strips upon cooling.

Purity (1) ***Soluble salts*—**Weigh 10.0 g of Magnesium Silicate and dissolve in 150 mL of water, and shake to mix on a steam bath for 60 minutes. After cooling it down, add water to make 150 mL. Pipet 75 mL of the resulting transparent solution from centrifugation, add water to make 100 mL, and use this solution as the test solution. Pipet 25 mL of the test solution to evaporate to dryness on a steam bath and ignite at 700 ℃ for 2 hours; the resulting solution is NMT 20 mg.

(2) ***Alkali*—**Pipet 20 mL of the test solution from (1) and add 2 drops of phenolphthalein TS and 1.0 mL of 0.1 mol/L hydrochloric acid solution; the resulting solution is colorless.

(3) ***Chloride*—**Pipet 10 mL of the test solution from (1) and add 6 mL of dilute nitric acid and water to make 50 mL. Use the resulting solution as the test solution and perform the test. Prepare the control solution with 0.75 mL of 0.01 mol/L hydrochloric acid solution (NMT 0.053%).

(4) ***Fluoride*—**Weigh 5.0 g of Magnesium Silicate, add 45 mL of 0.1 mol/L hydrochloric acid TS, shake to mix at room temperature for 15 minutes, and filter with a 0.45 μm membrane filter. Wash the filter with 1 mL of 0.1 mol/L hydrochloric acid TS repeat this procedure for 5 times, transfer the washings in a flask, and add 0.1 mol/L hydrochloric acid TS to make exactly 50 mL. Use this solution as the test solution. Separately dissolve alizarin complexone in 60% 2-propanol so that each mL contains 0.1 g, and if necessary, filter and use this solution as the indicator. Pipet 5.0 mL of the test solution and transfer to a 25 mL volumetric flask. Add 5.0 mL of indicator and water to make 25 mL, and allow it to stand at room temperature for 1 hour. With this solution, determine the absorbance of the test solution, as directed under Ultraviolet-visible Spectroscopy, using the blank test solution

made by adding 5.0 mL of indicator and 15.0 mL of water to 5.0 mL of 0.1 mol/L hydrochloric acid TS; the absorbance of the test solution at 620 nm is not greater than that of 5 mL of the following control solution (NMT 10 ppm).

Control solution—Dissolve sodium fluoride in 0.1 mol/L hydrochloric acid TS so that each mL contains 2.21 μg.

(5) ***Sulfate***—Add 3 mL of dilute hydrochloric acid to the residue from (1) and heat on a steam bath for 10 minutes, add 30 mL of water, and filter it. Wash with water, and combine the filtrate and the washings to make 50 mL. Pipet 4 mL of this solution, and add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use the resulting solution as the test solution and perform the test. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.480%).

(6) ***Heavy metals***—Weigh 1.0 g of Magnesium Silicate, add 20 mL of water and 3 mL of hydrochloric acid, boil for 2 minutes, filter, and wash twice with 5 mL of water, respectively. Combine the filtrate and the washings, evaporate to dryness on a steam bath, add 2 mL of dilute acetic acid to the residue, and warm to dissolve. If necessary, filter and add water to make 50 mL. Use the resulting solution as the test solution and perform the test. Prepare the control solution by adding 2 mL of dilute acetic acid and water to 2.0 mL of lead standard solution to make 50 mL (NMT 20 ppm).

(7) ***Arsenic***—Weigh 0.4 g of Magnesium Silicate in 5 mL of dilute hydrochloric acid, shake well to mix, and heat gently until it boils. Cool it down quickly, and then centrifuge. Add 5 mL of dilute hydrochloric acid to the residue, shake well to mix, and centrifuge. Add 10 mL of water again to perform the same procedure, add all the extracts, and heat to concentrate on a steam bath to make 5 mL. Use this solution as the test solution (NMT 5 ppm).

Loss on ignition NMT 34.0% (0.5 g, 850 ℃, 3 hours).

Acid-neutralizing capacity Weigh accurately about 0.2 g of Magnesium Silicate, transfer to a flask with a stopper, add exactly 30 mL of 0.1 mol/L hydrochloric acid and 20 mL of water, and shake to mix at 37 ± 2 ℃ for 1 hour. Cool, pipet 25 mL of the clear supernatant, and titrate excess hydrochloric acid with 0.1 mol/L sodium hydroxide solution by shaking well to mix until the pH becomes 3.5. The volume of 0.1 mol/L hydrochloric acid consumed, calculated on a residue basis from loss on ignition of Magnesium Silicate, is between 140 mL and 160 mL to per g of Magnesium Silicate.

Assay (1) ***Silicon dioxide***—Weigh accurately about 0.7 g of Magnesium Silicate, add 10 mL of 0.5 mol/L sulfuric acid TS, and evaporate to dryness on a steam bath. Add 25 mL of water to the residue, and heat on a steam bath for 15 minutes with occasional stirring. Filter the clear supernatant through a filter paper, add 25 mL of hot water to the residue, stir to mix, and decant the clear supernatant on the filter paper to filter. Wash the residue in the same manner twice with 25 mL of hot water respectively, transfer the residue onto the filter paper, and wash with hot water until the washings do not respond to the Qualitative Analysis (1) for sulfate. Transfer the residue to a platinum crucible with the filter paper, ignite to incinerate, and ignite again at 775 to 825 ℃ for 30 minutes. Cool and weigh the residue as a (g). Moisten the residue with water, and add 6 mL of hydrofluoric acid and 3 drops of sulfuric acid. Evaporate to dryness, ignite for 5 minutes, cool, and weigh the residue as b (g).

$$\text{Amount of silicon dioxide } (SiO_2)\ (\%) = \frac{a - b}{\text{Amount of sample (g)}} \times 100$$

(2) ***Magnesium oxide***—Weigh accurately about 0.3 g of Magnesium Silicate, transfer to a Erlenmeyer flask, add 10 mL of 0.5 mol/L sulfuric acid TS, and heat on a steam bath for 15 minutes. Transfer to a 100-mL volumetric flask after cooling, wash the Erlenmeyer flask with water, and add the washings and water to make 100 mL. Filter this solution, pipet 50 mL of the filtrate, add 50 mL of water and 5 mL of diluted 2,2′,2″-nitrilotriethanol (1 in 2), and shake well to mix. Add 2.0 mL of ammonia TS and 10 mL of ammonia-ammonium chloride buffer solution, pH 10.7, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid (EDTA) disodium salt solution (indicator: 40 mg of Eryochrome black T-sodium chloride indicator).

Each mL of 0.05 mol/L
ethylenediaminetetraacetic acid disodium salt VS
= 2.0152 mg of MgO

(3) ***Ratio of percentages (%) of silicon dioxide (SiO_2) to magnesium oxide (MgO)***—Calculate from the results obtained by the Assay (1) and (2).

Packaging and storage Preserve in well-closed containers.

Magnesium Sulfate Hydrate
황산마그네슘수화물

$MgSO_4 \cdot 7H_2O$: 246.48
Magnesium Sulfate Heptahydrate [10034-99-8]

Magnesium Sulfate Hydrate, when ignited, contains NLT 99.0% and NMT 101.0% of magnesium sulfate ($MgSO_4$: 120.37).

Description Magnesium Sulfate Hydrate occurs as a colorless or white crystalline. It has a bitter, cool, and salty taste.
It is very soluble in water, and practically insoluble in ethanol(95) or ether.

Identification An aqueous solution of Magnesium Sul-

fate Hydrate (1 in 40) changes blue litmus paper to red and responds to the Qualitative Analysis for magnesium salt and sulfate.

pH Dissolve 1.0 g of Magnesium Sulfate Hydrate in 20 mL of water; the pH of this solution is between 5.0 and 8.2.

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Magnesium Sulfate Hydrate in 20 mL of water; the resulting solution is colorless and clear.

(2) ***Chloride*—**Perform the test with 1.0 g of Magnesium Sulfate Hydrate. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid (NMT 0.014%).

(3) ***Heavy metals***—Proceed with 2.0 g of Magnesium Sulfate Hydrate according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Mercapto compounds***—Dissolve 2.0 g of Magnesium Sulfate Hydrate in 20 mL of water, and add 1 mL of acetic acid(31) and 5 drops of potassium hexacyanoferrate(II) TS; the resulting solution does not become turbid.

(5) ***Iron*—** (i) Perform the test when used in the manufacturing of oral preparations. Weigh accurately 0.5 g of Magnesium Sulfate Hydrate, dissolve in water to make 40 mL, dilute with water to make 45 mL if necessary, and add 2 mL of hydrochloric acid. Use this solution as the test solution. Add water to 1.0 mL of iron standard solution to make 45 mL, add 2 mL of hydrochloric acid, and use this solution as the standard solution. Add 50 mg of ammonium peroxydisulfate and 3 mL of 30% ammonium thiocyanate to the test solution and the standard solution and mix; the color obtained from the test solution is not more intense than that from the standard solution (NMT 20 ppm).

(ii) Perform the test when used in the manufacturing of parenteral preparations. However, wash all the glass containers used in this test with dilute hydrochloric acid before use. Weigh accurately 10.0 g of Magnesium Sulfate Hydrate, dissolve in 35 mL of hydrochloric acid (1 in 1000) by sonication, and use this solution as the test solution. Pipet 5.0 mL of iron standard solution, add hydrochloric acid (1 in 1000) to make exactly 50 mL, and use this solution as the iron standard solution. Separately, to each of three 50-mL volumetric flasks, add 2.0, 5.0, and 10.0 mL of iron standard solution, and add hydrochloric acid (1 in 1000) to make 35 mL of standard solutions containing 2.0, 5.0, and 10.0 μg of iron. Separately, transfer 35 mL of hydrochloric acid (1 in 1000) in a 50-mL volumetric flask, and use this solution as the blank test solution. To each of the test solution, the standard solution, and the blank test solution, add 5 mL of ascorbic acid and 5 mL of coloring agent, add hydrochloric acid (1 in 1000) to make 50 mL, allow to stand for 10 minutes, and perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy using the blank test solution as the control solution. Measure the absorbance at the absorption maximum wavelength around 594 nm, and determine the iron content in the test solution using the calibration curve obtained from the absorbance of the standard solution; it is NMT 0.5 ppm.

Ascorbic acid TS—Dissolve 1.34 g of L-ascorbic acid in water to make 100 mL. This preparation is prepared before use.

Coloring agent—Dissolve 0.38 g of the color reagent 3-(2-pyridyl)-5,6-di-(2-furyl)-1,2,4-triazine-5',5"-disulfonic acid sodium salt in ammonium acetate solution (1 in 2) to make 100 mL. This preparation is prepared before use.

(6) ***Calcium*—**Dissolve 1.0 g of Magnesium Sulfate Hydrate in 5.0 mL of dilute hydrochloric acid and water to make 100 mL, and use this solution as the test solution. Separately, dissolve 1.0 g of Magnesium Sulfate Hydrate, 5 mL of dilute hydrochloric acid, and water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbance, A_T and A_S, of the test solution and the standard solution as directed under the Atomic Absorption Spectroscopy according to the following conditions; A_T is less than (A_S - A_T) (NMT 0.02%).

Gas: Air–acetylene or hydrogen
Lamp: Calcium hollow cathode lamp
Wavelength: 422.7 nm

(7) ***Arsenic*—**Prepare the test solution with 1.0 g of Magnesium Sulfate Hydrate according to Method 1 and perform the test (NMT 2 ppm).

(8) ***Selenium*—**Weigh accurately 0.2 g of Magnesium Sulfate Hydrate, and burn as directed under the Oxygen Flask Combustion, using 50 mL of 0.25 mol/L nitric acid TS as the absorbent. Use a combustion flask with a volume of 1000 mL, combust, wash the stopper and the inner wall of the flask with 10 mL of water, and use 20 mL of water to move the solution in the combustion flask into a 150-mL beaker. Heat gently until it boils, boil for 10 minutes, cool to room temperature, and use this solution as the test solution. Separately, pipet 6.0 mL of standard selenium stock solution, add 25 mL of diluted nitric acid (1 in 30) and 25 mL of water, and use this solution as the standard solution. Add diluted ammonia water(28) (1 in 2) to each of the test and standard solutions, adjust the pH to 2.0 ± 0.2, dilute with water to make exactly 60 mL, and add 10 mL of water to move to a separatory funnel. Wash the separatory funnel with 10 mL of water. Add 0.2 g of hydroxylamine hydrochloride, dissolve by stirring, add 5.0 mL of 2,3-diaminonaphthalene TS, and put a stopper. Mix by stirring and allow to stand at room temperature for 100 minutes. To the resulting mixture, add 5.0 mL of cyclohexane, shake vigorously for two minutes, and allow to stand. If the layer is separated, remove the water layer, centrifuge cyclohexane extracts to remove water, and take the cyclohexane layer. With these solutions, perform the test as directed under the Ultraviolet-visible Spectros-

copy, using a solution obtained by proceeding with a solution of 25 mL of water in 25 mL of diluted nitric acid (1 in 30) in the same manner. Determine the absorption at absorption maximum wavelength of around 380 nm; the absorption of the solution from the test solution is not greater than the absorption from the standard solution (NMT 30 ppm).

Loss on ignition Between 45.0% and 52.0% (1 g, previously dried at 105 ℃ for 2 hours and ignited at 450 ℃ for 3 hours).

Assay Weigh accurately 0.6 g of Magnesium Sulfate Hydrate, previously dried at 105 ℃ for 2 hours and ignited at 450 ℃ for 3 hours, and dissolve in 2 mL of dilute hydrochloric acid and water to make exactly 100 mL. Pipet 25 mL of this solution, and perform the test as directed under the Assay of Magnesium Oxide.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 6.018 mg of $MgSO_4$

Packaging and storage Preserve in well-closed containers.

Magnesium Sulfate Injection
황산마그네슘 주사액

Magnesium Sulfate Injection, as an aqueous injection, contains NLT 95.0% and NMT 105.0% of the labeled amount of magnesium sulfate hydrate ($MgSO_4 \cdot 7H_2O$: 246.48).

Method of preparation Prepare as directed under Injections, with Magnesium Sulfate Hydrate.

Description Magnesium Sulfate Injection occurs as a colorless and clear liquid.

Identification Take Magnesium Sulfate Injection in the amount equivalent to 0.5 g of magnesium sulfate hydrate according to the labeled amount, and add water to make 20 mL; the solution responds to the Qualitative Analysis for magnesium salt and sulfate.

pH Between 5.5 and 7.0. When the labeled concentration is higher than 5%, use water to make a 5% solution and perform the test with this solution.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.09 EU per mg of Chlorpheniramine Maleate Injection. Use water for bacterial endotoxins test to dilute to 5 w/v% and perform the test.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

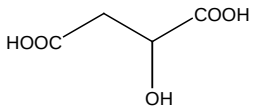
Extractable volume of injections Meets the requirements.

Assay Pipet Magnesium Sulfate Injection in the amount equivalent to about 0.3 g of magnesium sulfate hydrate ($MgSO_4 \cdot 7H_2O$), add water to make 75 mL, and add 5 mL of ammonia-ammonium chloride buffer solution, pH 10.7. Perform the test with this solution as directed under the Assay under Magnesium Sulfate.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 12.32 mg of $MgSO_4 \cdot 7H_2O$

Packaging and storage Preserve in hermetic containers. A plastic container for drugs may be used.

L-Malic Acid
L-말산



$C_4H_6O_5$: 134.09

2-Hydroxybutanedioic acid, [*97-67-6*]

L-Malic Acid, when dried, contains NLT 99.0% and NMT 101.0% of L-malic acid ($C_4H_6O_5$).

Description L-Malic Acid occurs as white or pale yellow crystals or a crystalline powder.
It is odorless.
It is freely soluble in water or in ethanol(95) and practically insoluble in chloroform.

Melting point—About 100 ℃.

Identification (1) An aqueous solution of L-Malic Acid (1 in 50) turns blue litmus test paper moistened with water to red.

(2) Put 0.1 g of L-Malic Acid and 0.1 g of resorcin in a test tube, shake well to mix, add 0.3 mL of sulfuric acid, heat until bubbles form. Then, carefully add 2 mL of cooled water and 15 mL of sodium hydroxide TS; the solution turns red and shows blue fluorescence when observed under UV light.

Optical rotation $[\alpha]_D^{20}$: Between -1.8° and -2.6° (after drying, 2 g, water 50 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g of L-Malic Acid in 10 mL of water; the solution is colorless and clear.

(2) ***Chloride***—Proceed with 0.5 g of L-Malic Acid and perform the test. Prepare the control solution with 0.3 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.02%).

(3) ***Sulfate***—Proceed with about 1.0 g of L-Malic Acid and perform the test. Prepare the control solution with 0.4 mL of 0.005 mol/L sulfuric acid VS (NMT 0.019%).

(4) ***Heavy metals***—Proceed with 2.0 g of L-Malic Acid according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Arsenic***—Prepare the test solution with 2.0 g of L-Malic Acid according to Method 1 and perform the test (NMT 1 ppm).

(6) ***Readily carbonizable substances***—Proceed with 0.5 g of L-Malic Acid and perform the test; the color of the test solution is not more intense than that of the matching fluid for color K.

Loss on drying NMT 10% (1 g, in vacuum, 60 ℃, 3 hours).

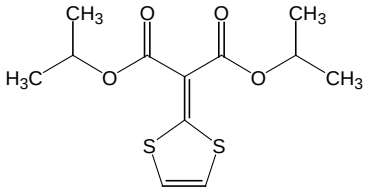
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.1 g of L-Malic Acid, previously dried, dissolve in 50 mL water, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 2 drops of phenolphthalein TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 6.704 mg of $C_4H_6O_5$

Packaging and storage Preserve in tight containers.

Malotilate
말로틸레이트



$C_{12}H_{16}O_4S_2$: 288.39
1,3-Dithiol-2-ylidenepropanedioic acid bis(1-methylethyl) ester; 1,3-bis(1-Methylethyl) 2-(1,3-dithiol-2-ylidene)-propanedioic acid ester, [*59937-28-9*]

Malotilate, when dried, contains NLT 98.5% and NMT 101.0% of malotilate ($C_{12}H_{16}O_4S_2$).

Description Malotilate occurs as white or pale yellow crystals or a crystalline powder.
It is freely soluble in methanol, in chloroform, or in ethyl acetate, soluble in ethanol(95) or in hexane and practically insoluble in water.
It is gradually colored by light.

Melting point—Between 60 and 63 ℃.

Identification (1) To 2 mL of a solution of Malotilate in chloroform (1 in 20), add 2 mL of 2,4,7-trinitro-9-fluorenone TS; the solution turns red.

(2) To 0.1 g of Malotilate, add 0.5 g of sodium hydroxide, heat slowly to melt, carbonize, cool, and add 10 mL of dilute hydrochloric acid; the gas generated turns lead acetate paper to black.

(3) Determine the absorption spectrum of a solution of Malotilate in methanol (1 in 200000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 221 nm and 225 nm and between 359 nm and 363 nm.

Absorption $E_{1cm}^{1\%}$ (361 nm): Between 830 and 870 (after drying, 5 mg, methanol, 100 mL).

Purity (1) ***Clarity and color of solution***—To 0.5 g of Malotilate, add 50 mL of methanol; the solution is colorless to pale yellow.

(2) ***Heavy metals***—Proceed with 2.0 g of Malotilate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Prepare the test solution with 1.0 g of Malotilate according to Method 3 and perform the test (NMT 2 ppm).

Loss on drying NMT 0.5% (0.5 g, phosphorus pentoxide, 4 hours).

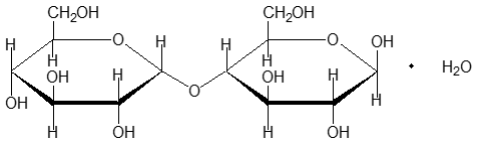
Residue on ignition NMT 0.1% (1 g, platinum crucible, 450 - 550 ℃).

Assay Weigh accurately about 0.1 g of Malotilate, previously dried, and dissolve in methanol to make exactly 200 mL. Pipet 1 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of malotilate RS, proceed in the same way as in the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at 361 nm as directed under the Ultraviolet-visible Spectroscopy, using methanol as the blank.

Amount (mg) of malotilate ($C_{12}H_{16}O_4S_2$)
= Amount (mg) of malotilate RS × (A_T / A_S)

Packaging and storage Preserve in well-closed containers.

Maltose Hydrate
말토오스수화물



Maltose $C_{12}H_{22}O_{11}\cdot H_2O$: 360.31
(2*R*,3*S*,4*S*,5*R*,6*R*)-2-(Hydroxymethyl)-6-[(2*R*,3*S*,4*R*,5*R*)-4,5,6-trihydroxy-2-(hydroxymethyl)oxan-3-yl]oxyoxane-3,4,5-triol hydrate [*6363-53-7*]

Maltose Hydrate, when dried, contains NLT 98.0% and NMT 101.0% of maltose ($C_{12}H_{22}O_{11}\cdot H_2O$).

Description Maltose Hydrate occurs as white crystals or a crystalline powder and has a sweet taste.
It is freely soluble in water, very slightly solution in ethanol(95) and practically insoluble in ether.

Identification (1) Dissolve 0.5 g of Maltose Hydrate in 5 mL of water, add 5 mL of ammonia TS, and heat on a steam bath for 5 minutes; an orange color appears.

(2) Add 2 to 3 drops of an aqueous solution of Maltose Hydrate (1 in 50) to 5 mL of boiling Fehling's TS; a red precipitate is formed.

Optical rotation $[\alpha]_D^{20}$: Between +126° and +131°. Weigh accurately about 10 g of Maltose Hydrate, previously dried, and dissolve in 0.2 mL of ammonia TS and water to make exactly 100 mL. Proceed with this solution to measure the specific optical rotation in a cell, 100-mm in path length.

pH The pH of an aqueous solution of Maltose Hydrate (1 in 10) is between 4.5 and 6.5.

Purity (1) ***Clarity and color of solution***—Weigh 10 g of Maltose Hydrate, put into a Nessler tube containing 30 mL of water, and dissolve it by heating on a steam bath at 60 ℃. After cooling, add water to make 50 mL; the solution is clear and the color of the solution is not more intense than the following control solution.

Control solution—To a mixture of 1.0 mL of cobalt(II) chloride hexahydrate colorimetric stock solution, 3.0 mL of iron(III) chloride hexahydrate colorimetric stock solution and 2.0 mL of copper(II) sulfate pentahydrate colorimetric stock solution, add water to make 10mL. Pipet 1.0 mL of this solution and add water to make 50 mL.

(2) ***Chloride***—Proceed with 2.0 g of Maltose Hydrate and perform the test. Prepare the control solution with 1.0 mL of 0.01 mol/L hydrochloric acid (NMT 0.018%).

(3) ***Sulfate***—Proceed with 2.0 g of Maltose Hydrate and perform the test. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.024%).

(4) ***Heavy metals***—Proceed with 5.0 g of Maltose Hydrate according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 4 ppm).

(5) ***Arsenic***—Dissolve 1.5 g of Maltose Hydrate in 5 mL of water, add 5 mL of dilute sulfuric acid and 1 mL of bromine TS, heat on a steam bath for 5 minutes, and concentrate further to reduce to 5 mL. After cooling, perform the test using the resulting solution as the test solution (NMT 1.3 ppm).

(6) ***Dextrin, soluble starch and sulfite***—Dissolve 1.0 g of Maltose Hydrate in 10 mL of water and add 1 drop of iodine TS; the solution turns yellow. Thereto add 1 drop of starch TS; the solution turns blue.

(7) ***Nitrogen***—Weigh accurately about 2.0 g of Maltose Hydrate and perform the test as directed under the Assay of nitrogen; the amount of nitrogen (N : 14.01) is NMT 0.01%. For decomposition, use 10 mL of sulfuric acid and add 45 mL of sodium hydroxide solution (2 in 5).

(8) ***Related substances***—Dissolve 0.5 g of Maltose Hydrate in 10 mL of water, and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas from the test solution and the standard solution by the automatic integration method; the sum of areas of the peaks which appear before the peak of Maltose Hydrate obtained from the test solution is not larger than 1.5 times the peak area of Maltose Hydrate obtained from the standard solution. Also, the sum of areas of the peaks which appear after the peak of Maltose Hydrate obtained from the test solution is not larger than half the peak area of Maltose Hydrate obtained from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase, flow rate and selection of column, proceed as directed in the operating conditions under the Assay.

Detection sensitivity: Adjust the sensitivity so that the peak height of maltose obtained from 20 μL of the standard solution is about 30 mm.

Time span of measurement: About 2 times the retention time of maltose.

Loss on drying NMT 0.5% (1 g, 80 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.1 g each of Maltose Hydrate and maltose hydrate RS, dissolve each in the internal standard solution to make exactly 10 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak area of maltose to that of the internal standard, Q_T and Q_S.

$$\text{Amount (mg) maltose hydrate } (C_{12}H_{22}O_{11}\cdot H_2O) = \text{Amount (mg) of maltose hydrate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of ethylene glycol (1 in 50).

Operating conditions

Detector: A differential refractometer

Column: A stainless steel column about 8 mm in internal diameter and about 55 cm in length, packed with gel-typed strongly acidic cation exchange resin for liquid chromatography (10 μm in particle diameter) (cross-linking rate: 8%).

Column temperature: A constant temperature about 50 °C.

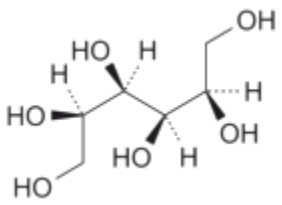
Mobile phase: Water

Flow rate: Adjust the flow rate so that the retention time of maltose is about 18 minutes.

Column selection: Dissolve 0.25 g of maltose, 0.25 g of glucose and 0.4 g of ethylene glycol in water to make 100 mL. Proceed with 20 μL of this solution under the above operating conditions. At this time, use a column from which maltose, glucose and ethylene glycol are eluted in this order with the resolution between the peaks of maltose and glucose being NLT 4.

Packaging and storage Preserve in tight containers.

D-Mannitol
D-만니톨



$C_6H_{14}O_6$: 182.17

(2*R*,3*R*,4*R*,5*R*)-Hexane-1,2,3,4,5,6-hexol [69-65-8]

D-Mannitol contains NLT 97.0% and NMT 102.0% of D-mannitol ($C_6H_{14}O_6$), calculated on the dried basis.

The label states, where applicable, the maximum concentration of bacterial endotoxins.

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral dosage forms.

Description D-Mannitol occurs as a white crystalline powder or grain. It is odorless, and has a sweet taste with a cold sensation.

It is freely soluble in water, and practically insoluble in ethanol(99.5).

It dissolves in sodium hydroxide TS.

It shows crystal polymorphism.

Identification Determine the infrared spectra of D-Mannitol and D-mannitol RS as directed in the potassium bromide disk method under Mid-infrared Spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the spectra, transfer 25 mg each of D-Mannitol and D-mannitol RS into glass vessels, dissolve in 0.25 mL of water without heating, dry the solutions in a 600 – 700 W microwave oven for 20 minutes or dry in vacuum in a dryer at 100℃ for 1 hour, and then cool. Perform the test in the same manner with white to pale yellow powders; both spectra exhibit similar intensities of absorption at the same wavenumbers. Repeat the test with this dried matter.

Melting point Between 165 and 170 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 5.0 g of D-Mannitol in 50 mL of water; the resulting solution is clear like water and colorless, and is not more intense than the control solution and not more turbid than the control suspension. The test tubes containing the test solution and the control solution should be identical, colorless and transparent, and made of glass with 15 to 25 mm in diameter and 40 mm in depth.

Control solution—To 3.0 mL of iron(III) chloride hexahydrate CS, 3.0 mL of cobalt(II) chloride hexahydrate CS and 2.4 mL of copper(II) sulfate pentahydrate CS, add hydrochloric acid solution (1 in 100) to make exactly 1000 mL.

Control suspension—Dissolve 2.5 g of hexamethylenetetramine in 25 mL of water, add 25 mL of hydrazinium sulfate TS that has been left for 4 to 6 hours, and allow to stand for 24 hours. Store in a glass container and use within 2 months. Take exactly 15 mL of this suspension and add water to make 1000-mL before use, and use this solution as the stock suspension. To 5.0 mL of this stock suspension, add 95 mL of water shake to mix well before use, and use this solution as the control suspension.

(2) ***Nickel***—Perform this procedure using a light-resistance container, protected from direct sunlight. Weigh 10.0 g of D-Mannitol, add 30 mL of 2 mol/L acetic acid, and add water to make 100 mL. Add 2.0 mL of a saturated solution of ammonium pyrrolidinedithiocarbamate (about 10 g/L) and 10.0 mL of water-saturated 4-methyl-2-pentanone, and shake for 30 seconds without exposure to light. Allow the layers to separate, and take the 4-methyl-2-pentanone layer, and use it as the test solution. Separately, put 10.0 g each of D-Mannitol in three containers, add exactly 0.5 mL, 1.0 mL and 1.5 mL of nickel standard solution for atomic absorption spectroscopy, respectively, and add 30 mL of 2 mol/L acetic acid and then water to make 100 mL. Then, proceed in the same manner as the test solution, and use the resulting solution as the standard solution. Additionally, take a 4-methyl-2-pentanone layer by proceeding in the same manner as the test solution without adding D-Mannitol, and use it as the blank test solution. Perform the test with the test solution, standard solution and blank test solution as directed under the standard addition method under the

Atomic Absorption Spectroscopy according to the following conditions. The concentration of nickel in the test solution is NMT 1 ppm.

Carrier Gas: Air–acetylen
Lamp: Nickel hollow-cathode lamp
Wavelength: 232.0 nm

(3) ***Related substances***—Dissolve 0.50 g of D-Mannitol in water to make 10 mL, and use this solution as the test solution. Pipet 2 mL of the test solution, dissolve in water to make exactly 100 mL, and use this solution as the standard solution (1). Pipet 0.5 mL of the standard solution (1), add water to make exactly 20 mL, and use this solution as the standard solution (2). Perform the test with exactly 20 μL each of the test solution and standard solutions (1) and (2) as directed under the Liquid Chromatography according to the following conditions. Determine each peak area by the automatic integration method; the peak area of D-sorbitol, having the relative retention time of about 1.2 to D-mannitol, obtained from the test solution is not larger than that of D-mannitol from the standard solution (1) (NMT 2.0%), the sum of peak area of maltitol, having the relative retention time of about 0.69, and isomalt, having the relative retention times of about 0.6 and about 0.73, is not larger than the peak area of D-mannitol from the standard solution (1) (NMT 2.0%), and each peak area other than D-mannitol from the test solution and the above related substance is not larger than 2 times the peak area of D-mannitol from the standard solution (2) (NMT 0.1%). In addition, the total peak area other than D-mannitol from the test solution is not larger than the peak area of D-mannitol from the standard solution (1) (NMT 2.0%). However, the peak of which area is not larger than the peak area of D-mannitol from the standard solution (2) is excluded (NMT 0.05%).

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

Time span of measurement: About 1.5 times the retention time of D-mannitol.

System suitability

System performance: Proceed as directed under the Assay.

(4) ***Reducing sugars***—To 7.0 g of D-Mannitol, add 13 mL of water and 40 mL of Fehling's TS, boil gently for 3 minutes, allow to stand for 2 minutes, and filter the formed precipitate of copper oxide(I) through a glass filter (10 − 16 μm). Wash the precipitate with 50 to 60 ℃ hot water until the washing is no longer alkaline, pass the washings through the glass filter described above, and discard all the filtrate at this step. Immediately, dissolve the precipitate in 20 mL of iron(III) sulfate TS, pass through the glass filter, and wash the filtrate with 15 to 20 mL of water. Combine the washings and the filtrate, heat to 80 ℃, and titrate with 0.002 mol/L potassium permanganate VS; NMT 3.2 mL is required to change the color of the solution (NMT 0.1% expressed as glucose). The endpoint of titration is when the green color turns to pale red, and the color persists at least 10s.

Conductivity Dissolve 20.0 g of D-Mannitol in a fleshly boiled and cooled water by heating to 40 to 50℃ to make 100 mL, and use this solution as the test solution. After cooling, adjust the temperature to 25 ± 1 ℃, and measure the conductivity of test solution every 5 minutes while gently shaking. When the change in conductivity is NMT 0.1 μS cm-1, the conductivity of D-Mannitol is NMT 20 $\mu s \cdot cm^{-1}$.

Loss on drying NMT 0.5% (1 g, 105%, 4 hours).

Microbiological examination of non-sterile products The acceptance criteria of the total aerobic microbial count (TAMC) is NMT 10^3 CFU/g and the total combined yeasts/molds count (TYMC) is NMT 10^2 CFU/g, respectively. Also, *Escherichia coli* and *Salmonella* are not detected. If intended for use in the manufacture of parenteral preparations, the acceptance criteria of TAMC is NMT 10^2 CFU/g.

Bacterial endotoxins This test is applicable if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins. Parenteral preparations having a concentration of 100 g/L or less of mannitol is less than 4 IU/g, and parenteral preparations having a concentration of more than 100 g/L of mannitol is less than 2.5 IU/g.

Assay Weigh accurately about 0.5 g each of D-Mannitol and D-mannitol RS (separately determine the loss on drying), dissolve separately in water to make exactly 10 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with exactly 20 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of D-mannitol in each solution.

$$\text{Amount (g) of D-mannitol } (C_6H_{14}O_6) = W_S \times A_T/A_S$$

W_S: Amount (g) of D-mannitol RS, calculated on the dried basis.

Operating conditions

Detector: Differential refractometer (A constant temperature of about 40 °C).

Column: A stainless steel column 7.8 mm in internal diameter and 30 cm in length, packed with strongly acidic ion-exchange resin for liquid chromatography (calcium type) composed with a sulfonated polystyrene cross-linked with 8% of divinylbenzene (9 μm in particle diameter).

Column temperature: 85 ± 2℃

Mobile phase: water

Flow rate: 0.5 mL per minute (the retention time of D-mannitol is about 20 minutes).

System suitability

System performance: Dissolve 0.25 g each of D-Mannitol and D-Sorbitol in water to make 10 mL, and use this solution as the system suitability solution (1). Separately, dissolve 0.5 g each of maltitol and isomalt in water to make 100 mL. To 2 mL of this solution, add water to make 10 mL, and use this solution as the system suitability solution (2). Proceed with 20 μL each of the system suitability solution (1) and the system suitability solution (2) according to the above operating conditions; isomalt (first peak), maltitol, isomalt (second peak), D-mannitol and D-sorbitol are eluted in this order. The relative retention time of isomalt (first peak), maltitol, isomalt (second peak) and D-sorbitol to D-mannitol is about 0.6, about 0.69, about 0.73 and about 1.2, respectively with the resolution between the peaks of D-mannitol and D-sorbitol being NLT 2.0. Coelution of maltitol and the second peak of isomalt may be observed.

Packaging and storage Preserve in well-closed containers.

D-Mannitol Injection
D-만니톨 주사액

D-Mannitol Injection is an aqueous injection and contains NLT 95.0% and NMT 105.0% of the labeled amount of D-mannitol ($C_6H_{14}O_6$: 182.17).

Method of preparation Prepare as directed under Injections, with D-Mannitol.
No preservative is added.

Description D-Mannitol Injection occurs a clear, colorless liquid and has a sweet taste.
It may precipitate crystals.

Identification Take 5 drops of a saturated solution of D-Mannitol Injection, previously concentrated on a steam bath, and add 1 mL of iron(III) chloride TS and 5 drops of a solution of sodium hydroxide (1 in 5); a yellow precipitate is produced, and the solution becomes clear when vigorously shaken to mix. On addition of a solution of sodium hydroxide (1 in 5), no precipitate is produced.

pH Between 4.5 and 7.0.

Residue on ignition Take exactly an amount of D-Mannitol Injection, equivalent to 1.0 g of D-mannitol, according to the labeled amount, evaporate to dryness on a steam bath, and perform the test; the residue is NMT 1.0 mg.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.5 EU per mL of D-Mannitol Injection.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

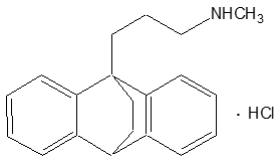
Extractable volume of injections Meets the requirements.

Assay Take exactly an amount of D-Mannitol Injection, equivalent to about 5 g of D-mannitol ($C_6H_{14}O_6$), add water to make exactly 250 mL. Take exactly 10 mL of this solution, add water to make exactly 100 mL, take exactly 10 mL of this solution into an iodine bottle, add exactly 50 mL of potassium periodate TS, and heat on a steam bath for 15 minutes. After cooling, add 2.5 g of potassium iodide, stopper, shake well to mix, allow to stand for 5 minutes in a dark place, and titrate the liberated iodine with 0.1 mol/L sodium thiosulfate VS (indicator: 1 mL of starch TS). Perform a blank test in the same manner.

Each mL of 0.1 mol/L sodium thiosulfate VS
= 1.822 mg of $C_6H_{14}O6$

Packaging and storage Preserve in hermetic containers.

Maprotiline Hydrochloride
마프로틸린염산염



$C_{20}H_{23}N·HCl$: 313.86
N-Methyl-9,10-ethanoanthracene-9(10*H*)-propanamine monohydrochloride [*10347-81-6*]

Maprotiline Hydrochloride, when dried, contains NLT 99.0% and NMT 101.0% of maprotiline hydrochloride ($C_{20}H_{23}N·HCl$).

Description Maprotiline Hydrochloride occurs as a white crystalline powder.
It is soluble in methanol or acetic acid(100), sparingly soluble in ethanol(99.5) and slightly soluble in water.

Melting point—About 244 ℃ (with decomposition).

Identification (1) Determine the absorption spectra of solutions of Maprotiline Hydrochloride and maprotiline hydrochloride RS in methanol (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Maprotiline

Hydrochloride and maprotiline hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If there is any difference between the two spectra, dissolve Maprotiline Hydrochloride and maprotiline hydrochloride RS in ethanol(99.5) respectively, evaporate ethanol(99.5) to dryness, and repeat the test in the same way with the residues.

(3) To 5 mL of an aqueous solution of Maprotiline Hydrochloride (1 in 200), add 2 mL of ammonia TS, heat on a steam bath for 5 minutes, cool, and filter. Acidify the filtrate with dilute nitric acid; the solution responds to the Qualitative Analysis for chloride.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Maprotiline Hydrochloride according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Dissolve 0.10 g of Maprotiline Hydrochloride in 5 mL of methanol, and use this solution as the test solution. Pipet 1.0 mL of this solution, add methanol to make exactly 200 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel (with a fluorescent indicator) for thin-layer chromatography. Next, develop the plate using a mixture of 2-butanol, diluted ammonia water(28) (1 in 3) and ethyl acetate (14 : 5 : 4) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the number of spots other than the principal spot obtained from the test solution is NMT 2, and those spots are not more intense than the spots obtained from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

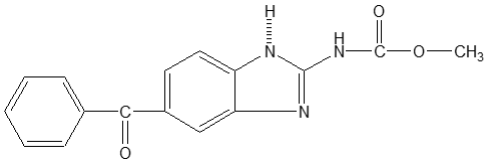
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.25 g of Maprotiline Hydrochloride, previously dried, dissolve in 180 mL of acetic acid(100), add 8 mL of a solution of bismuth nitrate pentahydrate in acetic acid(100) (1 in 50), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 31.386 mg of $C_{20}H_{23}N \cdot HCl$

Packaging and storage Preserve in well-closed containers.

Mebendazole
메벤다졸



$C_{16}H_{13}N_3O_3$: 295.29
Methyl (5-benzoyl-1*H*-benzimidazol-2-yl)carbamate
[*31431-39-7*]

Mebendazole contains NLT 98.0% and NMT 102.0% of mebendazole ($C_{16}H_{13}N_3O_3$), calculated on the dried basis.

Description Mebendazole occurs as a white to pale yellow crystalline powder.
It is practically insoluble in water, dilute hydrochloric acid, ethanol(95), chloroform and ether, and freely soluble in formic acid.

Melting point—About 290 °C.

Identification Determine the infrared spectra of Mebendazole and mebendazole RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit the similar intensities of absorption at the same wavenumbers.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Mebendazole according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 50 mg of Mebendazole in 1.0 mL of 96% formic acid, add chloroform to make exactly 10 mL, and use this solution as the test solution. Weigh accurately a suitable amount of mebendazole RS, proceed in the same manner as in the preparation of the test solution to make the concentration 5 mg per mL, and use this solution as the standard solution. To 1.0 mL of the standard solution, add a mixture of chloroform and 96% formic acid (9 : 1) to make exactly 200 mL, and use this solution as the standard dilution solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution, standard solution and standard dilution solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of chloroform, formic acid and methanol (90 : 5 : 5) as the developing solvent to a distance of about 15 cm and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f value of the principal spot from the test solution and the R_f value of the principal spot from the standard solution are the same, and the spot other than the principal spot from the test solution is not larger and not more intense than the spot from the standard dilution solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.225 g of Mebendazole, dissolve in 30 mL of acetic acid(100) and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 29.529 mg of $C_{16}H_{13}N_3O_3$

Packaging and storage Preserve in well-closed containers.

Mebendazole Syrup
메벤다졸 시럽

Mebendazole Syrup contains NLT 95.0% and NMT 105.0% of the labeled amount of mebendazole ($C_{16}H_{13}N_3O_3$: 295.29).

Method of preparation Prepare as directed under Syrups, with Mebendazole.

Identification (1) Weigh an amount of Mebendazole Syrup, equivalent to 0.2 g of mebendazole, evaporate to dryness on a steam bath, and dissolve in 20 mL of a mixture of formic acid and chloroform (1 : 9). Filter and use the filtrate as the test solution. Weigh 0.2 g of mebendazole RS and proceed in the same manner as for the preparation of the test solution, and use the solution as the standard solution. Spot each 10 μL of the test solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography as directed under the Thin Layer Chromatography, develop the plate with a mixture of chloroform, ethanol(95) and formic acid (198 : 1 : 1) as the developing solvent, and air-dry the plate. Expose the plate to ultraviolet rays (main wavelength: 254 nm); the R_f values and the colors of the spots obtained from the test solution and the standard solution are the same.

(2) Determine the absorption spectrum of the test solution prepared as directed under the Assay; it exhibits maxima at about 310 nm and 236 nm, respectively.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately an amount of Mebendazole Syrup, equivalent to 25 mg of mebendazole, dissolve in 10 mL of formic acid, and add isopropanol to make exactly 100 mL. Shake well to mix and filter. Discard the first 10 mL of the filtrate, take exactly 3 mL of the subsequent filtrate, add isopropanol to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately 25 mg of mebendazole RS, dissolve in 10 mL of formic acid, and add isopropanol to make exactly 100 mL. Pipet 3 mL of this solution, add isopropanol to make exactly 100 mL, and use the solution as the standard solution. Using 0.3% formic acid-isopropanol solution as a control solution, determine the absorbance, A_S and A_T, of the test solution and the standard solution at 310 nm.

Amount (mg) of mebendazole ($C_{16}H_{13}N_3O_3$)
= Amount (mg) of mebendazole RS × (A_T / A_S)

Packaging and storage Preserve in light-resistant, tight containers.

Mebendazole Tablets
메벤다졸 정

Mebendazole, when dried, contains NLT 90.0% and NMT 110.0% of mebendazole ($C_{16}H_{13}N_3O_3$: 295.29).

Method of preparation Prepare as directed under Tablets, with Mebendazole.

Identification Weigh the specific amount of Mebendazole Tablets, previously powdered and equivalent to 0.2 g of mebendazole RS, according to the labeled amount, add 20 mL of a mixture of chloroform and formic acid (19 : 1), and shake to mix. Warm the suspension on a steam bath for a few minutes, cool and filter through a glass filter and use this solution as the test solution. Dissolve mebendazole RS in a mixture of chloroform and formic acid (19 : 1) to obtain a solution having known concentration of 10 mg per mL and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of chloroform, formic acid and methanol (90 : 5 : 5) as the developing solvent to a distance of about 15 cm and air-dry the plate. Observe the plate under ultraviolet light (main wavelength: 254 nm); the R_f values of the spots obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 tablet of Mebendazole Tablets at 75 revolutions per minute according to the Method 2 under the Dissolution Test, using 900 mL of 0.1 mol/L hydrochloric acid containing sodium lauryl sulfate as the dissolution solution. Filter the dissolved solution 120 minutes after staring the dissolution test, and use this solution as the test solution. Separately, weigh accurately about 25 mg of mebendazole RS, add 10.0 mL of formic acid and add methanol to make exactly 50 ml. Pipet an appreciate amount of this solution, make the same concentration of the test solution and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions.

It meets the requirements if the dissolution rate of Mebendazole Tablets in 120 minutes is NLT 75%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 to 10 μm in particle diameter).

Mobile phase: A mixture of the buffer solution and acetonitrile mixture (3 : 7) For the buffer solution, 8.0 g of sodium hydroxide in 2000 mL of water, add 3.0 g of sodium lauryl sulfate phosphoric acid, and adjust the pH to 2.5.

Flow rate: 1 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of mebendazole is NMT 2.0%.

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following method.

Put 1 tablet of Mebendazole Tablets and 20 mL of 96% formic acid in a seam bath, heat and cool the steam bath for 15 minutes, and add 2-propanol to make 100 mL. Filter this solution, pipet 1 mg of mebendazole, add 2-propanol to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of mebendazole RS, dissolve in 4 mL of 96% formic acid, put 2-propanol to make exactly 10 mL. Pipet 0.5 mL of the resulting solution, dilute with 2-propanol to make 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution at the absorbance maximum wavelength (λmax) around 310 nm as directed under the Ultraviolet-visible Spectroscopy, using the formic acid (1 in 500) diluted with the test solution and the standard solution.

$$\text{Amount of mebendazole } (C_{16}H_{13}N_3O_3) \text{ in 1 tablet} = \frac{TC}{D} \times \frac{A_T}{A_S}$$

T: Labeled amount (mg) of mebendazole in 1 Tablet

C: Concentration (mg/mL) of mebendazole in the standard solution

D: Concentration (mg/mL) of mebendazole in the test solution, calculated on the labeled amount basis

Assay Weigh accurately the mass of NLT 20 tables of Mebendazole Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 500 mg of mebendazole ($C_{16}H_{13}N_3O_3$), add 50 mL of formic acid and warm at 50 ℃ for 15 minutes on a steam bath. Shake and mix the solution for 1 hour with a mechanical shaker, add water to make 100 mL, and filter the resulting solution. Pipet 5.0 mL of this solution, add a mixture of methanol and formic acid (9 : 1) to make 100 mL. Pipet 5.0 mL of the resulting solution, add the mobile phase to make 25 mL, shake to mix, filter, and use this solution as the test solution. Separately, weigh exactly 25 mg of mebendazole RS, add 10 mL of formic acid, warm 50 ℃ for 15 minutes on a steam bath. Shake and mix the solution for 5 minutes with a mechanical shaker, and add methanol to make 100 mL. Pipet 5.0 mL of this solution, add 25 mL of mobile phase, shake well and filter. Use this solution as the test solution. Perform the test with 15 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of mebendazole, respectively.

$$\text{Amount (mg) of mebendazole } (C_{16}H_{13}N_3O_3) = \text{Amount (mg) of mebendazole RS} \times \frac{A_T}{A_S} \times 20$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 247 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Add 0.1 mol/L hosphoric acid TS or 1 mol/L sodium hydroxide TS to a mixture of methanol and 0.05 mol/L of potassium dihydrogenphosphate TS (60 : 40) to adjust the pH to 5.5.

Flow rate: 1.5 mL/min

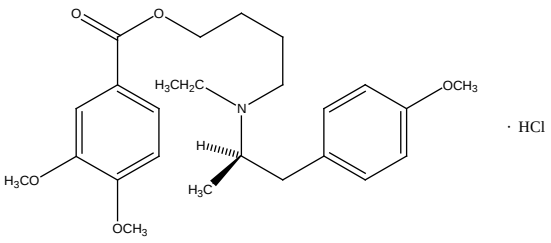
System suitability

System performance: Proceed with 15 μL of the standard solution under the above operating conditions; the symmetry factor is NMT 2.0.

System repeatability: Repeat the test 6 times with 15 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of mebendazole is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Mebeverin Hydrochloride
메베베린염산염



and enantiomer

$C_{25}H_{35}NO_5 \cdot HCl$: 466.01

(*RS*)-4-[Ethyl-[1-(4-methoxyphenyl)propan-2-

yl]amino]butyl-3,4-dimethoxybenzoate hydrochloride [*14664-75-6*]

Mebeverin Hydrochloride contains NLT 99.0% and NMT 101.0% of mebeverin hydrochloride ($C_{25}H_{35}NO_5 \cdot HCl$), calculated on the dried basis.

Description Mebeverin Hydrochloride occurs as white crystals or a crystalline powder.
It is very soluble in water, freely soluble in ethanol(95), and practically insoluble in ether.

Identification (1) Determine the infrared spectra of Mebeverin Hydrochloride and mebeverin hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve 25 mg of Mebeverin Hydrochloride in 25 mL of water, add 2 mol/L nitric acid to acidify, and centrifuge. The clear supernatant responds to the Qualitative Analysis (2) for chloride.

pH Dissolve 2 g of Mebeverin Hydrochloride in 100 mL of water; the pH of this solution is between 4.5 and 6.5.

Purity (1) ***Ether extract*—**Dissolve 40 mg of Mebeverin Hydrochloride in 25 mL of 2 mol/L hydrochloric acid TS, add 50 mL of ether, and mix by shaking for 1 minute. Wash the ether layer 3 times with 25 mL of water each time, evaporate to dryness, and dissolve the residue in methanol to make 20 mL. Determine the absorbance of this solution at 260 nm, using methanol as the control solution, as directed under the Ultraviolet-visible Spectroscopy; the absorbance is NMT 0.23.

(2) ***Non-tertiary amine*—**Dissolve 0.5 g of Mebeverin Hydrochloride in 5 mL of pyridine, add 5 mL of copper chloride-pyridine TS, and heat at 50 ℃ for 30 minutes. After cooling, add acetone to make 50 mL, and use this solution as the test solution. Separately, proceed in the same manner as in the preparation of the test solution with 5 mL of a solution of 0.0060 w/v% di-*n*-butylamine in pyridine, and use this solution as the control solution. Proceed in the same manner as in the preparation of the test solution with 5 mL of pyridine, and use this solution as the blank test solution. Perform the test with the test solution and the control solution, using the blank test solution as the control solution, as directed under the Ultraviolet-visible Spectroscopy and determine the absorbance of these solutions at 405 nm; the absorbance of the test solution is not greater than that of the control solution.

(3) ***Related substances*—**Dissolve 20 mg of Mebeverin Hydrochloride in acetone to make exactly 10 mL and use this solution as the test solution. Separately, dissolve 10 mg of Mebeverin Hydrochloride in acetone to make exactly 100 mL and use this solution as the standard solution (1). Dissolve 2.0 mg of veratric acid in acetone to make exactly 100 mL and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution, standard solution (1) and standard solution (2) on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethanol(99.5), chloroform and ammonia water(28) (50 : 50 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Expose the plate under ultraviolet light (main wavelength: 254 nm) and allow the plate to stand in iodine vapor for 1 hour. The spot corresponding to the veratric acid from the test solution is not more intense than that from the standard solution (2) and the spots other than the principal spot from the test solution are not more intense than the spot from the standard solution (1).

Loss on drying NMT 0.5% (1 g, 105 ℃, 1 hour).

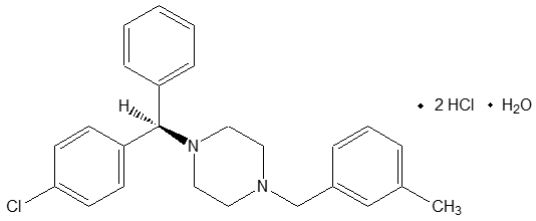
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Mebeverin Hydrochloride, dissolve in 50 mL of acetic acid(100), add 7 mL of mercury(II) acetate TS for non-aqueous titration, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 46.60 mg of $C_{25}H_{35}NO_5 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers at NMT 30 ℃.

Meclizine Hydrochloride Hydrate
메클리진염산염수화물



and enantiomer

Meclizine Hydrochloride
$C_{25}H_{27}ClN_2 \cdot 2HCl \cdot H_2O$: 481.89
(*RS*)-1-[(4-Chlorophenyl)(phenyl)methyl]-4-(3-methylbenzyl)piperazine hydrate dihydrochloride [*31884-77-2*]

Meclizine Hydrochloride Hydrate, when dried, contains NLT 97.0% and NMT 100.5% of meclizine hydrochloride ($C_{25}H_{27}ClN_2 \cdot 2HCl$: 463.87), calculated on the anhydrous basis.

Description Meclizine Hydrochloride Hydrate occurs as a white or pale yellow crystalline powder, and has a slight odor and no taste.
It is practically insoluble in water or ether, freely soluble in pyridine, chloroform or a mixture of acid, ethanol(95)

and water, and slightly soluble in dilute acid or ethanol(95).

Identification (1) Determine the absorption spectra of solutions of Meclizine Hydrochloride Hydrate and meclizine hydrochloride RS in diluted hydrochloric acid (1 in 100) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit absorption maxima at the same wavelengths.

(2) Determine the infrared spectra of Meclizine Hydrochloride Hydrate and meclizine hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 25 mg of Meclizine Hydrochloride Hydrate in a mixture of 2 mol/L nitric acid and ethanol (3 : 5); the solution responds to the Qualitative Analysis for chloride.

Purity ***Related substances***—Weigh an appropriate amount of Meclizine Hydrochloride Hydrate, dissolve in the mobile phase to prepare a solution containing 0.5 mg per mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of meclizine hydrochloride RS (previously determine the content of water), dissolve in the mobile phase to make a solution containing 2.5 μ*g* per mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine peak areas of both solutions; the total area of the peaks other than the major peak of the test solution is NMT 2 times the peak area of the standard solution (NMT 1.0%) and each peak area is not larger than the major peak area of the standard solution (NMT 0.5%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: Dissolve 1.5 g of sodium 1-heptanesulfonate in 300 mL of water, add 700 mL of acetonitrile, and adjust the pH to 4 with 0.05 mol/L of sulfuric acid.

Flow rate: 1.3 mL/min

System suitability

System performance: Weigh an appropriate amount of meclizine hydrochloride RS and 4-chlorobenzophenone, and dissolve in the mobile phase to make a solution containing 10 μg per mL. Proceed with 20 μL of this solution according to the above conditions; meclizine hydrochloride and 4-chlorobenzophenone are eluted in this order with the resolution between the peaks being NLT 2.0.

System repeatability: Perform the test 6 times with 20 mL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas is NMT 1.5%.

Water NMT 5.0% (0.5 g, volumetric titration, direct titration).

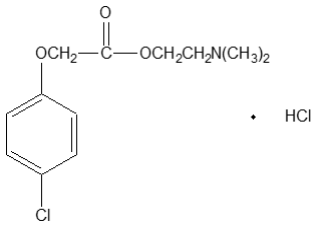
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.35 g of Meclizine Hydrochloride Hydrate, dissolve in 50 mL of chloroform, add 5 ml of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 23.195 mg of $C_{25}H_{27}ClN_2 \cdot 2HCl$

Packaging and storage Preserve in tight containers.

Meclofenoxate Hydrochloride
메클로페녹세이트염산염



$C_{12}H_{16}ClNO_3 \cdot HCl$: 294.17

2-Dimethylaminoethyl (4-chlorophenoxy)acetate hydrochloride [*3685-84-5*]

Meclofenoxate Hydrochloride contains NLT 98.0% and NMT 101.0% of meclofenoxate hydrochloride ($C_{12}H_{16}ClNO_3 \cdot HCl$), calculated on the anhydrous basis.

Description Meclofenoxate Hydrochloride occurs as white crystals or a crystalline powder and has a slight, distinctive odor and a bitter taste.

It is freely soluble in water or ethanol(95), sparingly soluble in acetic anhydride, and practically insoluble in ether.

Dissolve 1 g of Meclofenoxate Hydrochloride in 20 mL of water; the pH of this solution is between 3.5 and 4.5.

Identification (1) To 10 mg of Meclofenoxate Hydrochloride, add 2 mL of ethanol(95), dissolve by warming, if necessary, allow to cool, add 2 drops of a saturated ethanol solution of hydroxylamine hydrochloride and 2 drops of a saturated ethanol solution of potassium hydroxide, and heat on a steam bath for 2 minutes. After cooling, render the solution weakly acidic with dilute hydrochloric acid and add 3 drops of iron(III) chloride TS; the resulting solution exhibits a purple to dark violet color.

(2) Dissolve 50 mg of Meclofenoxate Hydrochlo-

ride in 5 mL of water, and add 2 drops of Reinecke salt TS; a pale red precipitate is produced.

(3) Determine the absorption spectra of the solutions of Meclofenoxate Hydrochloride and meclofenoxate hydrochloride RS (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) An aqueous solution of Meclofenoxate Hydrochloride (1 in 100) responds to the Qualitative Analysis for chloride.

Melting point Between 139 and 143 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Meclofenoxate Hydrochloride in 10 mL of water; the solution is clear and colorless.

(2) ***Sulfate***—Proceed with 1.0 g of Meclofenoxate Hydrochloride and perform the test. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.048%).

(3) ***Heavy metals***—Proceed with 1.0 g of Meclofenoxate Hydrochloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic***—Proceed with 1.0 g of Meclofenoxate Hydrochloride according to Method 3 and perform the test (NMT 2 ppm).

(5) ***Organic acids***—Weigh 2.0 g of Meclofenoxate Hydrochloride, add 50 mL of ether to it, shake to mix for 10 minutes, and then filter through a glass filter. Wash the residue with 5 mL of ether twice, and combine the washings with the filtrate. To this solution, add 50 mL of neutralized ethanol and 5 drops of phenolphthalein TS, and neutralize with 0.1 mol/L sodium hydroxide; the volume of sodium hydroxide consumed is NMT 0.54 mL.

Water NMT 0.5% (1 g, volumetric titration, direct titration).

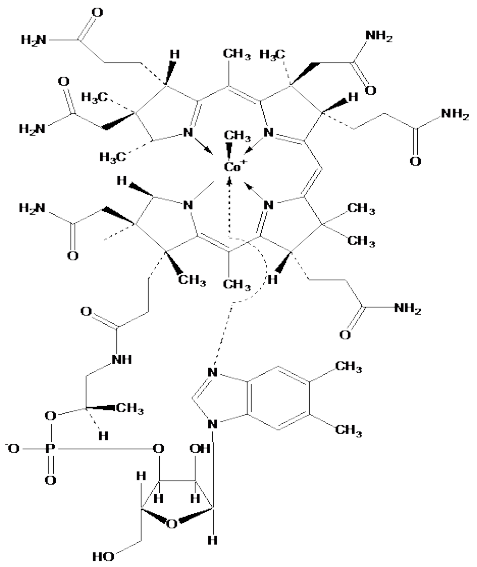
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Meclofenoxate Hydrochloride, dissolve in 70 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS [indicator: 3 drops of a solution of malachite green in acetic acid(100) (1 in 100)]. The endpoint of the titration is when the solution changes from bluish green, through yellowish green, to greenish pale yellow. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 29.417 mg of $C_{12}H_{16}ClNO_3 \cdot HCl$

Packaging and storage Preserve in tight containers.

Mecobalamin
메코발라민



$C_{63}H_{91}CoN_{13}O_{14}P$: 1344.38

Carbanide;Cobalt(3+);[5-(5,6-Dimethylbenzimidazol-1-yl)-4-hydroxy-2-(hydroxymethyl)oxolan-3-yl]-1-[3-[(4*Z*,9*Z*,14*Z*)-2,13,18-*tris*(2-amino-2-oxoethyl)-7,12,17-*tris*(3-amino-3-oxopropyl)-3,5,8,8,13,15,18,19-octamethyl-2,7,12,17-tetrahydro-1*H*-corrin-21-id-3-yl]propanoylamino]propan-2-ylphosphate [*13422-55-4*]

Mecobalamin contains NLT 98.0% and NMT 101.0% of mecobalamin ($C_{63}H_{91}CoN_{13}O_{14}P$), calculated on the anhydrous basis.

Description Mecobalamin occurs as dark red crystals or a crystalline powder.
It is sparingly soluble in water, slightly soluble in ethanol(99.5) and practically insoluble in acetonitrile.
It is affected by light.

Identification (1) Perform this procedure using light-resistant vessels. Determine the absorption spectra of the solutions of Mecobalamin and mecobalamin RS in hydrochloric acid-potassium chloride buffer solution, pH 2.0 (1 in 20000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths. Separately, determine the absorption spectra of the solutions of Mecobalamin and mecobalamin RS in phosphate buffer solution, pH 7.0 (1 in 20000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Add 50 mg of potassium hydrogen sulfate to 1 mg of Mecobalamin to mix and fuse by igniting. After cooling, break up the fused mass with a glass rod, add 3 mL of water, and heat to dissolve. Add 1 drop of phenolphthalein TS, then add sodium hydroxide TS in drops until a pale red color develops. Add 0.5 g of sodium acetate trihydrate, 0.5 mL of dilute acetic acid and 0.5 mL of a solution of 1-nitroso-2-naphthol-3,6-disulfonic acid

disodium salt (1 in 500); a red to orange color is immediately produced. And the red color does not disappear when adding 0.5 mL of hydrochloric acid and boiling for 1 minute.

Purity (1) ***Clarity and color of solution***—Dissolve 20 mg of Mecobalamin in 10 mL of water; the resulting solution is clear and exhibits a red color.

(2) ***Related substances***—Perform the test with 10 μL of the test solution obtained in the Assay, as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of the test solution by the automatic integration method; each area of the peaks other than mecobalamin is NMT 0.5% and the total area is NMT 2.0%.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

Test for required detectability: Pipet 1 mL of the test solution, add the mobile phase to make 100 mL, and use this solution as the system suitability solution. Pipet 1 mL of this solution and add the mobile phase to make exactly 100 mL. Confirm that the peak area of mecobalamin from 10 μL of this solution is equivalent to 7% to 13% of that of mecobalamin from 10 μL of the system suitability solution.

System performance: Proceed as directed under the Assay.

System repeatability: Repeat the test 6 times with 10 μL each of the system suitability solution according to the conditions above; the relative standard deviation of the peak area of mecobalamin is NMT 3.0%.

Time span of measurement: About 2.5 times the retention time of mecobalamin.

Water NMT 12% (0.1 g, volumetric titration, direct titration).

Assay Perform this procedure, using light-resistant vessels. Weigh accurately about 50 mg each of Mecobalamin and mecobalamin RS (previously measure water), dissolve in the mobile phase to make exactly 50 mL respectively, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of mecobalamin in each solution.

$$\text{Amount (mg) of mecobalamin } (C_{63}H_{91}CoN_{13}O_{14}P) = \text{Amount (mg) of mecobalamin RS, calculated on the anhydrous basis} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 266 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature at about 40 °C.

Mobile phase: Add 800 mL of 0.02 mol/L phosphate buffer solution, pH 3.5 to 200 mL acetonitrile and dissolve in 3.76 g of sodium 1-hexanesulfonate.

Flow rate: Adjust the flow rate so that the retention time of mecobalamin is about 12 minutes.

System suitability

System performance: Dissolve 5 mg each of cyanocobalamin and hydroxocobalamin acetate in the mobile phase to make 100 mL. Proceed with 10 μL of this solution under the conditions specified above; cyanocobalamin and hydroxocobalamin acetate are eluted in this order with the resolution being NLT 3. In addition, proceed with 10 μL of the standard solution according to the conditions above; the number of theoretical plates of the peak of mecobalamin is NLT 6000.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the conditions above; the relative standard deviation of the peak area of mecobalamin is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Mecobalamin Capsules
메코발라민 캡슐

Mecobalamin Capsules contain NLT 90.0% and NMT 130.0% of the labeled amount of mecobalamin ($C_{63}H_{91}CoN_{13}O_{14}P$: 1344.40).

Method of preparation Prepare as directed under Capsules, with Mecobalamin.

Identification (1) Weigh an amount of Mecobalamin Capsules equivalent to 0.5 mg of mecobalamin ($C_{63}H_{91}CoN_{13}O_{14}P$: 1344.40), add 10 mL of phosphate buffer solution, pH 7.0, shake to mix, and filter. Determine the absorption spectrum of the solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 266 nm and 269 nm, 289 nm and 292 nm, 316 nm and 319 nm, 341 nm and 344 nm, 374 nm and 377 nm and 520 and 524 nm. Perform this procedure with protection from light.

(2) Weigh an amount of Mecobalamin Capsules equivalent to about 1 mg of mecobalamin ($C_{63}H_{91}CoN_{13}O_{14}P$: 1344.40), add 50 mL of potassium cyanide solution (1 in 200), shake to mix, and filter. Discard the first filtrate, take 20 mL of the next filtrate, and use this solution as the test solution. Shake occasionally to mix, allow to stand under 20 W fluorescent light in a distance of 30 cm for 90 minutes, and determine the absorption spectrum of the solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 277 nm and 279 nm, 288 nm and 290 nm, 309 nm

and 311 nm, 367 nm and 369 nm, 540 nm and 543 nm and 579 nm and 584 nm.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT about 20 capsules of Mecobalamin Capsules. Weigh accurately about 1 mg of mecobalamin ($C_{63}H_{91}CoN_{13}O_{14}P$), dissolve in 100 mL of the mobile phase, filter, and use the filtrate as the test solution. Separately, weigh accurately about 10 mg of mecobalamin RS and dissolve in the mobile phase to make 50.0 mL. Pipet 2.0 mL of this solution, add the mobile phase to make 20 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of mecobalamin } (C_{63}H_{91}CoN_{13}O_{14}P) = \text{Amount (mg) of mecobalamin RS} \times \frac{A_T}{A_S} \times \frac{1}{2}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 266 nm).

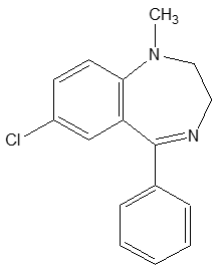
Column: A stainless steel column 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of 200 mL of acetonitrile, 800 mL of 0.02 mol/L phosphoric buffer solution, pH 3.5 and 3.76 g of sodium 1-hexanesulfonate.

Flow rate: 1.0 mL/min

Packaging and storage Preserve in light-resistant, tight containers.

Medazepam
메다제팜



$C_{16}H_{15}ClN_2$: 270.76

7-Chloro-1-methyl-5-phenyl-2,3-dihydro-1*H*-benzo[1,4]diazepine [*2898-12-6*]

Medazepam, when dried, contains NLT 98.5% and NMT 101.0% of medazepam ($C_{16}H_{15}ClN_2$).

Description Medazepam occurs as white or pale yellow crystals or a crystalline powder and is odorless.
It is freely soluble in methanol, ethanol, acetic acid(100) or in ether and practically insoluble in water.
It is gradually colored by light.

Identification (1) Dissolve 10 mg of Medazepam in 3 mL of citric acid-acetic acid TS; the solution turns deep orange color. Heat the solution on a steam bath for 3 minutes; it turns dark red.

(2) Determine the absorption spectra of solutions of Medazepam and medazepam RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Medazepam and medazepam RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) Perform the test with Medazepam as directed under the Flame Coloration (2); a green color is observed.

Melting point Between 101 and 104 °C.

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g of Medazepam in 10 mL of methanol; the solution is pale yellow to yellow and clear.

(2) ***Chloride***—Dissolve 1.5 g of Medazepam in 50 mL of ether, add 46 mL of water and 4 mL of sodium carbonate TS, shake to mix, and collect the water layer. Wash the water layer twice each time with 20 mL of ether and filter the water layer. To 20 mL of the filtrate, add diluted nitric acid to neutralize, add another 6 mL of diluted nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.018%).

(3) ***Heavy metals***—Proceed with 1.0 g of Medazepam according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic***—Prepare the test solution with 1.0 g of Medazepam according to Method 3 and perform the test (NMT 2 ppm).

(5) ***Related substances***—Dissolve 0.25 g of Medazepam in 10 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution and add methanol to make exactly 20 mL. Pipet 2 mL of this solution, add methanol to make exactly 50 mL, and use this solution as the standard solution. Perform the test with the test solution and standard solution as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel (with a fluorescent indicator) for thin-layer chromatography. Develop the plate using a mixture of cyclohexane, acetone and strong ammonia water (60 : 40 : 1) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other

than the principal spot obtained from the test solution are not more intense than those obtained from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, 60 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Medazepam, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L hydrochloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 27.076 mg of $C_{16}H_{15}ClN_2$

Packaging and storage Preserve in light-resistant, tight containers.

Medicinal Carbon
약용탄

Description Medicinal Carbon occurs as a black power, and is odorless and tasteless.

Identification Transfer 0.5 g of Medicinal Carbon into a test tube and heat by direct application of flame with the aid of a current of air; it burns without any flame. Pass the evolved gas through calcium hydroxide TS; a white turbidity is produced.

Purity (1) ***Acid or alkali***—Boil about 3.0 g of Medicinal Carbon with 60 mL of water for 5 minutes, allow to cool, dilute to 60 mL with water, and filter; the filtrate is colorless and neutral.

(2) ***Chloride***—Take 4.0 mL of the filtrate obtained in (1) in a Nessler tube, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.80 mL of 0.01 mol/L hydrochloric acid (NMT 0.142%).

(3) ***Sulfate***—Take 5 mL of the filtrate obtained in (1) in a Nessler tube, add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.192%).

(4) ***Sulfide***—Boil 0.5 g of Medicinal Carbon with a mixture of 15 mL of dilute hydrochloric acid and 10 mL of water; lead acetate paper does not become brown when held in the evolved gas within 5 minutes.

(5) ***Cyanogen compounds***—Weigh 5 g of Medicinal Carbon, put into a distilling flask, add 2 g of L-tartaric acid and 50 mL of water, and connect the flask to a distilling device. Add 2 mL of sodium hydroxide TS and 10 mL of water into the receiver, dip the end of the cooling device to this solution, cool the receiver in the iced water and distill until the volume of the solution becomes 25 mL. Add water to make 50 mL, take 25 mL of the diluted distillate, add 1 mL of iron(II) sulfate hexahydrate solution (1 in 20), heat the mixture almost to boiling, cool and filter. To the filtrate, add 1 mL of hydrochloric acid and 0.5 mL of dilute iron(III) chloride TS; no blue color is produced.

(6) ***Acid soluble substances***—Take about 1 g of Medicinal Carbon, accurately weighed, add 20 mL of water and 5 mL of hydrochloric acid, boil for 5 minutes, filter, wash the residue with 10 mL of hot water and add the washings to the filtrate. Add 5 drops of sulfuric acid to the filtrate, evaporate, and ignite the residue; the amount of residue is NMT 3.0%.

(7) ***Heavy metals***—Proceed with 0.5 g of Medicinal Carbon according to Method 2 and perform the test. Prepare the control solution with 2.5 mL of lead standard solution (NMT 50 ppm).

(8) ***Zinc***—Ignite 0.5 g of Medicinal Carbon to ash, add 5 mL of dilute nitric acid to the residue, boil gently for 5 minutes, filter, wash with 10 mL of water, and combine the washings and the filtrate. Add 3 mL of ammonia TS to the combined solution, filter again, wash with water, combine the washings and the filtrate to make 25 mL, add 1 drop of sodium sulfide TS, and allow to stand for 3 minutes; the solution produces no turbidity.

(9) ***Arsenic***—Proceed 1.0 g of Medicinal Carbon according to Method 3, and perform the test (NMT 2 ppm).

Loss on drying NMT 15.0% (1 g, 105 °C, 4 hours).

Residue on ignition NMT 4.0% (1 g).

Adsorptive power (1) To 1.0 g of Medicinal Carbon, previously dried, add a solution of 0.12g of quinine sulfate dissolved in 100 mL of water, shake the mixture vigorously for 5 minutes, filter immediately, and discard the first 20 mL of the filtrate. Take 10 mL of the subsequent filtrate; add 5 drops of iodine TS; no turbidity is produced.

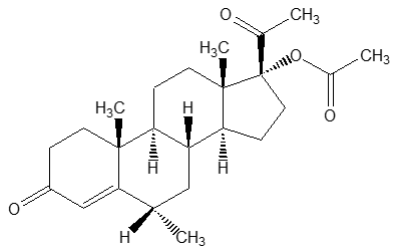
(2) Dissolve 0.25 g of methylene blue, exactly weighed, in water to make exactly 250 mL. Transfer two 50 mL volumes of this solution into each of two glass-stoppered flasks. To one flask, add exactly 0.25 g of Medicinal Carbon, previously dried and weighed accurately, and shake vigorously for 5 minutes for mixing. Filter the contents of each flask, discard the first 20 mL of each filtrate. Pipet 25 mL of the subsequent filtrate into two 250-mL volumetric flasks. To each volumetric flask, add 50 mL of a solution of sodium acetate (1 in 10), then add exactly 35 mL of 0.05 mol/L iodine solution. Allow them to stand for 50 minutes while shaking vigorously from time to time. Dilute each mixture to 250 mL with water. Allow to stand for 10 minutes, filter each solution at below 20 °C, discard the first 30 mL of each filtrate. Pipet accurately 100mL each of the subsequent filtrate, and titrate the excess iodine with 0.1 mol/L sodium thiosul-

fate VS. The difference between the amounts of 0.1 mol/L sodium thiosulfate VS consumed for the titration of each solution is NLT 1.2 mL.

Microbiological examination of non-sterile products The total aerobic microbial count is NMT 1000 CFU per g of Medicinal Carbon, and the total combined yeasts/molds count is NMT 100 CFU per g of Medicinal Carbon.

Packaging and storage Preserve in well-closed containers.

Medroxyprogesterone Acetate
메드록시프로게스테론아세테이트



$C_{24}H_{34}O_4$: 386.52

[(6*S*,8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-Acetyl-6,10,13-trimethyl-3-oxo-2,6,7,8,9,11,12,14,15,16-decahydro-1*H*-cyclopenta[a]phenanthren-17-yl] acetate [*71-58-9*]

Medroxyprogesterone Acetate contains NLT 97.0% and NMT 103.0% of medroxyprogesterone acetate ($C_{24}H_{34}O_4$), calculated on the dried basis.

Description Medroxyprogesterone Acetate occurs as a white, crystalline powder and is odorless.

It is freely soluble in chloroform, soluble in acetone or 1.4-dioxane, sparingly soluble in ethanol(95) or methanol, slightly soluble in ether, and practically insoluble in water.

It is stable in air.

Melting point—About 205 °C.

Identification (1) Determine the absorption spectra of solutions of Medroxyprogesterone Acetate and medroxyprogesterone acetate RS in ethanol(95) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit the same intensities of absorption at the same wavelengths. The difference in absorbances of the solutions, calculated on the dried basis, at the absorption maximum wavelength around 241 nm is NMT 2.0%.

(2) Determine the infrared spectra of Medroxyprogesterone Acetate and medroxyprogesterone acetate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit maxima at the same wavenumber.

Optical rotation $[\alpha]_D^{20}$: Between +47° and + 53° (0.250 g after drying, acetone, 25 mL, 100 mm).

Purity (1) ***Related substances I***—Weigh accurately 0.20 g of Medroxyprogesterone Acetate, dissolve in dichloromethane to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately 0.20 g of medroxyprogesterone acetate RS and 1.0 mg of medroxyprogesterone acetate related substances I RS, dissolve in dichloromethane to make 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test and standard solutions on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of hexane, *tert*-butylmethyl ether and tetrahydrofuran (45 : 45 : 10) to a distance of 10 cm, and air-dry the plate. Put the plate again in the developing solvent, develop to a distance of 10 cm, and air-dry the plate. Heat the plate at 120 ℃ for 10 minutes to dry, spray evenly a solution of p-toluenesulfonic acid monohydrate in ethanol(95) (1 in 5), and further heat at 120 ℃ for 10 minutes. Examine the plate under ultraviolet light (main wavelength 365 nm); a large blue fluorescent spot whose R_f value is larger than that of the principal spot from the test solution is not more intense than the fluorescent spot obtained from the standard solution (NMT 0.5%).

(2) ***Related substances***—Weigh accurately 62.5 mg of Medroxyprogesterone Acetate, dissolve in the mobile phase to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of medroxyprogesterone acetate RS, dissolve in the mobile phase to make a solution containing 50 μg per mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test and standard solutions as directed under the Liquid Chromatography according to the following conditions and determine the peak areas of these solutions; the peak area other than the major peak from the test solution and the peak area from the standard solution are NMT 1%, and the total area of the peaks is NMT 1.5%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and water (3 : 2).

Flow rate: 1.0 mL/min

System suitability

System performance: Weigh an appropriate amount of megesterol acetate RS and medroxyprogesterone acetate RS and dissolve in the mobile phase to make a solution containing 40 μg each per mL. Proceed with 20 μL of the solution according to the above operating conditions; the resolution between megesterol acetate and medroxyprogesterone acetate is NLT 1.5.

System reproducibility: Perform the test six times with 20 μL each of the standard solution according to the

above operating conditions; the relative standard deviation of the peak areas of medroxyprogesterone acetate is NMT 3.0%.

Loss on drying NMT 1.0% (1 g, 105 ℃, 3 hours).

Assay Weigh accurately about 25 mg of Medroxyprogesterone Acetate, dissolve in 25 mL of acetonitrile, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of medroxyprogesterone acetate RS, previously dried at 105℃ for 3 hours, dissolve in acetonitrile to make a solution containing 1 mg per mL, and use this solution as the standard solution. Perform the test with 10 mL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of medroxyprogesterone acetate for the test solution and the standard solution, respectively.

Amount (mg) of medroxyprogesterone acetate ($C_{24}H_{34}O_4$)

$$= 25\times C \times \frac{A_T}{A_S}$$

C: Concentration of the standard solution (mg/mL)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of water and acetonitrile (60 : 40).

Flow rate: 2.0 mL/min

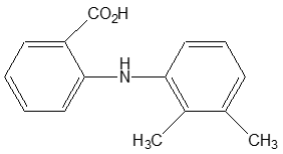
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; the symmetry factor is NMT 2.

System reproducibility: Perform the test six times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of medroxyprogesterone acetate is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Mefenamic Acid
메페남산



$C_{15}H_{15}NO_2$: 241.29

2-((2,3-Dimethylphenyl)amino)benzoic acid [*61-68-7*]

Mefenamic Acid, when dried, contains NLT 99.0% and NMT 101.0% of mefenamic acid ($C_{15}H_{15}NO_2$).

Description Mefenamic Acid occurs as a white to pale yellow powder and is odorless. It is tasteless initially but has a slight bitter taste.

It is sparingly soluble in ether, slightly soluble in methanol, ethanol(95) or chloroform, and practically insoluble in water.

It dissolves in sodium hydroxide TS.

Melting point—About 225 ℃ (with decomposition).

Identification (1) Dissolve 10 mg of Mefenamic Acid in 1 mL of methanol by warming. After cooling, add 1 mL of 4-nitrobenzendiazonium fluoroborate solution (1 in 1000), add 1 mL of sodium hydroxide TS, and shake for mixing. The resulting solution exhibits an orange color.

(2) Dissolve 10 mg of Mefenamic Acid in 2 mL of sulfuric acid and heat; the resulting solution exhibits a yellow color with green fluorescence.

(3) Dissolve 7 mg each of Mefenamic Acid and mefenamic acid RS in a solution of hydrochloric acid in methanol (1 in 1000) to make 500 mL each. Determine the absorption spectra of each solution as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Purity (1) ***Chloride***—To 1.0 g of Mefenamic Acid, add 20 mL of sodium hydroxide TS and heat to dissolve. After cooling, add 2 mL of acetic acid(100), add water to make 100 mL, and shake to mix. Filter the precipitate produced and discard the first 10 mL of the filtrate. To 25 mL of the subsequent filtrate, add 6 mL of dilute nitric acid, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 5 mL of sodium hydroxide TS, 0.5 mL of acetic acid(100), 6 mL of dilute nitric acid, and water to 0.50 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.071%).

(2) ***Heavy metals***—Proceed with 2.0 g of Mefenamic Acid according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Prepare the test solution with 1.0 g of Mefenamic Acid according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.10 g of Mefenamic Acid in 5 mL of a mixture of chloroform and

methanol (3 : 1) and use this solution as the test solution. Pipet 1 mL of this solution and add a mixture of chloroform and methanol (3 : 1) to make exactly 200 mL. Pipet 10 mL of this solution, add a mixture of chloroform and methanol (3 : 1) to make exactly 50 mL, and use the resulting solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 25 μL each of the test solution and standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of 2-methyl-1-propanol and ammonia water(28) (3 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, phosphorus (V) oxide, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Mefenamic Acid, previously dried, add 100 mL of neutralized ethanol, and warm at a low heat to dissolve. After cooling, titrate with 0.1 mol/L sodium hydroxide VS (indicator: 2 to 3 drops of phenol red TS). The endpoint of the titration is when the yellow color of this solution turns orange and then finally to purple. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 24.129 mg of $C_{15}H_{15}NO_2$

Packaging and storage Preserve in well-closed containers.

Mefenamic Acid Capsules
메페남산 캡슐

Mefenamic Acid Capsules contain equivalent to NLT 90.0% and NMT 110.0% the labeled amount of mefenamic acid ($C_{15}H_{15}NO_2$: 241.29).

Method of preparation Prepare as directed under Capsules, with Mefenamic Acid.

Identification (1) Take out the contents of Mefenamic Acid Capsules, mix well, weigh an amount equivalent to 0.25 g of mefenamic acid according to the labeled amount, and add 100 mL of a mixture of chloroform and methanol (3 : 1). Shake strongly to dissolve, add a mixture of chloroform and methanol (3 : 1) to make 250 mL, filter, and use the filtrate as the test solution. Separately, weigh 25 mg of mefenamic acid RS, dissolve in a mixture of chloroform and methanol (3 : 1) to make 25 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, ethyl acetate and acetic acid(100) (75 : 25 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under the iodine steam; the test solution and the standard solution exhibit the same spots at the same R_f value.

(2) Perform the test as directed under the Assay; the test solution and the standard solution exhibit peaks at the same retention time.

Dissolution Perform the test with 1 tablet of Mefenamic Acid Capsules at 100 revolutions per minute according to Method 1 under the Dissolution, using 900 mL of 0.05 mol/L tris buffer solution as the test solution. Take the dissolved solution 45 minutes after starting the test and filter. Take an appropriate amount of the filtrate to obtain a solution having known concentration of 0.2 mg per mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of mefenamic acid RS, dissolve in the test solution to make the same concentration with the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Assay.
Meets the requirements if the dissolution rate in 45 minutes is NLT 75%.

0.05 mol /L Tris buffer solution—Dissolve 60.5 g of 2-amino-2-hydroxymethyl-1,3-propanediol in 6 L of water, add water to make 10 mL, add phosphoric acid to adjust the pH to 9.0 ± 0.05. Take 6 L of this solution, dissolve 100 mg of sodium lauryl sulfate, and add this solution again in the first solution.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the contents of NLT 20 capsules of Mefenamic Acid Capsules, weigh accurately an amount equivalent to about 50 mg of mefenamic acid ($C_{15}H_{15}NO_2$), add 5.0 mL of tetrahydrofuran, and dissolve by sonicating for 5 minutes. To this, add the mobile phase to make exactly 250 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 50 mg of mefenamic acid RS, add 5.0 mL of tetrahydrofuran, shake, and dissolve. Add the mobile phase to make exactly 250 mL and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of mefenamic acid, A_T and A_S, respectively.

Amount (mg) of mefenamic acid ($C_{15}H_{15}NO_2$)
= Amount (mg) of mefenamic acid RS × $\frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 to 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile, buffer solution and tetrahydrofuran (23 : 20 : 7).

Flow rate: 1 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the symmetry factor is NMT 1.6.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of mefenamic acid is NMT 1.0%.

Buffer solution—To 5.7 g of ammonium dihydrogen phosphate, add 1000 mL of water, dissolve, and adjust the pH to 5.0 by adding 3 mol/L ammonia water.

Packaging and storage Preserve in well-closed containers.

Mefenamic Acid Tablets
메페남산 정

Mefenamic Acid Tablets contain NLT 92.5% and NMT 107.5% of the labeled amount of mefenamic acid ($C_{15}H_{15}NO_2$: 241.29).

Method of preparation Prepare as directed under Tablets, with Mefenamic Acid.

Identification The retention time of the major peaks obtained from the test solution and standard solution under the Assay are the same.

Dissolution Take 1 tablet of Mefenamic Acid Tablets, and perform the test according to Method 1 using 900 mL of 0.05 mol/mL tris buffer solution as the dissolution medium at 100 revolutions per minute. Take the dissolved solution 45 minutes after starting the dissolution test and filter it. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add the dissolution medium to make exactly *V'* mL so that each mL contains about 200 μg of mefenamic acid ($C_{15}H_{15}NO_2$) according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 20 mg of mefenamic acid RS, dissolve in methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the operating conditions under the Assay, and determine the peak areas, A_T and A_S, of mefenamic acid. It meets the requirements when the dissolution ratio of Mefenamic Acid Tablets in 45 minutes is NLT 75%.

Dissolution rate (%) of the labeled amount of mefenamic acid ($C_{15}H_{15}NO_2$)

$$= W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 900$$

W_S: Amount (mg) of mefenamic acid RS

C: Labeled amount (mg) of mefenamic acid ($C_{15}H_{15}NO_2$) in 1 tablet

0.05 mol/L tris buffer solution—Dissolve 60.5 g of 2-Amino-2-hydroxymethyl-1,3-propanediol in 6 L of water, add water to make 10 L, and adjust the pH to 9.0 ± 0.05 with phosphoric acid. Pipet 6 L of the resulting solution, dissolve with 100 g of sodium lauryl sulfate, and add this resulting solution to the original solution again.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately and powder NLT 20 tablets of Mefenamic Acid Tablets. Weigh accurately a portion of this powder, equivalent to about 50 mg of mefenamic acid ($C_{15}H_{15}NO_2$), add 5.0 mL of tetrahydrofuran, and sonicate for 5 minutes to dissolve. Add the mobile phase to make 250.0 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 50 mg of mefenamic acid RS, add 5.0 mL of tetrahydrofuran, and shake to dissolve. Add the mobile phase to make 250.0 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of mefenamic acid from each solution.

Amount (mg) of mefenamic acid ($C_{15}H_{15}NO_2$)

$$= \text{Amount (mg) of mefenamic acid RS} \times \frac{A_T}{A_S}$$

Buffer solution—Dissolve 5.7 g of ammonium dihydrogen phosphate in 1000 mL of water, and add 3 mol/L ammonia water to adjust the pH to 5.0.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm - 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile, buffer solution and tetrahydrofuran (23 : 20 : 7).

Flow rate: 1.0 mL/min

System suitability

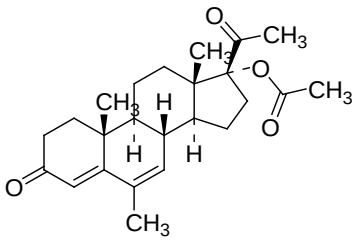
System performance: Proceed with 10 μL of the standard solution according to the above conditions; the symmetry factor is NMT 1.6.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above operating conditions, the relative standard deviation of the

peak areas of mefenamic acid is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Megestrol Acetate
메게스트롤아세테이트



$C_{24}H_{32}O_4$: 384.51

[(8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-Acetyl-6,10,13-trimethyl-3-oxo-2,8,9,11,12,14,15,16-octa-hydro-1*H*-cyclopenta[a]phenanthren-17-yl]acetate [*595-33-5*]

Megestrol Acetate contains NLT 97.0% and NMT 103.0% of megestrol acetate ($C_{24}H_{32}O_4$), calculated on the anhydrous basis.

Description Megestrol Acetate occurs as a white or almost white crystalline powder.
It is soluble in acetone, sparingly soluble in ethanol(95) and practically insoluble in water.

Identification Determine the infrared spectra of Megestrol Acetate and megestrol acetate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +8.8° and + 12.0° (0.2 g, calculated on the anhydrous basis, chloroform, 10 mL, 100 mm).

Melting point Between 213 and 220 °C.

Purity ***Heavy metals***—Proceed with 1.0 g of Megestrol Acetate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Water NMT 0.5% (0.25 g, volumetric titration, direct titration).

Residue on ignition NMT 0.2% (1 g, 600 ℃).

Assay Weigh accurately about 0.1 g of Megestrol Acetate and add acetonitrile to make 100 mL. Pipet 4 mL of this solution, add 5 mL of the internal standard solution, add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of megestrol acetate RS and add acetonitrile to make 100 mL. Pipet 4 mL of this solution, add 5 mL of the internal standard solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak area of megestrol acetate to that of the internal standard, Q_T and Q_S.

$$\text{Amount (mg) megestrol acetate } (C_{24}H_{32}O_4) = \text{Amount (mg) of megestrol acetate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of propylparaben in acetonitrile (8 in 10000).

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 280 nm).

Column: A stainless steel column 3.9 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and water (55 : 45).

Flow rate: 1 mL/minute

System suitability

System performance: Proceed with 25 μL of the standard solution as directed under the above operating conditions; the relative retention time of propylparaben with respect to megestrol acetate is about 0.4 with the resolution between their peaks being NLT 8.0.

System repeatability: Repeat the test 6 times with 25 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak areas is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Megestrol Acetate Oral Suspension
메게스트롤아세테이트 현탁액

Megestrol Acetate Oral Suspension contains NLT 90.0% and NMT 110.0% of the labeled amount of megestrol acetate ($C_{24}H_{32}O_4$: 384.51) per mg.

Method of preparation Prepare as directed under Suspensions, with Megestrol Acetate.

Identification Take an amount of Megestrol Acetate, equivalent to 160 mg of megestrol acetate, according to the labeled amount, put in a separatory funnel, add 50 mL of water and 40 mL of chloroform, and shake to mix. Take the chloroform layer and use it as the test solution. Separately, weigh accurately about 40 mg of megestrol acetate RS, dissolve in chloroform to make 10 mL, and use this solution as the standard solution. With these solu-

tions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescence indicator for thin-layer chromatography, develop the plate with a mixture of chloroform and ethyl acetate (4 : 1) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values of the principal spots obtained from the test solution and the standard solution are the same.

pH Between 3.0 and 4.7,

Dissolution Take an amount (V mL), equivalent to 160 mg of megestrol acetate according to the labeled amount of Megestrol Acetate Oral Suspension, and perform the test with it at 25 revolutions per minute according to Method 2, using 900 mL of 0.5% sodium lauryl sulfate solution as a dissolution medium. Take the dissolved solution 30 minutes after starting the test, filter through a membrane filter with the pore size of NMT 0.45 μm, and use the filtrate as the test solution. Separately, weigh accurately about 45 mg of megestrol acetate RS, add 12 mL of methanol, and allow to stand on a steam bath to dissolve. Add the dissolution medium to make exactly 250 mL and use this solution as the standard solution. If necessary, dilute the test solution and the standard solution to a suitable concentration using the dissolution medium. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as the control solution, and determine the absorbances, A_T and A_S, respectively, at the wavelength of 292 nm. It meets the requirements when the dissolution rate of Megestrol Acetate Oral Suspension in 30 minutes is NLT 80% (Q).

Dissolution rate (%) of the labeled amount of megestrol acetate ($C_{24}H_{32}O_4$)

$$= C \times \frac{A_T}{A_S} \times \frac{V_D}{V} \times \frac{100}{L}$$

C: Concentration (mg/mL) of the standard solution

V: Volume (mL) of Megestrol Acetate Oral Suspension

V_D: Volume of the solvent, 900 mL

L: Labeled amount (mg/mL) of Megestrol Acetate Oral Suspension

Microbiological examination of non-sterile products Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Take an amount of Megestrol Acetate Oral Suspension equivalent to 160 mg of megestrol acetate according to the labeled amount and add the mobile phase to make exactly 1000 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately 80 mg of megestrol acetate RS, dissolve in the mobile phase to make 1000 mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography and determine the peak areas, A_T and A_S, of megestrol acetate in each solution.

Amount (mg) of megestrol acetate ($C_{24}H_{32}O_4$)

$$= \text{Amount (mg) of megestrol acetate RS} \times \frac{A_T}{A_S} \times 2$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column 3.9 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and water (11 : 9).

Flow rate: 1.5 mL/min

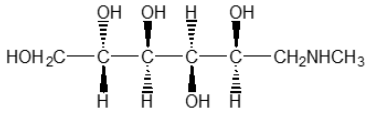
System suitability

System performance: Proceed with 25 μL of the standard solution according to the above conditions; the number of theoretical plate of the megestrol acetate peak is NLT 2500.

System repeatability: Repeat the test 6 times with 25 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of megestrol acetate is NMT 2.0%.

Packaging and storage Preserve in light-resistant, well-closed containers.

Meglumine
메글루민



$C_7H_{17}NO_5$: 195.21

(2*R*,3*R*,4*R*,5*S*)-6-(Methylamino)hexane-1,2,3,4,5-pentol [*6284-40-8*]

Meglumine, when dried, contains NLT 99.0% and NMT 101.0% of meglumine ($C_7H_{17}NO_5$).

Description Meglumine occurs as a white crystalline powder, is odorless and has a slightly bitter taste.
It is freely soluble in water, slightly solution in ethanol(95) and practically insoluble in ether.
The pH of an aqueous solution of Meglumine (1 in 10) is between 11.0 and 12.0.

Identification (1) To 1 mL of an aqueous solution of Meglumine (1 in 10), add 1 mL of potassium 1,2-naphthoquinone-4-sulfonate TS; the solution turns deep red.

(2) To 2 mL of an aqueous solution of Meglumine

(1 in 10), add 1 drop of methyl red TS, add 0.5 mol/L sulfuric acid TS to neutralize, and add 0.5 mL of dilute sodium hydroxide TS and 0.5 g of boric acid; the solution turns deep red.

(3) Dissolve 0.5 g of Meglumine in 1 mL of diluted hydrochloric acid (1 in 3) and add 10 mL of ethanol(99.5); a white precipitate is produced. Then, while rubbing the inside wall with a glass rod, cool the solution with ice to produce more precipitate, filter the precipitate by suction through a glass filter (G3), wash the precipitate with a small volume of ethanol(99.5), and dry at 105 °C for 1 hour; the resulting residue melts at between 149 and 152 °C.

Specific optical rotation $[\alpha]_D^{20}$: Between -16.0° and -17.0° (after drying, 1 g, water, 10 mL, 100 mm).

Melting point Between 128 and 131 °C.

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g of Meglumine in 10 mL of water; the solution is colorless and clear.

(2) ***Chloride***—Dissolve 1.0 g of Meglumine in 30 mL of water, add 10 mL of nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid (NMT 0.009%).

(3) ***Sulfate***—Dissolve 1.0 g of Meglumine in 30 mL of water and add 5 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid (NMT 0.019%).

(4) ***Heavy metals***—Proceed with 2.0 g of Meglumine according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Arsenic***—Prepare the test solution with 2.0 g of Meglumine according to Method 3 and perform the test (NMT 1 ppm).

(6) ***Reducing agents***—To 5 mL of an aqueous solution of Meglumine (1 in 20), add 5 mL of Fehling's TS, and boil for 2 minutes; no reddish brown precipitate is produced.

Loss on drying NMT 0.5% (1 g, 105 °C, 4 hours).

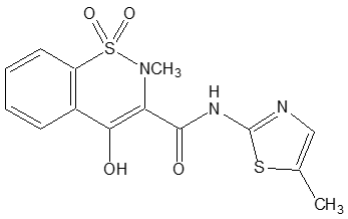
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Meglumine, previously dried, dissolve in 25 mL water, and titrate with 0.1 mol/L hydrochloric acid VS (indicator: 2 drops of methyl red TS).

Each mL of 0.1 mol/L hydrochloric acid VS
= 19.521 mg of $C_7H_{17}NO_5$

Packaging and storage Preserve in tight containers.

Meloxicam
멜록시캄



$C_{14}H_{13}N_3O_4S_2$: 351.40

4-Hydroxy-2-methyl-*N*-(5-methyl-1,3-thiazol-2-yl)-1,1-dioxo-1λ6,2-benzothiazine-3-carboxamide [*71125-38-7*]

Meloxicam contains NLT 99.0% and NMT 100.5% of meloxicam ($C_{14}H_{13}N_3O_4S_2$), calculated on the dried basis.

Description Meloxicam occurs as a pale yellow powder. It is soluble in *N*,*N*-dimethylformamide, slightly soluble in acetone, very slightly soluble in ethanol(95) or methanol, and practically insoluble in water.

Identification (1) Determine the absorption spectra of solutions of Meloxicam and meloxicam RS in methanol (1.5 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Meloxicam and meloxicam RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Meloxicam in 10 mL of *N*,*N*-dimethylformamide; the resulting solution is clear.

(2) ***Heavy metals***—Proceed with 2.0 g of Meloxicam according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 80 mg of Meloxicam in 5 mL of a mixture of methanol and 1 mol/L sodium hydroxide TS (50:3), add methanol to make exactly 20 mL, and use this solution as the test solution. Dissolve 12 mg of meloxicam RS in 5 mL of a mixture of methanol and 1 mol/L sodium hydroxide TS (50:3) and add methanol to make exactly 20 mL. To 2 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method and determine the amount of related substances in the test solution at the wavelength of 350 nm; meloxicam related substances I {ethyl 4-hydroxy-2-methyl-*2H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide} is NMT 0.1%, and meloxicam related substances III {*N*-(3,5-

dimethylthiazole -2(*3H*)-ylidene)-4-hydroxy-2-methyl-2H-benzo[e][1,2]thiazine-3-carboxamide 1,1-dioxide} and meloxicam related substances IV {*N*-(3-ethyl-5-methylthiazol-2(*3H*)-ylidene)-4-hydroxy-2-methyl-*2H*-benzo[e][1,2]thiazine-3-carboxamide 1,1-dioxide} are NMT 0.05%, respectively. But the peak area of meloxicam related substances I is obtained by dividing the area determined with the automatic integration method by the correction factor 0.5. Meloxicam related substances II {5-methylthiazole-2-ylamine} detected at the wavelength of 260 nm is NMT 0.1%. Any related substance other than the above related substances including meloxicam, detected at the wavelengths of 350 nm and 260 nm, are NMT 0.1% and the sum of all related substances is NMT 0.3%.

$$\text{Content (\%) of related substances} = 100 \times \frac{A_\text{i}}{A_\text{S}} \times \frac{C_\text{S}}{C_\text{T}}$$

A_i: Peak area of each related substance in the test solution

A_S: Peak area of meloxicam from the standard solution at the wavelength of 350 nm

C_S: Concentration (mg/mL) of meloxicam RS in the standard solution

C_T: Concentration (mg/mL) of meloxicam in the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 260 nm and 350 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 45 °C.

Mobile phase: Use mobile phases A and B to control a step or gradient elution as follows.

Mobile phase A: Dissolve 1 g of potassium dihydrogen phosphate in 1000 mL of water and adjust the pH to 6.0 with 1 mol/L sodium hydroxide TS.

Mobile phase B: Methanol

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 2	60	40
2 - 10	60 → 30	40 → 70
10 - 15	30	70
15 - 15.1	30 → 60	70 → 40
15.1 - 18	60	40

Flow rate: 1.0 mL/min

System suitability

System performance: Dissolve 4 mg each of meloxicam RS, meloxicam related substances I RS and meloxicam related substances II RS in 5 mL of a mixture of methanol and 1 mol/L sodium hydroxide TS (50:3), add methanol to make 50 mL, and use this solution as the system suitability solution. Proceed with 5 μL of this solution according to the above conditions; the resolution between meloxicam and related substances I detected at the wavelength of 350 nm is NLT 3.0, and the resolution between meloxicam and related substances II detected at the wavelength of 260 nm is NLT 3.0. The relative retention times of the related substances I, II, III, and IV to meloxicam are 1.4, 0.4, 1.7 and 1.9, respectively.

System repeatability: Perform the test 6 times with 5 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of meloxicam is NMT 10%.

Loss on drying NMT 0.5% (3.0 g, 105 ℃, constant mass).

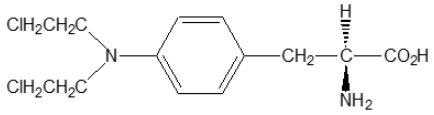
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.25 g of Meloxicam, dissolve in 50 mL of acetic acid(100) and 5 mL of anhydrous formic acid, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Separately, perform a blank test and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 35.14 mg of $C_{14}H_{13}N_3O_4S_2$

Packaging and storage Preserve in well-closed containers.

Melphalan
멜팔란



$C_{13}H_{18}Cl_2N_2O_2$: 305.20

(2*S*)-2-Amino-3-[4-[bis(2-chloroethyl)amino]phenyl]propanoic acid [*148-82-3*]

Melphalan contains NLT 93.0% and NMT 101.0% of melphalan ($C_{13}H_{18}Cl_2N_2O_2$), calculated on the dried basis.

Description Melphalan occurs as a white to pale yellowish white crystalline powder.

It is slightly soluble in water, methanol or ethanol(95) and practically insoluble in ether.

It is soluble in dilute hydrochloric acid or dilute sodium hydroxide TS.

It is gradually colored by light.

Optical rotation $[\alpha]_\text{D}^{20}$: About –32° (0.50 g, calculated on the dried basis, methanol, 100 mL, 100 mm).

Identification (1) Dissolve 20 mg of Melphalan in 50 mL of methanol by warming, add 1 mL of a solution of 4-(4-nitrobenzyl)pyridine in acetone (1 in 20), and evaporate to dryness on a steam bath. Dissolve the residue in 1 mL of warmed methanol and add 2 drops of ammonia water(28); the resulting solution exhibits a violet color.

(2) Dissolve 0.1 g of Melphalan in 10 mL of dilute sodium hydroxide TS and heat on a steam bath for 10 minutes. After cooling, add dilute nitric acid to acidify and filter. The filtrate responds to the Qualitative Analysis for chloride.

(3) Determine the absorption spectra of solutions of Melphalan and melphalan RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Purity (1) ***Ionizable chloride***—Weigh accurately about 0.5 g of Melphalan, dissolve in 80 mL of diluted nitric acid (1 in 40), stir for 2 minutes to mix, and titrate with 0.1 mol/L silver nitrate VS (potentiometric titration under the Titrimetry); the volume consumed is NMT 1.0 mL per 0.50 g of Melphalan.

(2) ***Heavy metals***—Proceed with 1.0 g of Melphalan as directed under Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Prepare the test solution with 1.0 g of Melphalan according to Method 3 and perform the test (NMT 2 ppm).

Loss on drying NMT 7.0% (1 g, NMT 0.67 kPa, 105 °C, 2 hours).

Residue on ignition NMT 0.3% (1 g).

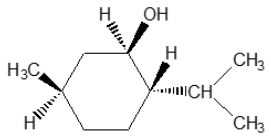
Nitrogen content Weigh accurately about 325 mg of Melphalan, dissolve in 0.1 mol/L sulfuric acid TS, and perform the test as directed under the Nitrogen Determination; the content of nitrogen (N:14.01) is NLT 8.90% and NMT 9.45%, calculated on the dried basis.

Assay Weigh accurately about 0.25 g of Melphalan, add 20 mL of potassium hydroxide solution (1 in 5), and heat under a reflux condenser on a steam bath for 2 hours. After cooling, add 75 mL of water and 5 mL of nitric acid. After cooling, titrate with 0.1 mol/L silver nitrate VS (potentiometric titration under the Titrimetry). Make any necessary correction by using the results obtained in Purity (1).

Each mL of 0.1 mol/L silver nitrate VS
= 15.260 mg of $C_{13}H_{18}Cl_2N_2O_2$

Packaging and storage Preserve in light-resistant, tight containers.

dl-Menthol
dl-멘톨



and enantiomer

$C_{10}H_{20}O$: 156.27
(1*R*,2*S*,5*R*)-and (1*S*,2*R*,5*S*)-5-Methyl-2-(propan-2-yl)cyclohexan-1-ol [*89-78-1*]

dl-Menthol contains NLT 98.0% and NMT 101.0% of *dl*-menthol ($C_{10}H_{20}O$).

Description *dl*-Menthol occurs as a colorless crystal, has a characteristic and refreshing odor, and has a stinging taste followed by a cool taste.
It is very soluble in ethanol(95) or ether, and very slightly soluble in water.
It sublimes gradually in room temperature.

Identification Perform the test according to the identification test of *l*-menthol.

Optical rotation $[\alpha]_D^{20}$: Between -2.0° and +2.0° (2.5 g, ethanol(95), 25 mL, 100 mm).

Congealing temperature Between 27 and 28 °C.

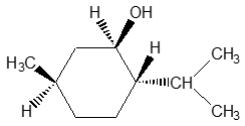
Purity Perform the test according to the Purity of *l*-menthol.

Assay Perform the test according to the Assay of *l*-menthol.

Each mL of 1 mol/L sodium hydroxide TS
= 156.27 mg of $C_{10}H_{20}O$

Packaging and storage Preserve in tight containers and store in a cool place.

l-Menthol
l-멘톨



$C_{10}H_{20}O$: 156.27
(1*R*,2*S*,5*R*)-5-Methyl-2-(propan-2-yl)cyclohexan-1-ol [*2216-51-5*]

l-Menthol contains NLT 98.0% and NMT 101.0% of *l*-menthol ($C_{10}H_{20}O$).

Description *l*-Menthol occurs as a colorless crystal, has

a characteristic and refreshing odor, and has a stinging taste followed by a cool taste.
It is very soluble in ethanol(95) or ether, and very slightly soluble in water.
It sublimes gradually in room temperature.

Identification (1) *l*-Menthol liquefies when mixed with an equal amount of camphor, chloral hydrate, or thymol.

(2) Add 1 g of *l*-Menthol in 20 mL of sulfuric acid and shake to mix; the resulting solution is turbid with a yellowish red color. Allow to stand for 3 hours; clear oil layer with no odor of menthol is separated.

Optical rotation $[\alpha]_D^{20}$: Between –45.0° and –51.0° (2.5 g, ethanol(95), 25 mL, 100 mm).

Melting point Between 42 and 44 ℃.

Purity (1) ***Residue on evaporation***—Evaporate 2.0 g of *l*-Menthol on a steam bath and dry the residue at 105 ℃ for 2 hours; the residue is NMT 1.0 mg.

(2) ***Thymol***—Dissolve 0.20 g of *l*-Menthol in a cold mixture of 2 mL of acetic acid(100), 6 drops of sulfuric acid and 2 drops of nitric acid; the resulting solution does not exhibit a green to bluish green color.

(3) ***Nitromethane or nitroethane***—Transfer 0.5 g of *l*-Menthol to a flask, add 2 mL of sodium hydroxide TS (1 in 2) and 1 mL of hydrogen peroxide(30), boil gently under a reflux condenser for 10 minutes. After cooling, add water to make exactly 20 mL, and filter. Transfer 1 mL of the filtrate to a Nessler tube, add water to make 10 mL, neutralize by adding dilute hydrochloric acid, and add 1 mL of dilute hydrochloric acid again. Cool, add 1 mL of sulfanilic acid (1 in 100), allow to stand for 2 minutes, add 1 mL of *N*-(1-Naphthyl)-*N'*-diethylethylenediamine oxalate (1 in 1000) and water to make 25 mL; the resulting solution does not exhibit a purple color.

Assay Weigh accurately about 1 g of *l*-Menthol, add the internal standard solution to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 100 mg of menthol RS, add the internal standard solution to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 0.5 μL each of the test solution and standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of menthol to internal standard for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of menthol } (C_{10}H_{20}O) = \text{Amount (mg) of menthol RS} \times (Q_T / Q_S) \times 10$$

Internal standard solution—A solution of 1-butanol in hexane (1 in 100).

Operating conditions

Detector: A flame ionization detector

Column: A fused silica column about 0.18 mm in internal diameter and 20 m in length, coated with polyethylene glycol 15000 for gas chromatography in 0.18 μm thickness.

Injection port temperature: A constant temperature of about 250 ℃.

Detector temperature: A constant temperature of about 260 ℃.

Column temperature: Start 60 ℃, raise the temperature to 110 ℃ at a rate of 20 ℃ per minute, and maintain at 110 ℃ for 10 minutes.

Carrier gas: Hydrogen

Flow rate: 0.9 mL/min

Split ratio: 50 : 1

System suitability

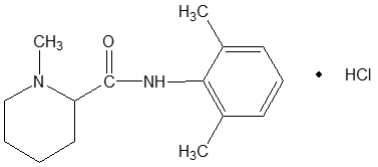
System performance: Proceed with 0.5 μL of the standard solution according to the above conditions; the relative retention time of the internal standard solution is 0.27 and the relative retention time of menthol is 1.0.

System repeatability: Perform the test 6 times with 0.5 μL each of the standard solution according to the above conditions; the relative standard deviation of the ratio peak area of menthol to the internal standard is NMT 2.0%.

Each mL of 1 mol/L sodium hydroxide VS
= 156.27 mg of $C_{10}H_{20}O$

Packaging and storage Preserve in tight containers and store in a cool place.

Mepivacaine Hydrochloride
메피바카인염산염



$C_{15}H_{22}N_2O \cdot HCl$: 282.81

N-(2,6-Dimethylphenyl)-1-methylpiperidine-2-carboxamide hydrochloride [*1722-62-9*]

Mepivacaine Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of mepivacaine hydrochloride ($C_{15}H_{22}N_2O \cdot HCl$).

Description Mepivacaine Hydrochloride occurs as white crystals or a crystalline powder.
It is freely soluble in water or methanol, soluble in acetic acid(100), and sparingly soluble in ethanol(99.5).
An aqueous solution of Mepivacaine Hydrochloride (1 in 10) shows no optical rotation.

Melting point—About 256 ℃ (with decomposition).

Identification (1) Determine the absorption spectra of solutions (1 in 2500) of Mepivacaine Hydrochloride and mepivacaine hydrochloride RS as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit simi-

lar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Mepivacaine Hydrochloride and mepivacaine hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Mepivacaine Hydrochloride (1 in 50) responds to the Qualitative Analysis for chloride.

pH Dissolve 0.2 g of Mepivacaine Hydrochloride in 10 mL of water; the pH of this solution is between 4.0 and 5.0.

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Mepivacaine Hydrochloride in 10 mL of water; the solution is colorless and clear.

(2) ***Sulfate*—**Perform the test with 0.5 g of Mepivacaine Hydrochloride. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid (NMT 0.038%).

(3) ***Heavy metals*—**Proceed with 2.0 g of Mepivacaine Hydrochloride according to Method 1 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 5 ppm).

(4) ***Related substances*—**Dissolve 0.10 g of Mepivacaine Hydrochloride in 5 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution and add methanol to make exactly 20 mL. Pipet 2 mL of this solution, add methanol to make exactly 50 mL, and use the resulting solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ether, methanol and aqueous ammonia (28) (100 : 5 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray the bismuth nitrate-potassium iodide TS evenly onto the plate; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

(5) ***2,6-Dimethylaniline*—**Weigh accurately about 5.0 g of Mepivacaine Hydrochloride, and dissolve in methanol to make exactly 10 mL. Pipet 2 mL of this solution, add 1 mL of a solution of 4-dimethylaminobenzaldehyde in methanol (1 in 100) and 2 mL of acetic acid(100), allow the mixture to stand for 10 minutes, and use the resulting solution as the test solution. Separately, weigh accurately about 5.0 mg of 2,6-dimethylaniline and dissolve in methanol to make exactly 10 mL. Pipet 1 mL of this solution and add methanol to make exactly 100 mL. Proceed in the same manner as in the preparation of the test solution with 2 mL of this solution and use this solution as the standard solution. The color of the test solution is not more intense than that of the standard solution, as exhibited at the same time (NMT 100 ppm).

Loss on drying NMT 1.0% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Mepivacaine Hydrochloride, previously dried, dissolve in 10 mL of acetic acid(100), add 70 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 28.281 mg of $C_{15}H_{22}N_2O \cdot HCl$

Packaging and storage Preserve in tight containers.

Mepivacaine Hydrochloride Injection
메피바카인염산염 주사액

Mepivacaine Hydrochloride Injection is an aqueous solution for injection. Mepivacaine Hydrochloride Injection contains NLT 95.0% and NMT 105.0% of the labeled amount of mepivacaine hydrochloride ($C_{15}H_{22}N_2O \cdot HCl$: 282.81).

Method of preparation Prepare as directed under Injections, with Mepivacaine Hydrochloride.

Description Mepivacaine Hydrochloride Injection occurs as a colorless and clear liquid.

pH—Between 4.5 and 6.8.

Identification Weigh an amount of Mepivacaine Hydrochloride Injection, equivalent to 20 mg of mepivacaine hydrochloride according to the labeled amount, add 1 mL of sodium hydroxide TS, and extract with 20 mL of hexane. To 8 mL of the hexane extract, add 20 mL of 1 mol/L hydrochloric acid TS, shake vigorously and determine the absorption spectrum of the water layer as directed under Ultraviolet-visible Spectrophotometry: it exhibits maxima between 261 nm and 265 nm and between 270 nm and 273 nm.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.6 EU per mg of mepivacaine hydrochloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Take exactly an amount of Mepivacaine Hydrochloride Injection, equivalent to about 40 mg of mepivacaine hydrochloride ($C_{15}H_{22}N_2O \cdot HCl$) according to the

labeled amount, add exactly 4 mL of the internal standard solution, add 0.001 mol/L hydrochloric acid TS to make 20 mL, and use this solution as the test solution. Separately, weigh accurately about 40 mg of mepivacaine hydrochloride RS, previously dried at 105 ℃ for 3 hours, dissolve in hydrochloric acid TS, add exactly 4 mL of the internal standard solution, add 0.001 mol/L hydrochloric acid TS to make 20 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under Liquid Chromatography according to the following conditions and calculate the ratios, Q_T and Q_S, of the peak area of mepivacaine hydrochloride to that of the internal standard for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of mepivacaine hydrochloride } (C_{15}H_{22}N_2O\cdot HCl) = \text{Amount (mg) of mepivacaine hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of benzophenone in methanol (1 in 4000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

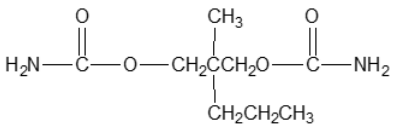
Mobile phase: Dissolve 2.88 g of sodium lauryl sulfate in a mixture of 550 mL of 0.02 mol/L phosphate buffer solution, pH 3.0 and 450 mL of acetonitrile, for a total volume of 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of mepivacaine is about 6 minutes.

Selection of column: Proceed with 5 μL of a standard solution under the above operating conditions; mepivacaine and benzophenone are eluted in this order with the resolution being NLT 6.0.

Packaging and storage Preserve in hermetic containers.

Meprobamate
메프로바메이트



$C_9H_{18}N_2O_4$: 218.25

[2-(Carbamoyloxymethyl)-2-methylpentyl] carbamate [*57-53-4*]

Meprobamate contains NLT 97.0% and NMT 101.0% of meprobamate ($C_9H_{18}N_2O_4$), calculated on the dried basis.

Description Meprobamate occurs as a white powder. It has a characteristic odor and a bitter taste.
It is slightly soluble in water, freely soluble in acetone or ethanol(95), and sparingly soluble in ether.

Identification (1) Determine the infrared spectra of Meprobamate and meprobamate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If the two spectra show a difference, use the steps as follows: dissolve each in acetone to make a solution containing 8 mg per mL, add 0.1 mL each of these solutions to 1 mL of n-heptane for mixing, evaporate the solvent in the nitrogen air flow at NMT 30 ℃, and dry the residue for 30 minutes at room temperature in vacuum. Perform the test with each resulting material.

(2) Perform the test as directed under the related substance test method; the R_f values and colors of the principal spots from the test solution and standard solution A are the same.

Melting point Between 103 and 107 ℃. The difference in the temperature between the start of melting and the completion of melting should be NMT 2 ℃.

Purity (1) ***Heavy metals***—Dissolve 2.0 g of Meprobamate in a mixture of water and acetone (15 : 85) to make 20 mL. Use this solution as the test solution and perform the test. Separately, add a mixture of water and acetone (15 : 85) to make 20 mL to 2.0 mL of lead standard solution. To 10 mL of this solution, add 2 mL of the test solution, and use the resulting solution as the control solution. Separately, add 2 mL of the test solution to 10 mL of a mixture of water and acetone (15 : 85), and use the resulting solution as the blank test solution. To 12 mL each of the test solution, control solution and blank test solution, add 2 mL of acetate buffer solution, pH 3.5, mix, add 1.2 mL of thioacetamide TS, and immediately mix. Allow the mixture to stand for 2 minutes; the color of the test solution is not more intense than that of the control solution (NMT 10 ppm).

System suitability: The control solution is slightly brown compared to the blank test solution.

(2) ***Related substances***—Weigh accurately a suitable amount of Meprobamate, dissolve in ethanol(95) to make a solution containing 0.1 g per mL, and use this solution as the test solution. To the test solution, add ethanol(95) for quantitative dilution to make a verification solution containing 1.0 mg per mL. Separately, weigh accurately a suitable amount of meprobamate RS, previously dried at 60 ℃ for 3 hours in vacuum, and dissolve in ethanol(95) to make a solution containing 1.0 mg per mL. To this solution, add ethanol(95) for quantitative dilution to make standard solutions as below.

Standard solution	Dilution ratio	Concentration (mg/mL)	Percentage (%) versus sample
A	(0)	1.0	1.0
B	(4 in 5)	0.8	0.8
C	(3 in 5)	0.6	0.6
D	(2 in 5)	0.4	0.4
E	(1 in 5)	0.2	0.2

With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the test solution, verification solution and standard solutions on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of hexane, acetone and pyridine (7 : 3 : 1) as the developing solvent to a distance of about 15 cm, air-dry the plate for 15 minutes, heat at 100 ℃ for 15 minutes, and cool. Spray a solution prepared by dissolving 1 g of vanillin in a mixture of sulfuric acid and ethanol (160 : 40) evenly on this plate, heat at 110 ℃ for 15 to 20 minutes and cool. Allow it to stand at room temperature until a bluish-purple spot appears. It usually takes about 30 to 60 minutes for the color reaction. The R_f value of the principal spot from the test solution is the same as the R_f value of the principal spot from the standard solution, the spots other than the principal spot from the test solution are not larger or more intense than the spots from the standard solution A (1.0%), and the sum of all spots other than the principal spot from the test solution are NMT 2.0%.

(3) ***Methyl carbamate***—Powder Meprobamate into fine powder, weigh accurately about 1.0 g of the powder, put it in a beaker, add 5.0 mL of water, and shake well for wetting. Filter using a funnel with glass wool, and use the filtrate as the test solution. Separately, weigh accurately a suitable amount of methyl carbamate RS, previously dried at 60 ℃ for 3 hours in vacuum, dissolve in water to obtain a solution containing 1.0 mg per mL, and use this solution as the standard solution. Perform the test with exactly 50 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas in the solutions; the peak area of methyl carbamate in the test solution is not greater than that in the standard solution (0.5%).

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 200 nm).

Column: A stainless steel column about 3.9 mm to 4.6 mm in internal diameter and 25 to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: Water

Flow rate: 1 mL/min

System suitability

System repeatability: Repeat the test 6 times with 20 μL of the standard solution each time according to the above operating conditions; the relative standard deviation of the peak area of methyl carbamate is NMT 2.0%.

Loss on drying NMT 0.5% (1.0 g, 60 ℃, in vacuum, 3 hours).

Assay Weigh accurately about 0.4 g of Meprobamate, put it into an Erlenmeyer flask, add 40 mL of hydrochloric acid and some boiling stones, and boil for 90 minutes with a reflux condenser attached. Detach the reflux condenser, keep boiling until the solution reaches the volume of 5 to 10 mL, and cool. Add 50 mL of water and 1 drop of methyl red TS, and carefully neutralize with 10 mol/L sodium hydroxide TS until the indicator changes in color. If necessary, add 1 mol/L hydrochloric acid VS until the solution turns red and carefully neutralize with 0.1 mol/L sodium hydroxide VS again. To this solution, add a mixture of 15 mL of formaldehyde solution TS, previously neutralized with phenolphthalein TS, and 15 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS until the solution turns yellow. Again, add 0.2 mL of phenolphthalein TS and titrate with 0.1 mol/L sodium hydroxide VS until the solution turns red. Perform a blank test in the same manner and make any necessary correction. Regarding the consumed amount of 0.1 mol/L sodium hydroxide VS, only the consumed amount after adding the formaldehyde solution TS is considered.

Each mL of 0.1 mol/L sodium hydroxide VS
= 10.91 mg of $C_9H_{18}N_2O_4$

Packaging and storage Preserve in tight containers.

Meprobamate Tablets
메프로바메이트 정

Meprobamate Tablets contain NLT 90.0% and NMT 110.0% of labeled amount of meprobamate ($C_9H_{18}N_2O_4$: 218.25).

Method of preparation Prepare as directed under Tablets, with Meprobamate.

Identification (1) Weigh an amount of powdered Meprobamate Tablets, equivalent to about 0.8 g of meprobamate according to the labeled amount, add 5 mL of anhydrous alcohol, and heat for 5 minutes, shaking occasionally, until just before boiling. After cooling, filter through 15 mL of hexane, and shake to mix. Filter the resulting precipitates by suction, and dry at 60 ℃. With the dry matter, perform the test as directed under the Identification (1) of Meprobamate.

(2) The retention times of the major peaks obtained from the test solution and the standard solution in the Assay are the same.

Dissolution Perform the test with 1 tablet of Meprobamate Tablets according to Method 1 under the Dissolution at 100 revolutions per minute, using 900 mL of water as the dissolution medium. After 30 minutes into the dis-

solution test, take 30 mL of the dissolved solution, filter, and perform the test with the filtrate according to the Assay.
Meets the requirements if the dissolution rate of Meprobamate Tablets for 30 minutes is NLT 75%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately NLT 20 tablets of Meprobamate Tablets, and powder finely. Weigh accurately a portion of this powder, equivalent to about 0.25 g of meprobamate ($C_9H_{18}N_2O_4$), add 15 mL of acetonitrile, shake to dissolve, add water to make exactly 50 mL, and filter. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 50 mg of meprobamate RS, add 3 mL of acetonitrile, shake to dissolve, add water to make exactly 10 mL; and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of meprobamate from the test solution and the standard solution, respectively.

$$\text{Amount (mg) of meprobamate } (C_9H_{18}N_2O_4) = \text{Amount (mg) of meprobamate RS} \times \frac{A_T}{A_S} \times 5$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 200 nm).

Column: A stainless steel column about 3.9 mm to 4.6 mm in internal diameter and 25 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of water and acetonitrile (7 : 3).

Flow rate: 1 mL/min

System suitability

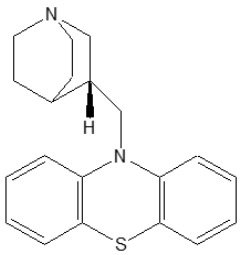
System performance: To 25 mg of meprobamate, add 1 mL of acetonitrile, shake to dissolve, add 1 mL of phenacetin solution, and add water to make 5 mL. Proceed with 20 μL of this solution according to the above conditions; meprobamate and phenacetin are eluted in this order with the resolution being NLT 2.0, and the peak area of phenacetin is 65% to 100% of that of meprobamate.

System repeatability: Repeat the test 6 times according to the above conditions with 20 μL each of the standard solution; the relative standard deviation of the peak areas is NMT 2.0%.

Phenacetin solution—Weigh 25 mg of phenacetin, and dissolve in acetonitrile to make exactly 200 mL. Take exactly 20 mL of this solution, add 30 mL of acetonitrile, and add water to make exactly 100 mL.

Packaging and storage Preserve in well-closed containers.

Mequitazine
메퀴타진



and enantiomer

$C_{20}H_{22}N_2S$: 322.47

(*RS*)-10-(1-Azabicyclo[2.2.2]octan-3-ylmethyl) phenothiazine [*29216-28-2*]

Mequitazine, when dried, contains NLT 98.5% and NMT 101.0% of mequitazine ($C_{20}H_{22}N_2S$).

Description Mequitazine occurs as a white crystalline powder.
It is freely soluble in methanol or acetic acid(100), soluble in ethanol(95) and practically insoluble in water.
A solution of Mequitazine in methanol (1 in 50) shows no optical rotation.
It is gradually colored by light.

Identification (1) Determine the absorption spectra of solutions of Mequitazine and mequitazine RS in ethanol(95) (1 in 250000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Mequitazine and mequitazine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 146 and 150 ℃.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Mequitazine as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Perform the test, using light-resistant vessels. Dissolve 50 mg of Mequitazine in 5 mL of methanol and use this solution as the test solution. Pipet 1.0 mL of this solution and add methanol to make exactly 50 mL. Pipet 5.0 mL of this resulting solution, add methanol to make exactly 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 mL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, methanol and diethylamine (7 : 2 : 2) to as the developing solvent a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light

(main wavelength: 254 nm); the number of spots other than the principal spot from the test solution is NMT 3 and they are not more intense than the spot from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, phosphorus pentoxide, 60 ℃, 3 hours).

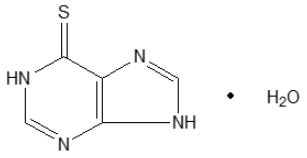
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.25 g of Mequitazine, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same way and make necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 32.247 mg of $C_{20}H_{22}N_2S$

Packaging and storage Preserve in light-resistant, tight containers.

Mercaptopurine Hydrate
메르캅토푸린수화물



Mercaptopurine $C_5H_4N_4S \cdot H_2O$: 170.19
3,7-Dihydropurine-6-thione hydrate [*6112-76-1*]

Mercaptopurine Hydrate contains NLT 98.0% and NMT 101.0% of mercaptopurine ($C_5H_4N_4S$: 152.18), calculated on the anhydrous basis.

Description Mercaptopurine Hydrate occurs as pale yellow to yellow crystals or a crystalline powder and is odorless.
It is practically insoluble in water, acetone or ether.
It dissolves in sodium hydroxide TS or ammonia TS.

Identification (1) Dissolve 0.6 g of mercaptopurine hydrate in 6 mL of sodium hydroxide (3 in 100), add slowly 0.5 mL of iodomethane with vigorous stirring, and shake well to mix for 10 minutes. Cool with ice and adjust pH to about 5 by adding acetic acid drop by drop. Collect the separated crystals by filtration, recrystallize from water, and dry at 120 ℃ for 30 minutes; the melting point is between 218 and 222 ℃ (with decomposition).

(2) Determine the absorption spectra of the solutions of Mercaptopurine Hydrate and mercaptopurine hydrate RS in 0.1 mol/L hydrochloric acid (1 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit the same intensities of absorption at the same wavelengths.

Purity (1) ***Clarity and color of solution***—Dissolve 0.20 g of Mercaptopurine Hydrate in 10 mL of ammonia TS; the solution is clear.

(2) ***Sulfate***—Dissolve 50 mg of Mercaptopurine Hydrate in 10 mL of dilute hydrochloric acid, add 5 drops of barium chloride TS, and allow to stand for 5 minutes; the solution does not become turbid.

(3) ***Heavy metals***—Proceed with 1.0 g of Mercaptopurine Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Hypoxanthine***—Weigh 50 mg of Mercaptopurine Hydrate, dissolve in exactly 10 mL of the ammonia water(28) in methanol (1 in 10), and use this solution as the test solution. Weigh 5.0 mg of hypoxantine, dissolve in the ammonia water(28) in methanol (1 in 10) to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of methanol, chloroform, *n*-butyl formate and ammonia water(28) (8 : 6 : 4 : 1) to a distance of 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spot obtained from the test solution, of which location corresponds to that of the spot from the standard solution, is neither larger nor more intense than the spot from the standard solution.

(5) ***Phosphorus***—Weigh 0.20 g of Mercaptopurine Hydrate, put in a crucible, and add 2 mL of diluted sulfuric acid (3 in 7). Heat at a low temperature and add slowly 0.5 mL portions of nitric acid dropwise until the liquid becomes colorless. Continue to heat until most of the liquid has evaporated. Cool, dissolve the residue in 10 mL of water, and transfer the solution into a 25 mL volumetric flask. Wash the crucible twice with 4 mL portions of water, combine the washings with the solution in the flask, and use this solution as the test solution. Dissolve 0.4396 g of potassium dihydrogen phosphate in water to make exactly 200 mL. Pipet 2.0 mL of this solution and add water to make 100 mL. Take another 2.0 mL of this solution, transfer into a 25 mL volumetric flask, add 16 mL of water, and use this solution as the standard solution. To the test solution and the standard solution, add 1 mL of diluted sulfuric acid (3 in 7), 0.5 mL of nitric acid, 0.75 mL of ammonium molybdate TS, 1 mL of 1-amino-2-naphthol-4-sulfonic acid TS, put water to make 25 mL, and allow to stand for 5 minutes. Perform the test with the test and standard solutions as directed under the Ultraviolet-visible Spectroscopy using water as the control solution; the absorbance obtained from the test solution at the wavelength of 750 nm is not larger than the absorbance from the standard solution.

Water Between 10.0% and 12.0% (0.2 g, volumetric titration, back titration).

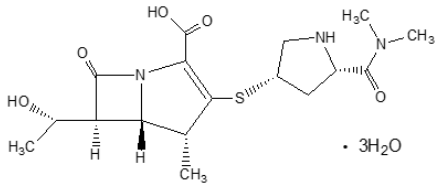
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately 0.25 g of Mercaptopurine Hydrate, dissolve in 90 mL of *N*,*N*-dimethylformamide, and titrate with 0.1 mol/L tetramethylammonium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test with a solution of 90 mL of *N*,*N*-dimethylformamide and 15 mL of water and make any necessary correction.

Each mL of 0.1 mol/L tetramethyl ammonium hydroxide VS
= 15.218 mg of $C_5H_4N_4S$

Packaging and storage Preserve in well-closed containers.

Meropenem Hydrate
메로페넴수화물



$C_{17}H_{25}N_3O_5S \cdot 3H_2O$: 437.51

(4*R*,5*S*,6*S*)-3-[(3*S*,5*S*)-5-(Dimethylcarbamoyl)pyrrolidin-3-yl]sulfanyl-6-[(1*S*)-1-hydroxy-ethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate [*119478-56-7*]

Meropenem Hydrate contains NLT 980 μg (potency) and NMT 1010 μg (potency) of meropenem ($C_{17}H_{25}N_3O_5$: 383.47 S) per mg, calculated on the anhydrous basis.

Description Meropenem Hydrate occurs as a white to pale yellow crystalline powder.
It is sparingly soluble in water and practically insoluble in ethanol(95) or ether.
It is soluble in sodium bicarbonate TS.

Identification (1) Dissolve 10 mg (potency) of Meropenem Hydrate in 2 mL of water, add 3 mL of hydroxylamine hydrochloride-ethanol TS, and allow to stand for 5 minutes. Add 1 mL of acidic ammonium iron(III) sulfate TS and shake to mix; the resulting solution exhibits a reddish brown color.

(2) Determine the absorption spectra of aqueous solutions of Meropenem Hydrate and meropenem RS (3 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Meropenem Hydrate and meropenem RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -17° and -21° (0.220 g, calculated on the anhydrous basis, water, 50 mL, 100 mm).

pH Dissolve 0.1 g (potency) of Meropenem Hydrate in 10 mL of water; the pH of this solution is between 4.0 and 6.0.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Meropenem Hydrate in 10 mL of sodium bicarbonate TS; the solution is clear and its color is not more intense than the following control solution.

Control solution—Take accurately 0.3 mL of cobalt(II) chloride hexahydrate colorimetric stock solution and 1.2 mL of iron(III) chloride colorimetric stock solution, and add 18.5 mL of diluted hydrochloric acid (1 in 40).

(2) ***Heavy metals***—Proceed with 2.0 g of Meropenem Hydrate and perform the test according to Method 2. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Weigh accurately 50 mg (potency) of Meropenem Hydrate, dissolve in triethylamine-phosphate buffer solution, pH 5.0 to make exactly 10 mL, and use this solution as the test solution. Prepare the test solution before use. Pipet 1 mL of this solution and add triethylamine-phosphate buffer solution, pH 5.0 to make exactly 100 mL. Pipet 3 mL of this solution, add triethylamine-phosphate buffer solution, pH 5.0 to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test and standard solutions as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas of these solutions by the automatic integration method; the peak area of ring-opened meropenem, having the relative retention time about 0.5 to meropenem, and the peak area of the dimmer, having the relative retention time about 2.2 to meropenem, obtained from the test solution are not larger than the peak area of meropenem from the standard solution, the area of the peak other than meropenem and the peaks mentioned above from the test solution is not larger than 1/3 times the peak area of meropenem from the standard solution. The total area of the peaks other than neropenem from the test solution is not larger than 3 times the peak area of neropenem from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 6.0 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of 1000 mL of triethyla-

mine-phosphate buffer solution, pH 5.0 and 70 mL of acetonitrile.

Flow rate: Adjust so that the retention time of meropenem is about 6 minutes.

System suitability

Test for required detectability: Pipet 5 mL of the standard solution and add triethylamine-phosphate buffer solution, pH 5.0 to make exactly 25 mL. Confirm that the peak area of meropenem obtained from 10 μL of this solution is equivalent to 16% to 24% of the peak area of meropenem from the standard solution.

System performance: Proceed with 10 μL of the test solution, previously warmed at 60 ℃ for 30 minutes, according to the above conditions; the ring-opened, meropenem and dimer are eluted in this order with the resolution between the ring-opened and meropenem being NLT 1.5.

System reproducibility: Perform the test six times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of meropenem is NMT 1.5%.

Time span of measurement: About 7 times the retention time of meropenem.

Water NLT 11.4% and NMT 13.4% (0.1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.10% (1 g).

Sterility It meets the requirements when used in sterile preparations.

Bacterial endotoxins Less than 0.12 EU per mg (potency) of meropenem when used in sterile preparations.

Assay Weigh accurately 50 mg (potency) each of Meropenem Hydrate and meropenem RS, add 10 mL of internal standard solution, dissolve in triethylamine-phosphate buffer solution, pH 5.0 to make 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of the peak area of meropenem to those of the internal standard from the test solution and the standard solution.

$$\text{Potency (μg) of meropenem } (C_{17}H_{25}N_3O_5S) = \text{Potency (μg) of meropenem RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Dissolve 1.0 mL of benzyl alcohol in triethylamine-phosphate buffer solution, pH 5.0 to make 300 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of triethylamine-phosphate buffer solution, pH 5.0 and methanol (5 : 1).

Flow rate: Adjust so that the retention time of meropenem RS is about 7 minutes.

System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; meropenem and the internal standard are eluted in this order with the resolution between these peaks being NLT 20.

System reproducibility: Perform the test 6 times with 5 μL each of the standard solutions according to the above conditions; the relative standard deviation of the ratios of the peak area of meropenem to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Meropenem for injection
주사용 메로페넴

Meropenem for injection is an injection to be dissolved before use and contains NLT 93.0% and NMT 107.0% of the labeled amount of meropenem ($C_{17}H_{25}N_3O_5S$: 383.47).

Method of preparation Prepare as directed under Injections, with Meropenem Hydrate and Sodium Carbonate.

Description Meropenem for injection occurs as a white to pale yellow crystalline powder.

Identification Determine the infrared spectra of Meropenem for injection as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; it exhibits absorption at the wavenumbers of about 3410 cm^{-1}, 1750 cm^{-1}, 1655 cm^{-1}, 1583 cm^{-1} and 1391 cm^{-1}.

pH Dissolve an amount of Meropenem for injection, equivalent to 0.25 g (potency) of meropenem, in 5 mL of water; the pH of the solution is between 7.3 and 8.3.

Purity (1) ***Clarity and color of solution***—Weigh an amount of Meropenem for injection, equivalent to 1.0 g (potency) of Meropenem Hydrate, according to the labeled amount, and dissolve in 20 mL of water; the color of the solution is not more intense than that of the following control solution.

Control solution—To 0.3 mL of cobalt(II) chloride hexahydrate colorimetric stock solution and 1.2 mL of Iron(III) chloride hexahydrate colorimetric stock solution, add 18.5 mL of diluted hydrochloric acid (1 in 40).

(2) ***Related substances***—Weigh accurately about 0.125 g (potency) of Meropenem for injection, dissolve in triethylamine-phosphate buffer solution, pH 5.0 to make exactly 25 mL, and use this solution as the test solution (prepared before use). Separately, weigh accurately about 25 mg (potency) of meropenem RS, dissolve in triethylamine-phosphate buffer solution, pH 5.0, and make exactly 10 mL. Pipet 1 mL of this solution, add triethylamine-phosphate buffer solution, pH 5.0, to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Purity (2) of Meropenem. Determine the peak areas of ring-opened and dimer from the test solution and the peak area of meropenem from the standard solution, and calculate the amounts of ring-opened and dimer according to the following equation (NMT 0.5% for ring-opened and dimer, respectively).

$$\text{Content (\%) of ring-opened compound} = \frac{A_{\mathrm{Ta}}}{A_{\mathrm{S}}} \times \frac{Potency\ (mg)\ of\ \text{meropenem RS}}{Amount\ (mg)\ of\ \text{Meropenem for injection}} \times \frac{5}{4}$$

$$\text{Content (\%) of dimers} = \frac{A_{\mathrm{Tb}}}{A_{\mathrm{S}}} \times \frac{Potency\ (mg)\ of\ \text{meropenem RS}}{Amount\ (mg)\ of\ \text{Meropenem for injection}} \times \frac{5}{4}$$

A_{Ta}: Peak area of ring-opened in the test solution
A_{Tb}: Peak area of dimer in the test solution
A_{S}: Peak area of meropenem in the standard solution

Loss on drying Between 9.5% and 12.0% (0.1 g, 0.7 kPa, 60 ℃, 3 hours).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.12 EU per mg (potency) of meropenem.

Particulate contamination: Visible particles Meets the requirements.

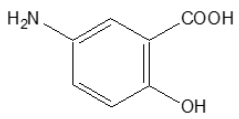
Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Perform the test according to the Assay under Meropenem Hydrate. However, weigh accurately the amount equivalent to about 50 mg (potency) of Meropenem for injection, according to the labeled potency, add exactly 10 mL of the internal standard solution, add triethylamine-phosphate buffer solution, pH 5.0 to make 100 mL, and use this solution as the test solution.

Packaging and storage Preserve in hermetic containers.

Mesalazine
메살라진



$C_7H_7NO_3$: 153.14
5-Amino-2-hydroxybenzoic acid [*89-57-6*]

Mesalazine, when dried, contains NLT 98.5% and NMT 101.0% of mesalazine ($C_7H_7NO_3$).

Description Mesalazine occurs as a white, light grey or light red powder or crystals.
It is very slightly soluble in water and practically insoluble in ethanol(95).
It dissolves in dilute sodium hydroxide TS and in dilute hydrochloric acid.

Identification (1) Dissolve 50.0 mg each of Mesalazine and mesalazine RS in 1.03 w/v% hydrochloric acid to make 100 mL. To 5.0 mL each of these solutions, add 1.03 w/v% hydrochloric acid to make 200 mL, respectively. Determine the absorption spectra of the resulting solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Mesalazine and mesalazine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 50 mg each of Mesalazine and mesalazine RS in 10 mL of a mixture of water and acetic acid(100) (1 : 1), respectively, add methanol to make 20 mL each, and use each of the resulting solutions as the test solution and the standard solution, respectively. Perform the test with the test solution and standard solution as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of 4-methyl-2-pentanone, methanol and acetic acid(100) (50 : 40 : 10) as the developing solvent to a distance of about 10 cm and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 365 nm). The colors and R_f values of the principal spots from the test solution and standard solution are the same.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Mesalazine in 1 mol/L hydrochloric acid TS to make 20 mL, and maintain the solution at 40 ℃; the solution is clear. While maintaining the solution at 40 ℃, determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy. The absorbance at 440 nm is NMT 0.15 and the absorbance at 650 nm is NMT 0.10.

(2) ***Reducing substances***—Dissolve 0.10 g of Mesalazine in dilute hydrochloric acid to make 25 mL,

add 0.2 mL of starch TS and 0.25 mL of 0.01 mol/L iodine TS, and allow to stand for 2 minutes; the solution exhibit a blue or purple-brown color.

(3) ***Chloride*—**Dissolve 1.50 g of Mesalazine in 50 mL of formic acid, add 100 mL of water and 5 mL of 2 mol/L nitric acid TS, and titrate with 0.005 mol/L silver nitrate VS (potentiometric titration under the Titrimetry) (NMT 0.1%).

Each mL of 0.005 mol/L silver nitrate VS
= 0.1773 mg of Cl

(4) ***Sulfate*—**To 1.0 g of Mesalazine, add 20 mL of water, shake for 1 minute to filter, and wash the filter paper and residue with a suitable amount of water. Combine the filtrate and washings, add water to make 40 mL, and use this solution as the test solution. Prepare the control solution with 0.42 mL of 0.005 mol/L sulfuric acid (NMT 0.02%).

(5) ***Heavy metals*—**Proceed with 1.0 g of Mesalazine according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(6) ***Related substances I and II*—**Dissolve 50.0 mg of Mesalazine in the mobile phase A to make exactly 50 mL, and use this solution as the test solution. Dissolve 5.0 mg of mesalazine related substance I (2-aminophenol) in the mobile phase A to make exactly 100 mL. To 10.0 mL of this solution, add the mobile phase A to make exactly 100 mL, and use the resulting solution as the standard solution (1). Dissolve 5.0 mg of mesalazine related substance II (4-aminophenol) in the mobile phase A to make exactly 250 mL. To 1.0 mL of this solution, add 1.0 mL of the standard solution (1), add the mobile phase A to make exactly 100 mL, and use the resulting solution as the standard solution (2). To 1.0 mL of the test solution, add the mobile phase A to make exactly 200 mL. To 5.0 mL of this solution, add 5.0 mL of the standard solution (1), and use the resulting solution as the standard solution (3). Perform the test with 20 µL each of the test solution, standard solution (2) and standard solution (3) as directed under the Liquid Chromatography according to the following conditions. Determine the peak area from each solution according to the automatic integration method; the peak area of the related substance II from the test solution is not greater than that from the standard solution (2) (NMT 0.02%), and the peak area of the related substance I from the test solution is not greater than 4 times that from the standard solution (2) (NMT 0.02%).

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 µm in particle diameter).

Mobile phase: Use mobile phases A and B to control stepwise or based on the gradient elution as follows.

Mobile phase A: Dissolve 2.2 g of perchloric acid and 1.0 g of phosphoric acid in water to make 1000 mL.

Mobile phase B: Dissolve 1.7 g of perchloric acid and 1.0 g of phosphoric acid in acetonitrile to make 1000 mL.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 8	100	0
8 - 25	100 → 40	0 → 60
25 - 30	40 → 100	60 → 0
30 - 40	100	0

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 20 µL of the standard solution (3) under the above operating conditions; the relative retention times are about 0.5, 0.9 and 1.0 for the related substance II, related substance I and mesalazine, respectively, and the resolution between the peaks of the related substance I and mesalazine is NLT 3.0.

(7) ***Related substance IV*—**Dissolve 40.0 mg of Mesalazine in the mobile phase to make exactly 20 mL, and use this solution as the test solution. Dissolve 27.8 mg of aniline hydrochloride in the mobile phase to make exactly 100 mL. To 0.2 mL of this solution, add the mobile phase to make exactly 20 mL. To 0.2 mL of this solution, add the mobile phase to make exactly 20 mL, and use the resulting solution as the standard solution. Perform the test with 50 µL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution according to the automatic integration method; the peak area of the mesalazine related substance IV (aniline) from the test solution is not greater than that from the standard solution (0.001%).

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 205 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 µm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of pH 8.0 phosphate buffer and methanol (85 : 15).

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 50 µL of the standard solution under the above operating conditions; the retention time of the related substance IV is about 15 minutes and the signal-to-noise ratio of the major peak is NLT 10.

Phosphate buffer solution, pH 8.0—Dissolve 1.41 g

of potassium dihydrogen phosphate and 0.47 g of sodium dihydrogen phosphate dihydrate in water to make 1000 mL, and adjust the pH to 8.0 with 1 mol/L sodium oxide TS.

(8) ***Related substances*—**Use freshly prepared test solution, standard solution and mobile phases. Dissolve 50.0 mg of Mesalazine in the mobile phase A to make exactly 50 mL, and use this solution as the test solution. To 1.0 mL of the test solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution (1). Dissolve 5.0 mg of mesalazine related substance V (3-aminobenzoic acid) in the mobile phase A to make exactly 100 mL. To 1.0 mL of this solution, add the test solution to make exactly 25 mL, and use the resulting solution as the standard solution (2). Dissolve 5.0 mg of related substance V in the mobile phase A to make exactly 100 mL. To 1.0 mL of this solution, add the mobile phase A to make exactly 50 mL, and use the resulting solution as the standard solution (3). Dissolve 10.0 mg of related substance III (3-aminophenol) in the mobile phase A to make exactly 100 mL. To 1.0 mL of this solution, add the mobile phase to make exactly 50 mL, and use the resulting solution as the standard solution (4). Dissolve 5.0 mg of mesalazine related substance VI (2,5-dihydroxybenzoic acid) in the mobile phase A to make exactly 100 mL. To 1.0 mL of this solution, add the mobile phase A to make exactly 50 mL, and use the resulting solution as the standard solution (5). Dissolve 15.0 mg of mesalazine related substance VII (salicylic acid) in the mobile phase A to make exactly 100 mL. To 1.0 mL of this solution, add the mobile phase A to make exactly 50 mL, and use the resulting solution as the standard solution (6). Use the mobile phase A as the blank test solution. Perform the test with 10 μL each of the blank test solution, test solution and standard solutions (1), (3), (4), (5) and (6) as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution according to the automatic integration method. The peak area of the related substance III from the test solution is not greater than the peak area of the major peak from the standard solution (4) (0.2%), the peak area of the related substance V is not greater than the peak area of the major peak from the standard solution (3) (0.1%), the peak area of the related substance VI is not greater than the peak area of the major peak from the standard solution (5) (0.1%), and the peak area of the related substance VII is not greater than the peak area of the major peak from the standard solution (6) (0.3%). The peak area of other related substance is not greater than 0.1 times the peak area of the major peak from the standard solution (1) (NMT 0.1%), and the sum of peak areas of all related substances is not greater than the peak area of the major peak from the standard solution (1) (1.0%). Exclude the peak whose area is not greater than 0.05 times the peak area of the major peak from the standard solution (1) and the peak from the blank test solution.

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Use mobile phases A and B to control stepwise or based on the gradient elution as follows.

Mobile phase A: Dissolve 2.2 g of perchloric acid and 1.0 g of phosphoric acid in water to make exactly 1000 mL.

Mobile phase B: Dissolve 1.7 g of perchloric acid and 1.0 g of phosphoric acid in acetonitrile to make exactly 1000 mL.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 7	100	0
7 - 25	100 → 40	0 → 60
25 - 30	40 → 100	60 → 0
30 - 40	100	0

Flow rate: 1.25 mL/min

System suitability

System performance: Proceed with 10 μL each of the standard solutions (2), (3), (4), (5) and (6) under the above operating conditions; the relative retention times to the mesalazine peak are about 0.8, 1.2, 3.1 and 3.9 for the peaks of the related substances III, V, VI and VII, respectively, and the ratio of the height to the peak top of the related substance V versus the height of valley between the mesalazine peak and related substance V peak is NLT 1.5.

Loss on drying NMT 0.5% (1.0 g, 105 ℃, constant mass).

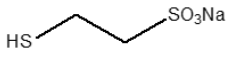
Residue on ignition NMT 0.2% (1.0 g).

Assay Weigh accurately about 50 mg of Mesalazine, previously dried, dissolve in 100 mL of boiling water, cool it to room temperature, and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry).

Each mL of 0.1 mol/L sodium hydroxide VS
= 15.31 mg of $C_7H_7NO_3$

Packaging and storage Preserve in light-resistant, tight containers.

Mesna
메스나



$C_2H_5NaO_3S_2$: 164.18

2-Mercaptoethanesulfonic acid sodium salt, [19767-45-4]

Mesna contains NMT 96.0% and NLT 102.2% of mesna ($C_2H_5NaO_3S_2$), calculated on the dried basis.

Description Mesna occurs as a white to pale yellow fine crystalline powder.
It is freely soluble in water, slightly soluble in methanol or ethanol(95), and practically insoluble in ether.

Identification (1) Put 5 mL of 5% lead acetate TS to 1 mL of an aqueous solution of Mesna (1 in 5); a pale yellow precipitate is formed.

(2) Determine the infrared spectra of Mesna and mesna RS, previously dried, as directed in the potassium bromide disk method as directed under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. However, due to the hygroscopic property of Mesna's fine powder, in some cases, there may be significant differences in the spectrum, compared to dried powder, resulting in strong absorptions at around 3,571 cm^{-1} to 3,509 cm^{-1} and 1,613 cm^{-1} wavenumbers.

Sodium content Between 13.44% and 14.28%. Weigh accurately about 1.0 g of Mesna, transfer into a quartz crucible, add a small amount of 50% sulfuric acid to moisten, and warm gently to dry. Then, incinerate at NMT 800 °C. Add 5 drops of 50% sulfuric acid to the residue, incinerate again, cool in a desiccator (silica gel), and weight the mass.

$$= \frac{\text{Amount (mg) of sodium (Na)}}{\text{Amount } (g) \text{ of ash x } 0.3238} \times 100$$

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Mesna as directed under Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Nitrogen content***—Weigh accurately about 0.5 g of Mesna and perform the test as directed under the Nitrogen Determination.

Each mL of 0.005 mol/L sulfuric acid VS
= 0.14007 mg of N

The amount of nitrogen in Mesna is NMT 0.1%.

(3) ***Ethylenediaminetetraacetic acid disodium salt***—Weigh accurately about 4.0 g of Mesna, dissolve in 90 mL of water, adjust the pH to 4.5 with 0.1 mol/L hydrochloric acid VS, and put 10 mL of acetic acid-ammonium acetate buffer solution, pH 4.5, and 2 mL of isopropyl alcohol. Titrate with 0.01 mol/L zinc sulfate VS until the color of the solution changes from gray to blue (indicator: dithizone TS 2 mL).

Each mL of 0.01 mol/L zinc sulfate VS
= 3.7224 mg of ethylenediaminetetraacetic acid disodium salt

The amount of ethylenediaminetetraacetic acid disodium salt in Mesna is NMT 0.05%.

Loss on drying NMT 1.0% (1 g, 60℃, in vacuum, 2 hours).

Assay Weigh accurately about 0.1 g of Mesna, dissolve in 10 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 16.418 mg of $C_2H_5NaO_3S_2$

Packaging and storage Preserve in tight containers.

Mesna Injection
메스나 주사액

Mesna Injection contains NLT 95.0% and NMT 105.0% of the labeled amount of mesna ($C_2H_5NaO_3S_2$: 164.18).

Method of preparation Prepare as directed under Injections, with Mesna.

Identification Take an amount of Mesna Injection equivalent to 0.1 g of mesna ($C_2H_5NaO_3S_2$: 164.18), add water to make 20 mL, and use this solution as the test solution. Separately, weigh 0.1 g of mesna RS, dissolve in 20 mL of water, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under Thin-layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography, develop the plate with a mixture of ethyl acetate, methanol and acetic acid(100) (5 : 2 : 2) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Apply iodine vapor to the plate; the R_f value and color of the spots obtained from the test solution and the standard solution are the same.

pH Between 6.5 and 8.5.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

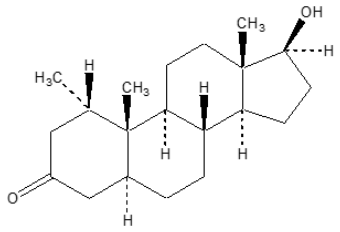
Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Mesna Injection equivalent to about 0.1 g of mesna ($C_2H_5NaO_3S_2$), add 20 mL of water, add 10 mL of 0.5 mol/L sulfuric acid and 10 mL of 0.1 mol/L iodine solution, and titrate the excess iodine with 0.1 mol/L sodium thiosulfate VS (indicator: starch TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium thiosulfate VS
= 16.42 mg of $C_2H_5NaO_3S_2$

Packaging and storage Preserve in hermetic containers.

Mesterolone
메스테롤론



$C_{20}H_{32}O_2$: 304.47
(1*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-17-Hydroxy-1,10,13-trimethyltetradecahydro-1*H*-cyclopenta[a]phenanthren-3(2*H*)-one [*1424-00-6*]

Mesterolone contains NLT 98.0% and NMT 102.0% of mesterolone ($C_{20}H_{32}O_2$), calculated on the dried basis.

Description Mesterolone occurs as a white or pale yellow crystalline powder.
It is sparingly soluble in acetone, ethyl acetate, and methanol and practically insoluble in water.

Identification Determine the infrared spectra of Mesterolone and mesterolone RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 206 and 211 ℃.

Optical rotation $[\alpha]_D^{20}$: Between +20° and +24° (0.2 g after drying, dichloromethane, 10 mL, 100 mm).

Purity (1) ***Related substances I***—Dissolve 0.1 g of Mesterolone in a mixture of methanol and dichloromethane (1 : 1) to make 10 mL, and use this solution as the test solution. Pipet 1 mL of the test solution, add the mixture of methanol and dichloromethane (1 : 1) to make 200 mL, and use this solution as the standard solution (1). Dissolve 5 mg of mesterolone-related substance I (1α-methyl-5α-androstan-3β,17β-diol) in the standard solution (1) to make 100 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution, the standard solution (1), and the standard solution (2) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of toluene, acetone and methanol (85 : 15 : 2) as a developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (366 nm), or spray evenly with a solution of 20% toluenesulphonic acid in ethanol, and heat the plate at 120 ℃ for 10 minutes; the blue spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution (1) (0.5%).

(2) ***Other related substances***—Dissolve 50.0 mg of Mesterolone in a mixture of acetonitrile and water (4 : 1) to make 25 mL, and use this solution as the test solution. Separately, dissolve 50.0 mg of mesterolone RS in a mixture of acetonitrile and water (4 : 1) to make 25 mL, and use this solution as the standard solution (1). Dissolve 10.0 mg of mesterolone-related substance II (17*β*-hydroxy-1*α*-methylandrost-4-en-3-one) in a mixture of acetonitrile and water (4 : 1) to make 5.0 mL, and use this solution as the standard solution (2). Put a mixture of acetonitrile and water (4 : 1) to 0.5 mL of the standard solution (1) and 0.5 mL of the standard solution (2) to make 100 mL, and use this solution as the standard solution (3). Perform the test with 50 μL each of the test solution and the standard solution (3) as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area of each solution by the automatic integration method; the peak area of related substance II other than the major peak obtained from the test solution is NMT the peak area of related substance II obtained from the standard solution (3) (0.5%). Additionally, the peak areas of all other related substances are NMT 0.5 times that of mesterolone, and the total area of these peaks is not greater than 1.5 times that of mesterolone obtained from the standard solution (3) (0.75%). However, exclude any peaks with peak areas being NMT 0.1 times that of mesterolone obtained from the standard solution (3).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 200 nm).

Column: A stainless steel column with 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Mobile phase: A mixture of methanol, water, and acetonitrile (3 : 2 : 1).

Flow rate: 0.9 mL/min

System suitability

System performance: Add a mixture of acetonitrile and water (4 : 1) to 0.5 mL of the standard solution (1) and 0.5 mL of the standard solution (2) to make 100 mL. Proceed with 50 μL of this solution according to the conditions above; the resolution between the peaks of mesterolone and the related substance II is NLT 6.0.

Loss on drying NMT 0.5% (1 g, 105 ℃, constant mass).

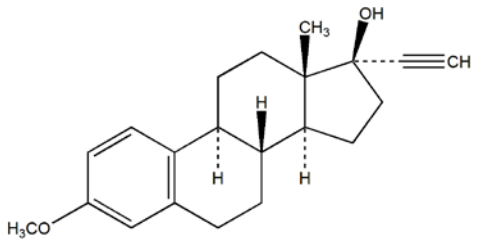
Residue on ignition NMT 0.1% (0.1 g).

Assay Weigh accurately about 50.0 mg each of Mesterolone and mesterolone RS, dissolve in a mixture of acetonitril and water (4 : 1) to make them exactly 25 mL, and use these solutions as the test solution and the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed in Liquid Chromatography according to the assay of related substances, and calculate the peak areas, A_T and A_S, of the test solution and the standard solution by the automatic integration method.

$$\text{Amount (mg) of mesterolone } (C_{20}H_{32}O_2) = \text{Amount (mg) of mesterolone RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers.

Mestranol
메스트라놀



$C_{21}H_{26}O_2$: 310.43
(8*R*,9*S*,13*S*,14*S*,17*R*)-17-Ethynyl-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-17-ol [*72-33-3*]

Mestranol, when dried, contains NLT 97.0% and NMT 102.0% of mestranol ($C_{21}H_{26}O_2$).

Description Mestranol occurs as a white to pale yellow crystalline powder, which is odorless.
It is freely soluble in chloroform, soluble in 1,4-dioxane, sparingly soluble in ethanol(99.5) or ether and practically insoluble in water.

Identification (1) Determine the absorption spectra of aqueous solutions of Mestranol and mestranol RS in ethanol(99.5) (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Mestranol and mestranol RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +1° and +7° (0.1 g after drying, ethanol(95), 10 mL, 100 mm).

Melting point Between 148 and 154 ℃.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Mestranol as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Mestranol as directed under Method 3 and perform the test (NMT 2 ppm).

(3) ***Related substances***—Dissolve 0.10 g of Mestranol in 20 mL of chloroform and use this solution as the test solution. Pipet 1.0 mL of this solution, add chloroform to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform and ethanol(99.5) (29 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly diluted sulfuric acid (1 in 5) on the plate and heat at 105 ℃ for 15 minutes; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (0.5 g, 105 ℃, 3 hours).

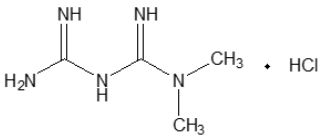
Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately about 10 mg each of Mestranol and mestranol RS, previously dried, dissolve in ethanol(99.5) to make them exactly 100 mL, and use these solutions as the standard solution and the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution as directed under Ultraviolet-visible Spectroscopy at 279 nm wavelengths.

$$\text{Amount (mg) of mestranol } (C_{21}H_{26}O_2) = \text{Amount (mg) of mestranol RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in light-resistant, tight containers.

Metformin Hydrochloride
메트포르민염산염



$C_4H_{11}N_5 \cdot HCl$: 165.63
3-(Diaminomethylidene)-1,1-dimethylguanidine hydrochloride [*1115-70-4*]

Metformin Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

Description Metformin Hydrochloride occurs as white crystals.
It is freely soluble in water, slightly soluble in ethanol(95) and practically insoluble in acetone or dichloromethane.

Identification (1) Dissolve 20 mg each of Metformin Hydrochloride and metformin hydrochloride RS in water to make 5 mL, and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of water, 1-butanol and acetic acid(100) (50 : 40 : 10) as a developing solvent to a distance of about 15 cm, and dry the plate at 100 to 105 °C for 15 minutes. Spray a mixture of sodium nitroprusside solution (1 in 10), potassium hexacyanoferrate(II) TS and sodium hydroxide solution (1 in 10) (1 : 1 : 1) evenly on the dried plate (prepare this solution before use); the R_f value and the color of the principal spot obtained from the test solution is the same as those obtained from the standard solution.

(2) Determine the infrared spectra of Metformin Hydrochloride and metformin hydrochloride RS, as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) A solution of Metformin Hydrochloride (1 in 200) responds to the Qualitative Analysis for chloride.

Melting point Between 222 and 226 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 2.0 g of Metformin Hydrochloride in 20 mL of water; the solution is colorless and clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Metformin Hydrochloride according to Method 1 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 0.5 g of Metformin Hydrochloride in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, dissolve 20.0 mg of cyanoguanidine in water to make exactly 100 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 200 mL, and use this solution as the standard solution (1). Pipet 1 mL of the test solution, add the mobile phase to make exactly 50 mL, pipet 1 mL of this solution, add the mobile phase to make exactly 20 mL, and use this solution as the standard solution (2). Dissolve 10.0 mg of melamine in 90 mL of water, add 5 mL of the test solution, and add water to make exactly 100 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution (3). Perform the test with 20 μL each of the test solution, the standard solution (1) and the standard solution (2) as directed under the Liquid Chromatography according to the following conditions. The area of the peak corresponding to cyanoguanidine obtained from the test solution is not larger than that obtained from the standard solution (1) (0.02%), and the peak area other than the major peak and the peak corresponding to cyanoguanidine is not larger than that obtained from the standard solution (2) (0.1%).

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 218 nm).

Column: A stainless steel column about 4.7 mm in internal diameter and about 25 cm in length, packed with benzenesulphonic acid silica gel for liquid-chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 17 g of ammonium dihydrogen phosphate in water to make 1000 mL, and adjust the pH to 3.0 with phosphoric acid.

Flow rate: 1 mL/minute

System suitability

Detection sensitivity: Adjust the detection sensitivity so that the peak height of metformin hydrochloride obtained from 20 μL of the standard solution (2) is at least 50% of the full scale.

System performance: Proceed with 20 μL of the standard solution (3) under the above operating conditions; the resolution between the peaks of melamine and metformin hydrochloride is NLT 10.

Time span of measurement: About twice the retention time of Metformin Hydrochloride.

Loss on drying NMT 0.5% (1 g, 105 ℃, 5 hours).

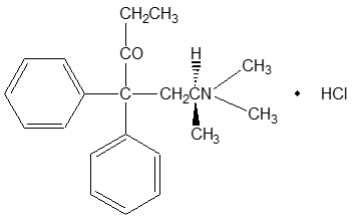
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 60 mg of Metformin Hydrochloride, dissolve in 4 mL of anhydrous formic acid, add 50 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry).

Each mL of 0.1 mol/L perchloric acid VS
= 8.281 mg of $C_4H_{11}N_5 \cdot HCl$

Packaging and storage Preserve in well-closed containers.

Methadone Hydrochloride
메타돈염산염



and enantiomer

$C_{21}H_{27}NO \cdot HCl$: 345.91

6-(Dimethylamino)-4,4-diphenyl-3-heptanone hydrochloride [*1095-90-5*]

Methadone Hydrochloride contains NLT 98.5% and NMT 100.5% of methadone hydrochloride ($C_{21}H_{27}NO \cdot HCl$), calculated on the dried basis.

Description Methadone Hydrochloride occurs as a colorless or white crystalline powder and is odorless.
It is freely soluble in ethanol or chloroform, soluble in water, and practically insoluble in ether or glycerin.

Identification (1) Determine the infrared spectra of Methadone Hydrochloride and methadone hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Methadone Hydrochloride responds to the Qualitative Analysis for chloride.

pH Dissolve 1.0 g of Methadone Hydrochloride in 100 mL of water; the pH of this solution is between 4.5 and 6.5.

Purity ***Related substances***—Weigh 0.1 g of Methadone Hydrochloride, dissolve in 10 mL of ethanol, and use this solution as the test solution. Separately, weigh 10 mg of methadone hydrochloride RS, previously dried at 105℃ for 1 hour, and dissolve in ethanol to make 10 mL. Pipet 0.1 mL, 0.5 mL, 1.0 mL and 2.0 mL each of the test solution, add ethanol to make 10 mL respectively, and use these solutions as the standard solutions (1), (2), (3) and (4). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and standard solutions (1), (2), (3) and (4) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of methanol and ammonia TS (200 : 3) as a developing solvent to a distance of 15 cm, and air-dry the plate. Spray evenly a coloring agent on the plate; the sum of intensities of all spots other than the principal spot is NMT 1.0%.

Coloring agent—Dissolve 0.85 g of bismuth subnitrate in 40 mL of water and 10 mL of acetic acid(100), and use this solution as the solution A. Dissolve 8 g of potassium iodide in 20 mL of water and use this solution as the solution B. To 10 mL of a mixture of the solution A and the solution B, add 20 mL of acetic acid(100) and water to make 100 mL.

Loss on drying NMT 0.3% (0.5 g, 105 ℃, 1 hour).

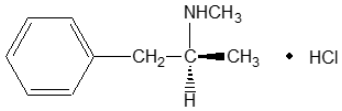
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Methadone Hydrochloride, dissolve in a mixture of 10 mL of acetic acid(100) and 10 mL of mercury(II) acetate TS for nonaqueous titration while warming slightly, if necessary. Allow to cool the solution to room temperature, add 10 mL of dioxane, and titrate rapidly with 0.1 mol/L perchloric acid VS (indicator: methylrosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 34.591 mg of $C_{21}H_{27}NO \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Methamphetamine Hydrochloride
메탐페타민염산염



$C_{10}H_{15}N \cdot HCl$: 185.69

(*S*)-*N*-Methyl-1-phenylpropan-2-amine hydrochloride [*51-57-0*]

Methamphetamine Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of methamphetamine hydrochloride ($C_{10}H_{15}N \cdot HCl$).

Description Methamphetamine Hydrochloride occurs as colorless crystals or a white crystalline powder and is odorless.
It is freely soluble in water, ethanol or chloroform, and practically insoluble in ether.
Dissolve 1.0 g of Methamphetamine Hydrochloride in 10 mL of water; the pH of the solution is between 5.0 and 6.0.

Identification (1) To 5 mL of an aqueous solution of Methamphetamine Hydrochloride (1 in 100), add 0.5 mL of hexachloroplatinic acid TS; an orange crystalline precipitate is produced.

(2) To 5 mL of an aqueous solution of Methamphetamine Hydrochloride (1 in 100), add 0.5 mL of iodine TS; a brown precipitate is produced.

(3) To 5 mL of an aqueous solution of Methamphetamine Hydrochloride (1 in 100), add 0.5 mL of trinitrophenol TS; a yellow crystalline precipitate is produced.

(4) An aqueous solution of Methamphetamine Hydrochloride (1 in 20) responds to the Qualitative Analysis for chloride.

Optical rotation $[\alpha]_D^{20}$: Between +16° and +19° (0.2 g after drying, water, 10 mL, 100 mm).

Melting point Between 171 and 175 ℃.

Purity (1) ***Acid or alkali***—Dissolve 2.0 g of Methamphetamine Hydrochloride in 40 mL of freshly boiled and cooled water, add 2 drops of methyl red TS, and use this solution as the test solution.

(i) To 20 mL of the test solution, add 0.20 mL of 0.01 mol/L sulfuric acid; the resulting solution exhibits a red color.

(ii) To 20 mL of the test solution, add 0.20 mL of 0.02 mol/L sodium hydroxide TS; the resulting solution exhibits a yellow color.

(2) ***Sulfate***—Dissolve 50 mg of Methamphetamine Hydrochloride in 40 mL of water, add 1 mL of dilute hydrochloric acid and 1 mL of barium chloride TS, and allow to stand for 10 minutes; the solution remains unchanged.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

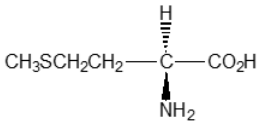
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately 0.4 g of Methamphetamine Hydrochloride, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 18.569 mg of $C_{10}H_{15}N \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

DL-Methionine
DL-메티오닌



and enantiomer

$C_5H_{11}NO_2S$: 149.21
(*RS*)-2-Amino-4-methylsulfanylbutanoic acid [*59-51-8*]

DL-Methionine contains NLT 99.0% and not than 101.0% of DL-methionine ($C_5H_{11}NO_2S$), calculated on the dried basis.

Description DL-Methionine occurs as white crystals or small flakes.
It is sparingly soluble in water, very slightly soluble in ethanol(95) and practically insoluble in ether.
It dissolves in dilute hydrochloric acid or in dilute sodium hydroxide TS.

Melting point—About 270 °C.

Identification (1) Dissolve about 0.1 g of DL-Methionine and 0.1 g of glycine in 4.5 mL of 2 mol/L sodium hydroxide TS, add 1 mL of 2.5% sodium pentacyanonitrosylferrate(III) dihydrate solution, and heat at 40 °C for 10 minutes. After cooling, add 2 mL of a mixture of hydrochloric acid and phosphoric acid (9 : 1); the solution turns deep red.

(2) Determine the infrared spectra of DL-Methionine and DL-methionine RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Perform the test as directed under the section of Related substances under the Purity, the R_f value and the color of the principal spot obtained from the test solution (2) are the same as those obtained from the standard solution (1).

Optical rotation $[\alpha]_D^{20}$: Between -0.05° and +0.05° (2.5 g, 1 mol/L hydrochloric acid TS, 50 mL, 100 mm).

pH Dissolve 1.0 g of DL-Methionine in 50 mL of water; the pH of this solution is between 5.4 and 6.1.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of DL-Methionine in 50 mL of water; the solution is colorless and clear.

(2) ***Chloride***—Dissolve 0.5 g of DL-Methionine in 20 mL of water and add 6 mL of dilute nitric acid and water to make 40 mL. Perform the test using this solution as the test solution. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid VS, 6 mL of dilute nitric acid and water to make 40 mL. To each of the test solution and the control solution, add 10 mL of silver nitrate TS (NMT 0.021%).

(3) ***Sulfate***—Proceed with 1.0 g of DL-Methionine in 20 mL of water, dissolve it by heating at 60 ℃, then cool down to 10 ℃, filtrate, and add water to the filtrate to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution with 0.4 mL of 0.005 mol/L sulfuric acid (NMT 0.02%).

(4) ***Heavy metals***—Proceed with 1.0 g of DL-Methionine according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(5) ***Related substances***—Weigh 0.5 g of DL-Methionine, dissolve in water to make exactly 10 mL, and use this solution as the test solution (1). Pipet 1 mL of this solution, add water to make exactly 50 mL, and use this solution as the test solution (2). Separately, dissolve 20 mg of DL-Methionine in water to make exactly 50 mL, and use this solution as the standard solution (1). Pipet 1 mL of this solution, add water to make exactly 10

mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution (1), test solution (2), standard solution (1) and standard solution (2) on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Then, develop the plate with a mixture of 1-butanol, water and acetic acid(100) (60 : 20 : 20) to a distance of about 10 cm, and air-dry the plate. Spray ninhydrin TS evenly on the plate and heat the plate at 100 to 105 ℃ for 15 minutes; any spot other than the principal spot obtained from the test solution (1) is not more intense than that obtained from the standard solution (2) (NMT 0.2%).

Loss on drying NMT 0.5% (1 g, 105 ºC).

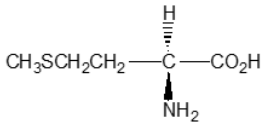
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.14 mg of DL-Methionine, dissolve in 3 mL of anhydrous formic acid, add 30 mL of acetic acid(100), and then immediately titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Separately, perform a blank test and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 14.921 mg of $C_5H_{11}NO_2S$

Packaging and storage Preserve in light-resistant, tight containers.

L-Methionine
L-메티오닌



$C_5H_{11}NO_2S$: 149.21
(2*S*)-2-Amino-4-methylsulfanylbutanoic acid [*63-68-3*]

L-Methionine, when dried, contains NLT 98.5% and NMT 101.0% of L-methionine ($C_5H_{11}NO_2S$).

Description L-Methionine occurs as white crystals or a crystalline powder and has a distinctive odor.
It is freely soluble in formic acid, soluble in water and very slightly soluble in ethanol(95).
It dissolves in dilute hydrochloric acid.

Identification (1) Weigh 25 mg of L-Methionine, put in 1 mL of sulfuric acid saturated with anhydrous copper(II) sulfate; the resulting solution exhibits a yellow color.

(2) Add 1 mL of ninhydrin TS to 5 mL of the aqueous solution of L-Methionine (1 in 5000) and heat on a steam bath for 2 minutes; the resulting solution exhibits a bluish purple color.

(3) Dissolve 0.3 g of L-Methionine in 10 mL of water and add 10 drops of dilute hydrochloric acid and 2 mL of sodium nitrate TS; a colorless gas is evolved with effervescence.

Optical rotation $[\alpha]_D^{20}$: Between +21.0° and +25.0° (0.5 g after drying, 6 mol/L hydrochloric acid TS, 25 mL, 100 mm).

pH Dissolve 0.5 g of L-Methionine in 20 mL of water; the pH is between 5.2 and 6.2.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of L-Methionine in 20 mL of water; the resulting solution is clear and colorless.

(2) ***Chloride***—Dissolve 0.5 g of L-Methionine in 20 mL of water and add 6 mL of dilute nitric acid, and water to make 40 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid, 6 mL of dilute nitric acid and water to make 40 mL. However, add 10 mL each of silver nitrate TS to the test solution and the control solution (NMT 0.021%).

(3) ***Sulfate***—Weigh 0.6 g of L-Methionine and perform the test. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid (NMT 0.028%).

(4) ***Ammonium***—Weigh 0.25 g of L-Methionine and perform the test. Prepare the control solution with 5.0 mL of the ammonium standard solution (NMT 0.02%).

(5) ***Heavy metals***—Weigh 1.0 g of L-Methionine, add 40 mL of water and 2 mL of dilute acetic acid, warm to dissolve, after cooling, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with a solution prepared by adding 2 mL of dilute acetic acid and water to 2.0 mL of lead standard solution to make 50 mL (NMT 20 ppm).

(6) ***Iron***—Dissolve 0.333 g of L-Methionine in water to make 45 mL, add 2 mL of hydrochloric acid, and use this solution as the test solution. Add water to 1.0 mL of the iron standard solution to make 45 mL, add 2 mL of hydrochloric acid, and use this solution as the standard solution. To the test solution and the standard solution, add 50 mg of ammonium peroxydisulfate and 3 mL of 30% ammonium thiocyanate and mix; the color obtained from the test solution is not more intense than that from the standard solution (NMT 30 ppm).

(7) ***Arsenic***—Put 1.0 g of L-Methionine into a 100-mL decomposition flask, add 5 mL of nitric acid and 2 mL of sulfuric acid, put a small funnel into the opening of the flask, and heat gently until white smoke is evolved. After cooling, add 2 mL each of nitric acid twice and heat. Next, add 2 mL each of hydrogen peroxide solution (30) multiple times and heat until the solution exhibits colorless to pale yellow color. After cooling, add 2 mL of a saturated solution of ammonium oxalate, and then heat again until white smoke is generated. After cooling, add water to make 5 mL and perform the test by using this solution as the test solution (NMT 2 ppm).

(8) ***Related substances***—Dissolve 0.10 g of L-Methionin in 10 mL of water and use this solution as the test solution. Pipet 1 mL of the test solution and add wa-

ter to make exactly 50 mL. Pipet 5 mL of this resulting solution, add water to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. After air-drying the plate, develop the plate with a mixture of 1-butanol, water and acetic acid(100) (3 : 1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly a solution of ninhydrin in acetone (1 in 50) on the plate and heat at 80℃ for 5 minutes; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.3% (1 g, 105 ℃, 4 h.).

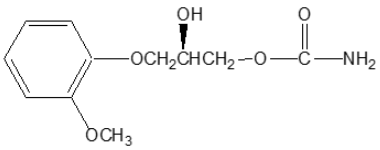
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.15 g of L-Methionine, previously dried, and dissolve in 3 mL of formic acid, add 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 14.921 mg of $C_5H_{11}NO_2S$

Packaging and storage Preserve in tight containers.

Methocarbamol
메토카르바몰



and enantiomer

$C_{11}H_{15}NO_5$: 241.24
2-Hydroxy-3-(2-methoxyphenoxy)propyl carbamate
[*532-03-6*]

Methocarbamol contains NLT 98.5% and NMT 101.5% of methocarbamol ($C_{11}H_{15}NO_5$), calculated on the dried basis.

Description Methocarbamol occurs as a white powder and is odorless or has a characteristic odor.
It is soluble in heated ethanol, sparingly soluble in chloroform and practically insoluble in benzene or in *n*-hexane.

Identification (1) Determine the absorption spectra of solutions of Methocarbamol and methocarbamol RS in ethanol(95) (1 in 25000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Methocarbamol and methocarbamol RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Heavy metals***—Dissolve 1.0 g of Methocarbamol in a mixture of 7 mL of methanol and 3 mL of 1 mol/L acetic acid, add water to make 25 mL, and perform the test according to Method 1. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 0.1 g of Methocarbamol in 13 mL of methanol, add pH 4.5 buffer solution to make exactly 50 mL, and use this solution as the test solution. Use this solution within 24 hours. Separately, weigh 20 mg of methocarbamol RS, put into a 10-mL volumetric flask, dissolve in 1.0 mL of a solution prepared by dissolving 20.0 mg of guaifenesin RS in methanol to make exactly 50 mL and 2.0 mL of methanol, and fill the pH 4.5 buffer solution up to the gauge line. Use this solution as the standard solution. Use this solution within 24 hours. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Measure the peak area of methocarbamol and the areas of all peaks of which relative retention times with respect to methocarbamol are greater than 0.5 (NMT 2.0%).

$$\text{Content (\%) of related substances} = 100 \times \frac{2.4}{A_S} \times \frac{A_i}{A_T}$$

A_S: Peak area (%) of guaifenesin in the standard solution

A_i: Peak areas of all related substances in the test solution

A_T: Sum of peak areas of all related substances and methocarbamol in the test solution

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 274 nm).

Column: A stainless steel column about 4 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid-chromatography (about 3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of pH 4.5 buffer solution and methanol (75 : 25).

System suitability

System performance: Proceed with 20 μL of the standard solution under the above operating conditions; the ratio of the peak area of guaifenesin is 2.4 ± 1.0%, and guaifenesin and methocarbamol are eluted in this order with the resolution between their peaks being NLT 2.0.

System repeatability: Repeat the test 6 times with

20 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak area percentage is NMT 4.0%.

pH 4.5 buffer solution—Dissolve 6.8 g of potassium dihydrogen phosphate in 1000 mL of water, and add 6 mol/L phosphoric acid or 10 mol/L potassium hydroxide solution to adjust the pH to 4.5 ± 0.05.

Loss on drying NMT 0.5% (1 g, 60 °C, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.1 g of Methocarbamol, transfer it to a 100-mL volumetric flask, add methanol to the gauge line, and mix. Pipet 4.0 mL of this solution, transfer it to a 100-mL volumetric flask, add methanol to the gauge line, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of methocarbamol RS, dissolve in methanol, proceed in the same way as in the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength at about 274 nm as directed under the Ultraviolet-visible Spectroscopy, using methanol as the control solution.

$$\text{Amount (mg) of methocarbamol } (C_{11}H_{15}NO_5) = \text{Amount (mg) of methocarbamol RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers.

Methocarbamol Injection
메토카르바몰 주사액

Methocarbamol Injection is an aqueous injection, and contains NLT 95.0% and NMT 105.0% of the labeled amount of methocarbamol ($C_{11}H_{15}NO_5$: 241.24).

Method of preparation Prepare as directed under Injections, with Methocarbamol.

Description Methocarbamol Injection occurs as a colorless and clear liquid.

Identification Take an amount of Methocarbamol Injection equivalent to about 0.5 g of methocarbamol according to the labeled amount, transfer to a separating funnel with 40 mL of water, and extract with 10 mL of ethyl acetate. Dry the ethyl acetate layer with sodium sulfate anhydrous, evaporate to dryness in a 40 °C water bath with nitrogen gas, and perform the test with the residue as directed under the Identification (1) of Methocarbamol.

pH Between 3.5 and 6.0.

Purity ***Aldehydes***—Take an amount of Methocarbamol Injection equivalent to about 0.4 g of methocarbamol according to the labeled amount, add 2.0 mL of the filtrate of phenylhydrazinum hydrochloride (1 in 100) in diluted ethanol (1 in 5), and allow to stand for 10 minutes. Add 1 mL of potassium hexacyanoferrate(III) solution (1 in 100), allow to stand for 5 minutes, add 4 mL of hydrochloric acid, add ethanol(95) to make exactly 25 mL, and use this solution as the test solution. Separately, take 4 mL of formaldehyde solution (1 in 100000) to prepare under the same conditions as for the test solution, and use this solution as the control solution. Perform the test with the test solution and the control solution as directed under Ultraviolet-visible Spectroscopy to determine the absorbance at the absorbance maximum wavelength at about 515 nm; the absorbance of the test solution is not greater than that of the control solution (NMT 0.01%).

Sterility Meets the requirements.

Bacterial endotoxins Methocarbamol Injection contains less than 0.2 EU/mg of methocarbamol.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Take exactly an amount of Methocarbamol Injection, equivalent to about 0.1 g of methocarbamol ($C_{11}H_{15}NO_5$), add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of methocarbamol RS, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of methocarbamol, respectively.

$$\text{Amount (mg) of methocarbamol } (C_{11}H_{15}NO_5) = \text{Amount (mg) of methocarbamol RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 274 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 5 μm in particle diameter).

Column temperature: 30 °C

Mobile phase: A mixture of pH 4.5 buffer solution and methanol (70 : 30).

Flow rate: 1 mL/min

System suitability

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above

operating conditions; the relative standard deviation of the peak area for methocarbamol is NMT 2.0%.

pH 4.5 buffer solution—Dissolve 6.8 g of potassium dihydrogen phosphate in 1000 mL of water, and add 6 mol/L phosphoric acid or 10 mol/L potassium hydroxide solution to adjust the pH to 4.5 ± 0.05.

Packaging and storage Preserve in hermetic containers.

Methocarbamol Tablets
메토카르바몰 정

Methocarbamol Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of methocarbamol ($C_{11}H_{15}NO_5$: 241.24).

Method of preparation Prepare as directed under tablets, with Methocarbamol.

Identification Weigh an amount of Methocarbamol Tablets, previously powdered, equivalent to 1 g of methocarbamol according to the labeled amount, add to 25 mL of water in a separatory flask, and extract with 25 mL of chloroform. Filter the extract and evaporate to dryness, and perform the test with the residue as directed under the Identification (1) of methocarbamol.

Dissolution Take 1 tablet of Methocarbamol Tablets, proceed with 900 mL of water as the test solution at 50 revolutions per minute according to Method 2, and perform the test. After 45 minutes from starting the test, proceed with the dissolved solution as the test solution according to in the Assay, and perform the test.
It meets the requirements if the dissolution rate of Methocarbamol Tablets after 45 minutes is NLT 75%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Methocarbamol Tablets, and powder. Weigh accurately an amount equivalent to about 0.1 g of methocarbamol ($C_{11}H_{15}NO_5$), add about 50 mL of the buffer solution (pH 4.5), 25 mL of methanol and 5.0 mL of the internal standard solution, shake vigorously for 10 minutes, and add the buffer solution (pH 4.5) to make exactly 100 mL. Filter this solution, discard the first 20 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately about 0.1 g of methocarbamol RS, dissolve in about 50 mL of the buffer solution, pH 4.5, and 25 mL of methanol, add 5.0 mL of the internal standard solution and the buffer solution, pH 4.5, to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following solution, and determine the peak area ratios of methocarbamol, Q_T and Q_S, to the internal standard solution in each solution.

$$\text{Amount (mg) of methocarbamol } (C_{11}H_{15}NO_5) = \text{Amount (mg) of methocarbamol RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of 3 mg/mL caffeine in methanol.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 274 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 to 5 μm in particle diameter).

Column temperature: 30 °C

Mobile phase: A mixture of pH 4.5 buffer solution and methanol (70 : 30).

Flow rate: 1 mL/min

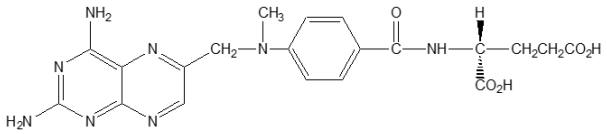
System suitability

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area for methocarbamol is NMT 2.0%.

Buffer solution, pH 4.5—Dissolve 6.8 g of potassium dihydrogen phosphate in 1000 mL of water, and add 6 mol/L phosphoric acid or 10 mol/L potassium hydroxide solution to adjust the pH to 4.5 ± 0.05.

Packaging and storage Preserve in tight containers.

Methotrexate
메토트렉세이트



$C_{20}H_{22}N_8O_5$: 454.44

(2*S*)-2-[[4-[(2,4-Diaminopteridin-6-yl)methyl-methylamino]benzoyl]amino]pentanedioic acid [*59-05-2*]

Methotrexate is a mixture of 4-amino-10-methylfolic acid and the closely related compounds. Methotrexate contains NLT 94.0% and NMT 102.0% of methotrexate ($C_{20}H_{22}N_8O_5$), calculated on the anhydrous basis.

Description Methotrexate occurs as a yellowish brown, crystalline powder.
It is slightly soluble in pyridine and practically insoluble in water, ethanol(95), acetonitrile or ether.
It dissolves in dilute sodium hydroxide TS or in dilute sodium carbonate TS.
It is gradually changed by light.

Identification (1) Determine the absorption spectra of

solutions of 1 mg each of Methotrexate and methotrexate RS in 100 mL of 0.1 mol/L hydrochloric acid TS as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Methotrexate and methotrexate RS, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Heavy metals***—Weigh 0.1 g of Methotrexate, add 4 mL of a solution of magnesium sulfate heptahydrate in dilute sulfuric acid (1 in 4), mix, heat on a steam bath, and evaporate to dryness. Ignite the residue at the temperature not exceeding 800 °C to incinerate. Allow to cool and moisten the residue with a small amount of dilute sulfuric acid. Evaporate to dryness and ignite to incinerate within 2 hours. Allow to cool, take two portions of the residue and to each, add 5 mL of 2 mol/L hydrochloric acid TS. Add 0.1 mL of phenolphthalein TS and add ammonia water(28) dropwise until the solution turns pale red. After cooling, add acetic acid(100) until the color disappears, and add another 0.5 mL. Filter and wash, if necessary. Add water to make 20 mL and use this solution as the test solution. Separately, proceed in the same manner as in the test solution using 5.0 mL of lead standard solution instead of Methotrexate. To 10 mL of this solution, add 2 mL of the test solution, and use this solution as the control solution. Separately, add 2 mL of the test solution to 10 mL of water and use this solution as the blank test solution. To 12 mL each of the test solution, the control solution and the blank test solution, add 2 mL of pH 3.5 acetate buffer solution, mix, add 1.2 mL of thioacetamide TS, and mix immediately. Allow to stand for 2 minutes; the color of the test solution is no more intense than that of the control solution (NMT 50 ppm).

System suitability: The color of the control solution is faint brown compared to that of the blank test solution. To the test solution, add 5.0 mL of lead standard solution. Then, to 10 mL of this solution, add 2 mL of the test solution, and use this solution as the system suitability solution. The color of the system suitability solution is the same as or more intense than that of the control solution.

(2) ***Related substances***—Weigh accurately about 100 mg of Methotrexate, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately an amount each of methotrexate RS, methotrexate related substance I {[(S)-2-{4-[(2,4-diaminopteridin-6-yl)methylamino]benzamido}pentanedioic acid} RS, methotrexate related substance II {(S)-2(4-{[(2-amino-4-oxo-1,4-dihydropteridin-6-yl)methyl(methyl)amino}benzamido)pentanedioic acid} RS and methotrexate related substance III {4-{[(2,4-diaminopteridin-6-yl)methyl]methylamino}benzoic acid 1/2 hydrochloride} RS, dissolve in the mobile phase to make a solution containing 0.003 mg each per mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the amount of each related substances according to equation (1); the amount of methotrexate related substance I is NMT 0.3% and the amount of methotrexate related substance II is NMT 0.5%. Determine the amount of 4-[[(2,4-diaminopteridin-6-yl)methyl]methylamino]benzoic acid according to equation (2); it is NMT 0.3%. Determine the amount of each related substance according to equation (3); it is NMT 0.1%, and the total amount of related substances is NMT 0.5%. However, exclude any peak having an area smaller than 0.1 times the peak area of methotrexate obtained from the standard solution.

$$\text{Content (\%) of related substances} = 100 \times \frac{C_S}{C_T} \times \frac{A_T}{A_S} \quad (1)$$

C_S: Concentration (mg/mL) of each related substance in the standard solution

C_T: Concentration (mg/mL) of methotrexate in the test solution

A_T: Peak area of each related substance obtained from the test solution

A_S: Peak area of each related substance obtained from the standard solution

$$\text{Content (\%) of 4-[[(2,4-diaminopteridin-6-yl)methyl]methylamino]benzoic acid} = 100 \times \frac{325.33}{343.56} \times \frac{C_S}{C_T} \times \frac{A_T}{A_S} \quad (2)$$

325.33: Molecular weight of 4-[[(2,4-diaminopteridin-6-yl)methyl]methylamino]benzoic acid

343.56: Molecular weight of methotrexate related substance III {4-{[(2,4-diaminopteridin-6-yl)methyl]methyl-amino}benzoic acid 1/2 hydrochloride}

C_S: Concentration (mg/mL) of methotrexate related substance III in the standard solution

C_T: Concentration (mg/mL) of methotrexate in the test solution

A_T: Peak area of 4-[[(2,4-diaminopteridin-6-yl)methyl]methylamino]benzoic acid obtained from the test solution

A_S: Peak area of 4-[[(2,4-diaminopteridin-6-yl)methyl]methylamino]benzoic acid obtained from the standard solution

$$\text{Content (\%) of each related substance} = 100 \times \frac{C_S}{C_T} \times \frac{A_T}{A_S} \quad (3)$$

C_S: Concentration (mg/mL) of methotrexate in the standard solution

C_T: Concentration (mg/mL) of methotrexate in the test solution

A_i: Peak area of each related substance obtained from the test solution

A_S: Peak area of methotrexate obtained from the standard solution

Operating conditions

For the detector and column, proceed as directed in the operating conditions under the Assay.

Mobile phase: To 900 mL of pH 6.0 disodium hydrogen phosphate-citric acid buffer solution, add 100 mL of acetonitrile, and mix.

Flow rate: 1.2 mL/min

Relative retention time: The relative retention times of methotrexate related substance I, methotrexate related substance II and methotrexate related substance III with respect to methotrexate are about 0.59, 0.52 and 2.16, respectively.

System suitability

System performance: Dissolve 10 mg each of Methotrexate and folic acid in 100 mL of the mobile phase. Proceed with 10 μL of this solution under the above operating conditions; the relative retention time of folic acid with respect to the retention time of methotrexate is 0.35 with the resolution between their peaks being NLT 8.0.

Time span of measurement: About 3 times the retention time of methotrexate.

Water Take 5 mL of pyridine for water determination and 20 mL of methanol for water determination in a dried titration flask and titrate with a test solution for water determination until the endpoint is reached. Next, weigh accurately about 0.2 g of Methotrexate, transfer it immediately into a titration flask, and add a known excess volume of test solution for water determination. After mixing well by stirring for 30 minutes, perform the test; the water content is NMT 12.0%.

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately 20 mg each of Methotrexate and methotrexate RS, dissolve each in the mobile phase to make exactly 250 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and measure the peak areas, A_T and A_S, of methotrexate for the test solution and the standard solution, respectively.

$$\text{Content (\%) of methotrexate } (C_{20}H_{22}N_8O_5) = \text{Amount (mg) of methotrexate RS, calculated on the anhydrous basis} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 302 nm).

Column: A stainless steel column about 4 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 5 - 10 μm in particle diameter).

Mobile phase: A mixture of 890 mL of potassium monohydrogen phosphate-citric acid buffer solution, pH 6.0 and 110 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of methotrexate is about 8 minutes.

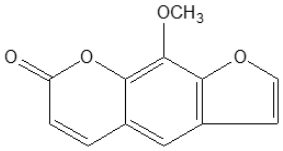
System suitability

System performance: Dissolve 10 mg each of Methotrexate and folic acid in 100 mL of the mobile phase. Proceed with 10 μL of this solution under the above operating conditions; folic acid and methotrexate are eluted in this order with the resolution between their peaks being NLT 8.0.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of methotrexate is NMT 2.5%.

Packaging and storage Preserve in light-resistant, tight containers.

Methoxsalen
메톡살렌



$C_{12}H_8O_4$: 216.19

9-Methoxyfuro[3,2-g]chromen-7-one [*298-81-7*]

Methoxsalen contains NLT 98.0% and NMT 102.0% of methoxsalen ($C_{12}H_8O_4$), calculated on the anhydrous basis.

Description Methoxsalen occurs as white to pale yellow crystals or a crystalline powder, and is odorless and tasteless.

It is freely soluble in chloroform, slightly soluble in methanol, in ethanol(95) or in ether and practically insoluble in water.

Identification (1) To 10 mg of Methoxsalen, add 5 mL of dilute nitric acid and heat; the solution turns yellow. Make this solution alkaline with a sodium hydroxide solution (2 in 5); the color of the solution changes to reddish brown.

(2) To 10 mg of Methoxsalen, add 5 mL of dilute sulfuric acid and shake to mix; the solution turns yellow.

(3) Determine the absorption spectra of solutions of Methoxsalen and methoxsalen RS in ethanol(95) (1 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Melting point Between 145 and 149 °C.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Methoxsalen as directed under Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Prepare the test solution with 1.0 g of Methoxsalen according to Method 3 and perform the test (NMT 2 ppm).

(3) ***Related substances***—Dissolve 10 mg of Methoxsalen in 10 mL of chloroform and use this solution as the test solution. Pipet 2 mL of this solution and add chloroform to make exactly 50 mL. Pipet 1 mL of this solution, add chloroform to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel (with a fluorescent indicator) for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, hexane and ethyl acetate (40 : 10 : 3) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than those obtained from the standard solution.

Water NMT 0.5% (1, volumetric titration, direct titration).

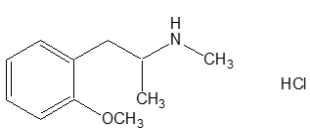
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg each of Methoxsalen and methoxsalen RS and dissolve each in ethanol(95) to make exactly 100 mL. Pipet 2 mL each of these solutions and dilute each with ethanol(95) to make exactly 25 mL. Pipet 10 mL each of these solutions and dilute each again with ethanol(95) to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at 300 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of methoxsalen ($C_{12}H_8O_4$)
=Amount (mg) of methoxsalen RS, calculated on the anhydrous basis$\times \frac{A_T}{A_S}$

Packaging and storage Preserve in light-resistant, well-closed containers.

Methoxyphenamine Hydrochloride
메톡시페나민염산염



$C_{11}H_{17}NO \cdot HCl$: 215.72
2-Methoxy-*N*,α-dimethyl-benzeneethanamine hydrochloride (1:1), [*5588-10-3*]

Methoxyphenamine Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of methoxyphenamine hydrochloride ($C_{11}H_{17}NO \cdot HCl$: 215.72).

Description Methoxyphenamine Hydrochloride occurs as white crystals or a crystalline powder and is odorless.
It is very soluble in water, soluble in acetic acid(100), in methanol, in ethanol(95) or in chloroform, sparingly soluble in acetic anhydride and practically insoluble in ethyl acetate or in ether.

Identification (1) Weigh 0.5 g of Methoxyphenamine Hydrochloride, transfer it into a small distillation flask, add 5 mL of hydroiodic acid, and distill by slightly heating. Immersed the receptacle in cold water and allow the tip of the condenser line to reach the bottom of the receptacle so that the distillate drops are formed at the bottom of the distillate.

(2) Add 5 mL of water to the residue in the distillation flask of (1), cool at 10 °C, add 0.3 mL of 4-nitrobenzenediazonium chloride TS, and add sodium carbonate TS to make the solution alkaline; An orange-red precipitate is formed.

(3) Determine the absorption spectrum of a solution of Methoxyphenamine Hydrochloride in methanol (1 in 20000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 271 nm and 273 nm and between 278 nm and 279 nm.

(4) An aqueous solution of Methoxyphenamine Hydrochloride (1 in 50) responds to the Qualitative Analysis for chloride.

pH Dissolve 4.0 g of Methoxyphenamine Hydrochloride in 20 mL of water; the pH of this solution is between 4.0 and 6.5.

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g of Methoxyphenamine Hydrochloride in 5 mL of water; the solution is colorless and clear.

(2) ***Sulfate***—Proceed with 1.0 g of Methoxyphenamine Hydrochloride as directed under the Sulfate and perform the test. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid VS (NMT 0.017%).

(3) ***Heavy metals***—Proceed with 2.0 g of Methoxyphenamine Hydrochloride according to Method 1 of the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic***—Prepare the test solution with 1.0 g of Methoxyphenamine Hydrochloride according to Method 1 of the Arsenic and perform the test (NMT 2 ppm).

(5) ***Related substances***—Weigh 0.10 g of Methoxyphenamine Hydrochloride, dissolve in methanol to make exactly 10 mL, and use this solution as the test solution. Pipet 0.1 mL of this solution, add methanol to make 10 mL, and use it as the standard solution. Perform the test

with these solutions as directed under the Thin Layer Chromatography. Spot 30 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, ethanol and strong ammonia water (50 : 30 : 1) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Spray Dragendorff TS on the dried plate; the spots other than the principal spot obtained from the test solution are not more intense than those obtained from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, P_2O_5, 24 hours).

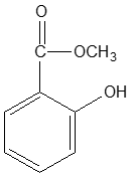
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.35 g of Methoxyphenamine Hydrochloride, previously dried, dissolve in 30 mL of acetic acid(100), add 30 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 21.57 mg of $C_{11}H_{17}NO \cdot HCl$

Packaging and storage Preserve in tight containers.

Methyl Salicylate
살리실산메틸



$C_8H_8O_3$: 152.15
Methyl 2-hydroxybenzoate [*119-36-8*]

Methyl Salicylate contains NLT 98.0% and NMT 101.9% of methyl salicylate ($C_8H_8O_3$), calculated on the dried basis.

Description Methyl Salicylate occurs as a colorless to pale yellow liquid and has a strong, characteristic odor.
Miscible with ethanol(95) or ether.
It is very slightly soluble in water.

Specific gravity—d_{20}^{20}: Between 1.182 and 1.192.
Boiling point—Between 219 and 224 ℃.

Identification Add a drop of Methyl Salicylate to 5 mL of water, shake well to mix for 1 minute, and add a drop of iron(III) chloride TS; the resulting solution shows a purple color.

Purity (1) ***Acidity***—To 5.0 mL of Methyl Salicylate, add 25 mL of freshly boiled and cooled water and 1.0 mL of 0.1 mol/L sodium hydroxide solution, shake well to mix for 1 minute, and add 2 drops of phenol red TS. Titrate the resulting solution with 0.1 mol/L hydrochloric acid VS until the red color of the solution disappears; NMT 0.45 mL of 0.1 mol/L sodium hydroxide solution is consumed.

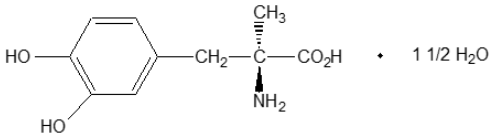
(2) ***Heavy metals***—Proceed with 1.0 g of Methyl Salicylate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Assay Weigh accurately about 2 g of Methyl Salicylate, add exactly 50 mL of 0.5 mol/L potassium hydroxide-ethanol solution, and heat on a steam bath for 2 hour under a reflux condenser. After cooling, titrate the resulting solution with 0.5 mol/L hydrochloric acid VS (indicator: 3 drops of phenolphthalein TS). Perform a blank test in the same manner.

Each mL of 0.5 mol/L potassium hydroxide-ethanol VS
= 76.07 mg of $C_8H_8O_3$

Packaging and storage Preserve in tight containers.

Methyldopa Hydrate
메틸도파수화물



Methyldopa $C_{10}H_{13}NO_4 \cdot 1½H_2O$: 238.24
(2*S*)-2-Amino-3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid sesquihydrate [*41372-08-1*]

Methyldopa Hydrate contains NLT 98.0% and NMT 101.0% of methyldopa ($C_{10}H_{13}NO_4$: 211.22), calculated on the anhydrous basis.

Description Methyldopa Hydrate occurs as a white or slightly grayish white crystalline powder.
It is slightly soluble in water, methanol or acetic acid(100), very slightly soluble in ethanol(95) and practically insoluble in ether.
It dissolves in dilute hydrochloric acid.

Identification (1) Add 3 drops of ninhydrin TS to 10 mg of Methyldopa Hydrate and heat on a steam bath for 3 minutes; the resulting solution exhibits a violet color.

(2) Determine the absorption spectra of solutions of Methyldopa Hydrate and methyldopa RS in 0.1 mol/L hydrochloric acid TS (1 in 25000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Methyldopa Hydrate and methyldopa RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -25° and -28° (1 g, calculated on the anhydrous basis, aluminum chloride TS, 20 mL, 100 mm).

Purity (1) ***Acid***—Add 100 mL of freshly boiled and cooled water to 1.0 g of Methyldopa Hydrate, shake to mix, and then add 0.20 mL of 0.1 mol/L sodium hydroxide and 2 drops of methyl red TS; the resulting solution exhibits a yellow color.

(2) ***Chloride***—Weigh 0.5 g of Methyldopa Hydrate and perform the test. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid (NMT 0.028%).

(3) ***Heavy metals***—Proceed with 2.0 g of Methyldopa Hydrate as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Dissolve 1.0 g of Methyldopa Hydrate in 5 mL of dilute hydrochloric acid and use this solution as the test solution (NMT 2 ppm).

(5) ***3-O-Methylmethyldopa***—Weigh 0.10 g of Methyldopa Hydrate, dissolve in methanol to make exactly 10 mL, and use this solution as the test solution. Separately, weigh 5 mg of 3-*o*-methylmethyldopa RS, dissolve in methanol to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of cellulose for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, water and acetic acid(100) (13 : 5 : 3) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly 4-nitroaniline-sodium nitrite TS on the plate and air-dry the plate. Then, spray again a solution of sodium carbonate (1 in 4) on the plate; the spots obtained from the test solution at the positions of the spots obtained from the standard solution are not more intense than the spots obtained from the standard solution.

Water Between 10.0% and 13.0% (0.2 g, Volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Methyldopa Hydrate, dissolve in 80 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 - 3 drops of methylrosaniline chloride TS). The endpoint of the titration is when the color of the solution changes from violet through blue to bluish green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 21.121 mg of $C_{10}H_{13}NO_4$

Packaging and storage Preserve in light-resistant, well-closed containers.

Methyldopa Tablets
메틸도파 정

Methyldopa Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of methyldopa ($C_{10}H_{13}NO_4$: 211.21).

Method of preparation Prepare as directed under Tablets, with Methyldopa.

Identification (1) Weigh an amount of Methyldopa Tablets, previously powdered, equivalent to 0.1 g of methyldopa according to the labeled amount, add 10 mL of water, and heat on a steam bath for 5 minutes with occasional shaking. After cooling, centrifuge the resulting solution for 5 minutes at 2000 rotations per minute, apply 1 drop of the supernatant to a filter paper and dry with warm air. Put 1 drop of ninhydrin TS on the filter again and heat for 5 minutes at 100 ℃; it exhibits a purple color.

(2) Pipet 0.5 mL of the supernatant obtained from (1) of the Identification, add 2 mL of 0.05 mol/L sulfuric acid TS, 2 mL of iron(II) tartrate TS and 4 drops of ammonia TS, and shake well; it exhibits a dark purple color.

(3) Pipet 0.7 mL of the supernatant obtained from (1) of the Identification, and add 0.1 mol/L hydrochloric acid TS to make 20 mL. Pipet 10 mL of the resulting solution, add 0.1 mol/L hydrochloric acid TS to make 100 mL, and determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectroscopy; it exhibits a maximum between 277 nm and 283 nm.

Dissolution Perform the test with 1 tablet of Methyldopa Tablets at 50 revolutions per minute according to Method 2 under the Dissolution Test, using 900 mL of water as the dissolution solution. Take NLT 30 mL of the dissolved solution after 60 minutes from the start of the test, and filter through a membrane filter with a pore size of NMT 0.8 μm. Discard the first 10 mL of the filtrate, pipet the subsequent V mL, add water to make exactly V' mL so that each mL contains about 25 μg of methyldopa ($C_{10}H_{13}NO_4$) according to the labeled amount and use this solution as the test solution. Separately, weigh accurately about 56 mg of Methyldopa RS (separately, determine its loss after dried at 125 ℃ for 2 hours) Weigh accurately about 56 g of Methyldopa Tablets, and add water to make exactly 200 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 280 nm as directed under Ultraviolet-visible Spectroscopy.
Meets the requirements if the dissolution rate of Methyldopa Tablets after 60 minutes is NLT 75%.

Dissolution rate (%) of the labeled amount of methyldopa ($C_{10}H_{13}NO_4$)

$$= W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 45$$

WS: Amount (mg) of methyldopa RS, calculated on the dried basis

C: Labeled amount (mg) of methyldopa RS ($C_{10}H_{13}NO_4$) in 1 tablet

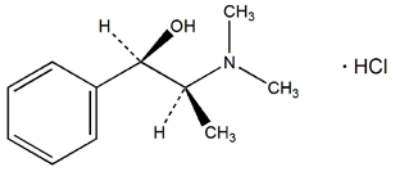
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tables of Methyldopa Tablets, and powder. Weigh accurately an amount, equivalent to about 0.1 g of methyldopa (C10H13NO4), add 50 mL of 0.05 mol/L sulfuric acid TS, shake thoroughly for 15 minutes, add 0.05 mol/L sulfuric acid TS to make exactly 100 mL and filter through a dry filter paper. Discard the first 20 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 0.11 g of methyldopa RS (separately determine its loss after dried at 125 ℃ for 2 hours), dissolve in 0.05 mol/L sulfuric acid TS to make exactly 100 mL and use this solution as the standard solution. Pipet 5.0 mL each of the test solution and the standard solution, add exactly 5 mL of iron(II) tartrate TS, and add ammonia-ammonium acetate buffer solution (pH 8.5) to make exactly 100 mL. Perform the test with the test solution and the standard solution as directed under Ultraviolet-visible Spectroscopy, using a solution prepared with 5 mL of 0.05 mol/L sulfuric acid TS in the same manner as the control solution. Determine the absorbances, A_T and A_S, obtained from the test solution and the standard solution at the wavelength of 520 nm, respectively.

Amount (mg) of methyldopa ($C_{10}H_{13}NO_4$)
= Amount (mg) of methyldopa RS, calculated on the anhydrous basis$\times \frac{A_T}{A_S}$

Packaging and storage Preserve in well-closed containers.

dl-Methylephedrine Hydrochloride
dl-메틸에페드린염산염



and enantiomer

$C_{11}H_{17}NO \cdot HCl$: 215.72

(*RS*)-2-(Dimethylamino)-1-phenylpropan-1-ol hydrochloride [*18760-80-0*]

dl-Methylephedrine Hydrochloride, when dried, contains NLT 99.0% and NMT 101.0% of *dl*-methylephedrine hydrochloride ($C_{11}H_{17}NO \cdot HCl$).

Description *dl*-Methylephedrine Hydrochloride occurs as colorless crystals or a white crystalline powder and it has no odor but a bitter taste.
It is freely soluble in water, soluble in ethanol(95), slightly soluble in acetic acid(100) and practically insoluble in acetic anhydride or ether.
An aqueous solution of *dl*-Methylephedrine Hydrochloride (1 in 20) has no optical rotation.

Identification (1) Determine the absorption spectra of *dl*-Methylephedrine Hydrochloride and *dl*-methylephedrine hydrochloride RS (1 in 2000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of *dl*-Methylephedrine Hydrochloride and *dl*-methylephedrine hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of dl-Methylephedrine Hydrochloride (1 in 10) responds to the Qualitative Analysis for chloride.

Melting point Between 207 and 211 ℃.

pH Dissolve 1.0 g of *dl*-Methylephedrine Hydrochloride in 20 mL of water; the pH is between 4.5 and 6.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of *dl*-Methylephedrine Hydrochloride in 10 mL of water; the solution is clear and colorless.

(2) Proceed with 1.0 g of *dl*-Methylephedrine Hydrochloride as directed under Method 4 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 50 mg of *dl*-Methylephedrine Hydrochloride in 20 mL of water and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 100 mL, and use this resulting solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution according to the following conditions as directed under the Liquid Chromatography. Determine each peak area by the automatic integration method; the total area of the peaks other than the peak of methylephedrine is not greater than the peak area of methylephedrine from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 257 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 13.6 g of potassium dihydrogen phosphate and 3 g of sodium 1-heptane sulfonate in 1000 mL of water, and adjust the pH to 2.5 with phos-

phoric acid. To 900 mL of this solution, add 200 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of methylephedrine is about 10 minutes.

System suitability

Test for required detectability: Pipet 2 mL of the standard solution, add water to make exactly 20 mL. Confirm that the peak area of methylephedrine obtained from 20 μL of this solution is equivalent to 7% to 13% of that of methylephedrine obtained from the standard solution.

System performance: Dissolve 50 mg of *dl*-Methylephedrine Hydrochloride and 0.4 mg of methyl *p*-hydroxybenzoate in 50 mL of water. Proceed with 20 μL of this resulting solution according to the above conditions; methylephedrine and methyl *p*-hydroxybenzoate are eluted in this order with the resolution being NLT 3.0.

System repeatability: Perform the test six times with 20 μL each of the standard solutions under the above conditions; the relative standard deviation (RSD) of the peak area of methylephedrine is NMT 2.0%.

Time span of measurement: About 2 times the retention time of methylephedrine beginning after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

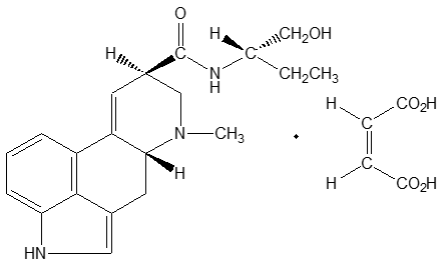
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately 0.4 g of *dl*-Methylephedrine Hydrochloride, previously dried, and dissolve in 80 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 21.572 mg of $C_{11}H_{17}NO \cdot HCl$

Packaging and storage Preserve in light-resistant, well-closed containers.

Methylergometrine Maleate
메틸에르고메트린말레산염



Methylergonovine Maleate

$C_{20}H_{25}N_3O_2 \cdot C_4H_4O_4$: 455.50

(6a*R*,9*R*)-*N*-[(2*S*)-1-Hydroxybutan-2-yl]-7-methyl-6,6a,8,9-tetrahydro-4*H*-indolo[4,3-fg] quinoline-9-carboxamide;(*Z*)-but-2-enedioic acid [*57432-61-8*]

Methylergometrine Maleate, when dried, contains NLT 95.0% and NMT 105.0% of methylergometrine maleate ($C_{20}H_{25}N_3O_2 \cdot C_4H_4O_4$).

Description Methylergometrine Maleate occurs as a white to pale yellow crystalline powder, which is odorless.

It is slightly soluble in water, methanol, or ethanol(95) and practically insoluble in ether.

It is gradually colored to yellow by light.

Melting point—About 190 °C (with decomposition).

Identification (1) The aqueous solution of Methylergometrine Maleate (1 in 200) exhibits a blue fluorescence.

(2) The coloring solution obtained in the Assay shows a dark blue color. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a similar intensity of absorption at the same wavelengths with that of methylergometrine maleate RS prepared in the same procedure.

(3) Add 1 drop of potassium permanganate TS to 5 mL of an aqueous solution of Methylergometrine Maleate (1 in 500); the red color of the test solution disappears immediately.

Optical rotation $[\alpha]_D^{20}$: Between +44° and +50° (0.1 g after drying, water, 20 mL, 100 mm).

Purity ***Related substances***—Perform this procedure without exposure to direct sunlight, using light-resistant containers. Weigh 8 mg of Methylergometrine Maleate, dissolve in exactly 2 mL of a mixture of ethanol(95) and ammonia water(28) (9 : 1), and use this solution as the test solution. Pipet 1.0 mL of this solution, add a mixture of ethanol(95) and ammonia water(28) (9 : 1) to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Immediately develop the plate with a mixture of chloroform, methanol and water (75 : 25 : 3) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 365 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 2.0% (0.2 g, in vacuum, phosphorus pentoxide, 4 hours).

Assay Dry Methylergometrine Maleate and separately dry methylergometrine maleate RS in a desiccator (with silica gel) for 4 hours. Weigh accurately 10 mg each, dissolve in water to make exactly 250 mL, and use these

solutions as the test solution and the standard solution, respectively. Pipet 2 mL each of the test solution and the standard solution, transfer into separate test tubes with brown stoppers, and add exactly 4 mL of 4-dimethylaminobenzaldehyde-iron(III) chloride TS while cooling with ice. After warming the tubes at 45 °C for 10 minutes, allow to stand at room temperature for 20 minutes. With these solutions, perform the test as directed under the Ultraviolet-visible Spectroscopy and determine the absorption spectra of each solution obtained from the test solution and the standard solution, A_T and A_S, at the wavelength of 545 nm, using a solution, prepared with 2.0 mL of water in the same procedure as the control.

Amount (mg) of methylergometrine maleate ($C_{20}H_{25}N_3O_2 \cdot C_4H_4O_4$)
= Amount (mg) of methylergometrine maleate RS $\times \frac{A_T}{A_S}$

Packaging and storage Preserve in light-resistant, tight containers.

Methylergometrine Maleate Tablets
메틸에르고메트린말레산염 정

Methylergonovine Maleate Tablets

Methylergometrine Maleate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of methylergometrine maleate ($C_{20}H_{25}N_3O_2$-$C_4H_4O_4$).

Method of preparation Prepare as directed under Tablets, with Methylergometrine Maleate.

Identification (1) The test solution obtained in the Assay shows a blue fluorescence.

(2) The coloring solution obtained in the Assay shows a deep blue color. Determine the absorption spectrum of this coloring solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 543 nm and 547 nm and between 620 nm and 630 nm.

Dissolution Take 1 tablet of Methylergometrine Maleate Tablets, and perform the test with 900 mL of water as the dissolution medium at 100 revolutions per minute according to Method 2. Take NLT 20 mL of the dissolution medium 30 minutes after starting the dissolution test, and filter through a membrane filter with a pore size of NMT 0.8 μm. Discard the first 10 mL of the filtrate, and use the subsequent filtrate as the test solution. Alternatively, pipet *V* mL of this filtrate, add water to make exactly *V* mL so that each mL contains about 0.13 μg of methylergometrine maleate ($C_{20}H_{25}N_3O_2C_4H_4O_4$) according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 25 mg of methylergometrine maleate RS, previously dried in a desiccator for 4 hours (in vacuum, phosphorus pentoxide), and dissolve in water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, pipet 1 mL of this solution again, add water to make exactly 100 mL, and use this solution as the standard solution. Determine the fluorescence intensities, F_T and F_S, of the test solution and the standard solution, respectively, at the excitation wavelength of 338 nm and the fluorescence wavelength of 427 nm as directed under the Fluorescence Spectroscopy.

Meets the requirements if the dissolution rate of Methylergometrine Maleate Tablets for 30 minutes is NLT 70%.

Dissolution rate (%) with respect to the labeled amount of methylergometrine maleate ($C_{20}H_{25}N_3O_2$-$C_4H_4O_4$)

$$= W_S \times \frac{V'}{V} \times \frac{F_T}{F_S} \times \frac{1}{C} \times 0.45$$

WS: Amount (mg) of methylergometrine maleate RS

C: Labeled amount (mg) of methylergometrine maleate in 1 tablet

Uniformity of dosage units It meets the requirements when the Content uniformity test is performed according to the following procedure.

Put 1 tablet of Methylergometrine Maleate Tablets in a light-resistant glass-stoppered centrifuge tube, add 10 mL of water, shake for 10 minutes vigorously to disintegrate, and add 3 g of sodium chloride and 2 mL of ammonia water(28). Add exactly 25 mL of chloroform, shake vigorously to mix for 10 minutes, centrifuge for 5 minutes, and discard the aqueous layer. Take the extract of the chloroform, separately, add chloroform to make exactly *V* mL so that each mL contains about 5 μg of methylergometrine maleate ($C_{20}H_{25}N_3O_2$ $C_4H_4O_4$) according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 1.25 mg of methylergometrine maleate RS, previously dried in a desiccator (silica gel) for 4 hours, dissolve in water to make exactly 100 mL. Pipet 10 mL of the resulting solution, put in a light-resistant stoppered centrifuge tube, add 3 g of sodium chloride and 2 mL of ammonia water(28). Add exactly 25 mL of chloroform, shake vigorously to mix for 10 minutes, centrifuge for 5 minutes. Discard the aqueous layer and take the extract of chloroform separately, and use this solution as the standard solution. Pipet 20 mL each of the test solution and the standard solution, put in a light-resistant stoppered centrifuge tube, immediately add exactly 10 mL of dilute 4-dimethylaminobenzaldehyde-iron(III) chloride TS, and shake vigorously to mix for 5 minutes. Centrifuge these solutions for 5 minutes, take the water layers and allow to stand for 1 hour. Perform the test with these solutions as directed under the Ultraviolet-visible Spectroscopy, using dilute 4-dimethylaminobenzaldehyde-iron(III) chloride TS as the control solution, and determine the absorbances, A_T and A_S, at the wavelength of 545 nm of each solution obtained from the test solution and the standard solution.

Amount (mg) of methylergometrine maleate ($C_{20}H_{25}N_3O_2 \cdot C_4H_4O_4$)

= Amount (mg) of methylergometrine maleate RS

$$\times \frac{A_T}{A_\Sigma} \times \frac{V}{250}$$

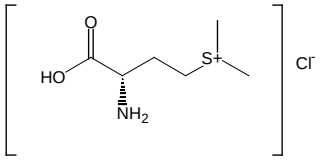
Assay Weigh accurately and powder NLT 20 tables of Methylergometrine Maleate Tablets. Weigh accurately a portion of this powder, equivalent to about 0.3 mg of methylergometrine maleate ($C_{20}H_{25}N_3O_2 \cdot C_4H_4O_4$), transfer to a light-resistant separatory funnel, add 15 mL of sodium bicarbonate solution (1 in 20), and extract 4 times with 20 mL each of chloroform. Filter each volume of the chloroform extracts through a absorbent cotton, previously moistened with chloroform, into another dried and light resistant separatory funnel in turn, combine all the filtrates, and use this combined filtrate as the test solution. Separately, weigh accurately about 10 mg of methylergometrine maleate RS, previously dried in a desiccator (silica gel) for 4 hours, dissolve in water to make exactly 100 mL. Pipet 3.0 mL of this solution and transfer to a light-resistant separatory funnel, proceed in the same manner as the preparation of the test solution, and use this filtrate as the standard solution. Add exactly 25.0 mL each of dilute 4-dimethylaminobenzaldehyde-iron(III) chloride TS to each total volume of the test solution and the standard solution, shake vigorously to mix for 5 minutes, and allow to stand for 30 minutes. Draw off the water layer, centrifuge and allow to stand for 1 hour. Perform the test with these solutions as directed under the Ultraviolet-visible Spectroscopy, using dilute 4-dimethylaminobenzaldehyde-iron(III) chloride TS as the control solution, and determine the absorbances, A_T and A_S, at the wavelength of 545 nm of each solution obtained from the test solution and the standard solution.

Amount (mg) of methylergometrine maleate ($C_{20}H_{25}N_3O_2 \cdot C_4H_4O_4$)
= Amount (mg) of methylergometrine maleate RS

$$\times \frac{A_T}{A_S} \times \frac{3}{100}$$

Packaging and storage Preserve in light-resistant, well-closed containers.

Methylmethioninesulfonium Chloride
메틸메티오닌설포늄염화물



$C_6H_{14}ClNO_2S$: 199.70

(*S*)-(3-Amino-3-carboxypropyl)dimethyl-sulfonium chloride, [*1115-84-0*]

Methylmethioninesulfonium Chloride, when dried, contains NLT 98.5% and NMT 102.0% of methylmethioninesulfonium chloride ($C_6H_{14}ClNO_2S$).

Description Methylmethioninesulfonium Chloride occurs as white crystals or a crystalline powder, which has a slightly distinctive odor.
It is freely soluble in water and practically insoluble in ethanol(99.5), acetone, or ether.
The pH of the aqueous solution of Methylmethioninesulfonium Chloride (1 in 20) is between 4.0 and 5.0.
The aqueous solution of Methylmethioninesulfonium Chloride (1 in 50) has no optical rotation.
It is hygroscopic.

Identification (1) The aqueous solution of Methylmethioninesulfonium Chloride (1 in 50) responds to the Qualitative Analysis (2) for chloride.

(2) Add 1 mL of ninhydrin TS to 5 mL of the aqueous solution of Methylmethioninesulfonium Chloride (1 in 1000) and heat for 1 minute; the resulting solution exhibits a bluish purple color.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Methylmethioninesulfonium Chloride in 10 mL of water; the resulting solution is clear and colorless.

(2) ***Sulfate***—Weigh 0.6 g of Methylmethioninesulfonium Chloride as directed under the Sulfate and perform the test. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid (NMT 0.028%).

(3) ***Heavy metals***—Proceed with 1.0 g of Methylmethioninesulfonium Chloride as directed under Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic***—Proceed with 1.0 g of Methylmethioninesulfonium Chloride as directed under Method 1 and perform the test (NMT 2 ppm).

(5) ***Methionine***—Dissolve 0.1 g of Methylmethioninesulfonium Chloride in 5 mL of water, add 2 mL of sodium hydroxide TS, shake well to mix, and add 0.3 mL of sodium nitroprusside TS. After shaking well to mix, allow to stand on a steam bath at 35 to 40 °C for 10 minutes and cool in cold water for 2 minutes. Add 2 mL of dilute hydrochloric acid to this solution and shake well to mix; the resulting solution does not exhibit a yellow orange color.

Loss on drying NMT 1.0% (1 g, in vacuum, silica gel, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Methylmethioninesulfonium Chloride, previously dried, dissolve in 70 mL of water and 1 mL of 0.1 mol/L hydrochloric acid, and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Calculate the difference in consumption of 0.1 mol/L sodium hydroxide between the first and second inflection points.

Each mL of 0.1 mol/L sodium hydroxide VS
= 19.97 mg of $C_6H_{14}ClNO_2S$

Packaging and storage Preserve in tight containers.

Methyl-*N*,*S*-diacetylcysteine
메틸-*N*,*S*-디아세틸시스테인

$C_8H_{13}NO_4S$: 219.26

Methyl *N*,*S*-diacetyl-L-cysteinate ester, [*19547-88-7*]

Methyl-*N*,*S*-diacetylcysteine, when dried, contains NLT 98.0% and NMT 102.0% of methyl-*N*,*S*-diacetylcysteine ($C_8H_{13}NO_4S$: 219.26).

Description Methyl-*N*,*S*-diacetylcysteine occurs as a white crystalline powder and has a distinctive odor. It is soluble in water and ethanol, freely soluble in chloroform, and slightly soluble in ether.

Identification (1) Weigh 20 mg each of Methyl-*N*,*S*-diacetylcysteine and methyl-*N*,*S*-diacetylcysteine RS, dissolve in 1 mL of water respectively, and use the resulting solutions as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of *n*-butanol, water and acetic acid (8 : 2 : 2) as the developing solvent to a distance of about 15 cm, and air-dry the plate at 100℃ for 10 minutes. Spray 0.1 mol/L sodium hydroxide on the plate and immediately spray 2% sodium nitroprusside TS; the R_f values and colors of the spots obtained from the test solution and the standard solution are the same.

(2) Determine the absorption spectrum with a 0.002% solution of Methyl-*N*,*S*-diacetylcysteine in ethanol as directed under the Ultraviolet-visible Spectroscopy; the spectrum exhibits absorption maximum at 228 nm to 232 nm and no absorption at over 260 nm.

Melting point Between 96 and 100℃.

pH The pH of 1% aqueous solution of Methyl-*N*,*S*-diacetylcysteine is between pH 3.5 and pH 5.5.

Purity (1) ***Clarity and color of solution***—Determine the absorption spectrum of the solution, prepared by dissolving 0.5 g of Methyl-*N*,*S*-diacetylcysteine in 10 mL of ethanol, as directed under the Ultraviolet-visible Spectroscopy; the absorbance is NMT 0.02 at 400 nm.

(2) ***Heavy metals***—Proceed with 1.0 g of Methyl-*N*,*S*-diacetylcysteine as directed under Method 2 of the Heavy Metals and perform the test. Prepare the control solution with 2 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Weigh 200 mg of Methyl-*N*,*S*-diacetylcysteine, dissolve in 10 mL of water, and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Separately, dissolve 10 mg each of L-cysteine and L-methylcysteine hydrochloride RS in water to make a 50 mL solution respectively. Use these solutions as the standard solutions for L-cysteine and the L-methylcysteine hydrochloride. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of *n*-propanol, water and 27% ammonia (70 : 30 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray a 0.01% solution of fluorescamine in acetone as a coloring solution, and after 5 minutes, examine the plate under ultraviolet light (main wavelength: 365 nm); the spots of L-cysteine and L-methylcysteine hydrochloride obtained from the test solution are not more intense than the spots obtained from each standard solution (NMT 1.0% respectively). In addition, the spots other than the principal constituent obtained from the test solution, L-cysteine and L-methylcysteine hydrochloride are not more intense than the spots obtained from the standard methyl-*N*,*S*-diacetylcysteine solution (NMT 1.0% for the others).

Optical rotation $[\alpha]_D^{20}$: Between -38° and -47° (2 g after drying, ethanol, 100 mL, 100 mm).

Loss on drying NMT 2.0% (1.0 g, 60℃, in vacuum, 6 hours).

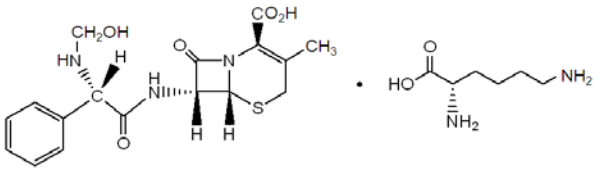
Residue on ignition NMT 0.2% (1.0 g).

Assay Weigh accurately about 100 mg each of Methyl-*N*,*S*-diacetylcysteine and methyl-*N*,*S*-diacetylcysteine RS, previously dried, and add 96% ethanol to make exactly 100 mL. Pipet 1 mL each of these solutions, add 96% ethanol to make exactly 50 mL, and use these solutions as the test solution and the standard solution. Determine the absorption spectra of the test solution and the standard solution, A_T and A_S, at the absorbance maximum wavelength around 230 nm, as directed under the Ultraviolet-visible Spectroscopy, using 96% ethanol as the control solution.

$$\text{Amount (mg) of methyl-}N,S\text{-diacetylcysteine } (C_8H_{13}NO_4S) = \text{Amount (mg) of methyl-}N,S\text{-diacetylcysteine RS (mg)} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers.

Methylolcefalexin Lysinate
메틸올세팔렉신리시네이트



$C_{17}H_{19}N_3O_5S \cdot C_6H_{14}N_2O_2$: 523.60

L-Lysine (6*R*,7*R*)-7-[[(2*R*)-2-amino-2-phenylacetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (1:1)

Methylolcefalexin Lysinate contains NLT 630 μg and NMT 696 μg (potency) per mg of cefalexin ($C_{16}H_{17}N_3O_4S$: 363.39), calculated on the anhydrous basis.

Description Methylolcefalexin Lysinate occurs as a yellowish white crystalline powder and has a slight, characteristic odor.
It is soluble in water and practically insoluble in ethanol.

Identification (1) Dissolve about 2 mg (potency) of Methylolcefalexin Lysinate in the ninhydrin saturated solution; the resulting solution exhibits a purple color.

(2) Weight about 4 mg (potency) of Methylolcefalexin Lysinate, dissolve in water to make 100mL, and determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy; it exhibits absorption maximum between 259 nm and 263 nm.

(3) Weigh about 0.1 g (potency) of Methylolcefalexin Lysinate, dissolve in water to make 100 mL, and use this solution as the test solution. Separately, dissolve about 0.1 g (potency) of cefalexin RS in water to make 100 mL and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution each on a plate made of silica gel for thin-layer chromatography and develop the plate with the mixture of butanol, water and acetic acid (60 : 25 : 15) as the developing solvent. Air-dry the plate and examine it under ultraviolet rays (main wavelength: 254 nm); the R_f value of the spot from the test and the standard solutions are the same.

(4) Perform the test with Methylolcefalexin Lysinate as directed in the paste method under the Mid-infrared Spectroscopy; it exhibits absorption at the wavenumbers of about 2950 cm^{-1}, 1750 cm^{-1}, 1630 cm^{-1}, 1580 cm^{-1} and 1500 cm^{-1}.

pH Dissolve 0.1 g of Methylolcefalexin Lysinate (potency)/mL in water; the pH of the solution is between 6.5 and 8.5.

Absorbance $E_{1cm}^{1\%}$ (261 nm): Between 156 and 176 (4.0 mg, water, 100 mL).

Purity ***Heavy metals***—Proceed with about 1.0 g of Methylolcefalexin Lysinate according to Method 2 of the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Sterility It meets the requirements when Methylolcefalexin Lysinate is used in a sterile preparation. However, it is excluded in cases where there is a final sterilization process in the manufacturing of a sterile preparation.

Pyrogen It meets the requirements when Methylolcefalexin Lysinate is used in a sterile preparation. With a solution of isotonic sodium chloride injection made so that 1 mL of Methylolcefalexin Lysinate contains 7.0 mg (potency), inject 1 mL per kg of a rabbit's weight to perform the test.

Water NMT 2.5% (0.5 g, volumetric titration, direct titration).

Assay Perform the test as directed under the Assay of Cefalexin Lysinate. Weigh accurately 0.1 g of Methylolcefalexin Lysinate and cefalexin RS, add 0.1 mol/L phosphate buffer (pH 7.0) each to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively.

Packaging and storage Preserve in light-resistant, tight containers.

Methylolcefalexin Lysinate Capsules
메틸올세팔렉신리시네이트 캡슐

Methylolcefalexin Lysinate Capsules contain NLT 90.0% and NMT 120.0% the labeled amount of cefalexin ($C_{16}H_{17}N_3O_4S$: 347.39).

Method of preparation Prepare as directed under Capsules, with Methylolcefalexin Lysinate.

Identification Perform the test as directed under the Identification (1) and (2) of Methylolcefalexin Lysinate Tablets.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Water NMT 5.0% (0.2 g, volumetric titration, direct titration)

Assay Proceed as directed in the Assay of Methylolcefalexin Lysinate. Weigh accurately the contents of NLT 20 capsules of Methylolcefalexin Lysinate Capsules. According to the marked potency, weigh accurately about 0.1 g (potency) and dissolve in 0.1 mol/L phos-

phate buffer solution (pH 7.0) to make exactly 100 mL, and use this solution as the solution.

Packaging and storage Preserve in tight containers.

Methylolcefalexin Lysinate Tablets
메틸올세팔렉신리시네이트 정

Methylolcefalexin Lysinate Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of cefalexin ($C_{16}H_{17}N_3O_4S$: 363.39).

Method of preparation Prepare as directed under Tablets, with Methylolcefalexin Lysinate.

Identification (1) Perform the test according to (2) and (3) under the Identification for Methylolcefalexin Lysinate.

(2) Weigh about 0.1 g (potency) of Methylolcefalexin Lysinate according to the labeled amount, add water, shake vigorously to mix, and add water to make 1000 mL. To 0.5 mL of this solution, add 0.1 mL of 1.6% stannic chloride-citric acid buffer solution, pH 5.0, and 2.0 mL of ninhydrin TS, and heat at 100 ℃ for 20 minutes; the resulting solution exhibits a violet color.

Disintegration Meets the requirements.

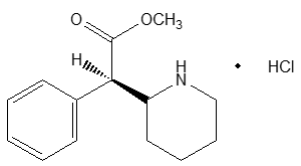
Uniformity of dosage units Meets the requirements.

Water NMT 5.0% (0.2 g, volumetric titration, direct titration)

Assay Perform the test according to the Assay for Methylolcefalexin Lysinate. Weigh accurately the mass of NLT 20 tablets of Methylolcefalexin Lysinate, and powder. Weigh accurately about 0.1 g (potency) of this powder according to the labeled potency, add water, shake vigorously to mix, add again water to make exactly 100 mL, and use this solution as the test solution.

Packaging and storage Preserve in light-resistant, tight containers.

Methylphenidate Hydrochloride
메틸페니데이트염산염



$C_{14}H_{19}NO_2 \cdot HCl$: 269.77

Methyl 2-phenyl-2-piperidin-2-ylacetate hydrochloride [*298-59-9*]

Methylphenidate Hydrochloride contains NLT 98.0% and NMT 102.0% of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$), calculated on the dried basis.

Description Methylphenidate Hydrochloride occurs as a white fine crystalline powder and is odorless.
It is freely soluble in water or methanol, soluble in ethanol(95), and slightly soluble in acetone or chloroform.
An aqueous solution of Methylphenidate Hydrochloride changes the litmus paper into a red color.

Identification (1) Determine the infrared spectra of Methylphenidate Hydrochloride and methylphenidate hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Methylphenidate Hydrochloride (1 in 50) responds to the Qualitative Analysis (2) for chloride.

Purity (1) ***Erythro [(R*, S*)] isomer***—Dissolve Methylphenidate Hydrochloride and methylphenidate hydrochloride erythro isomer in methanol so that each solution contains 50 mg per mL and 0.5 mg per mL, and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of chloroform, methanol, aqueous ammonia (28) (190 : 10 : 1) as the developing solvent to a distance of about 15 cm and air-dry the plate. Spray evenly the color former on the plate and spray 0.5 mol/L sulfuric acid; the spot from the test solution shown in the same R_f value of the standard solution is not more intense or larger than the spot from the standard solution (NMT 1%).

Coloring agent—Weigh 0.7 g of bismuth subnitrate, dissolve in 40 mL of a mixture of water and acetic acid(100) (4 : 1), add 40 mL of potassium iodide solution (2 in 5), and add 120 mL of acetic acid(100) and 250 mL of water.

(2) ***α-phenyl-2-piperidine acetate***—Weigh accurately about 0.4 g of Methylphenidate Hydrochloride, add sodium hydroxide in methanol solution (1 in 2500) to make 10 mL, and use this solution as the test solution (prepared before use). Weigh a suitable amount of α-phenyl-2-piperidine acetate RS, dissolve in sodium hydroxide in methanol solution (1 in 2500), make a solution where 1 mL contains about 0.24 mg, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, methanol, and acetic acid(31) (65 : 25 : 5) as the developing solvent to a distance of about 15 cm and air-

dry the plate. Spray evenly the color former to this and spray hydrogen peroxide solution; the spot from the test solution shown in the same R_f value of the standard solution is not more intense or larger than the spot from the standard solution (NMT 0.6%).

Coloring agent—Dissolve 0.85 g of bismuth subnitrate in 40 mL of water and 10 mL of acetic acid(100) and use this solution as the solution A. Dissolve 8 g of potassium iodide in 20mL of water and use this solution as the solution B To 10 mL of the mixture of solution A and solution B, add 20 mL of acetic acid(100) and water to make 100 mL.

(3) ***Heavy metals***—Proceed with 1.0 g of Methylphenidate Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

Loss on drying NMT 0.5% (1 g, in vacuum, 60 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg each of Methylphenidate Hydrochloride and methylphenidate hydrochloride RS, dissolve in the mobile phase to make exactly 100 mL and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas, A_T and A_S, for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of methylphenidate hydrochloride } (C_{14}H_{19}NO_2 \cdot HCl) = \text{Amount (mg) of methylphenidate hydrochloride RS} \times (A_T / A_S)$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 209 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Add phosphoric acid in methanol and 0.02 mol/L potassium dihydrogen phosphate RS (1 : 2) and adjust the pH to 4.6 ± 0.1.

Flow rate: 1.0 mL/min

System suitability

System performance: Weigh accurately 5 mg of α-phenyl-2-piperidine acetate RS and 0.5 g of methylphenidate hydrochloride RS and dissolve in 1000 mL of the mobile phase. Proceed with 10 μL of this solution according to the above conditions; the resolution between the peak of α-phenyl-2-piperidine acetate RS and that of methylphenidate peak is NLT 2.5.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of methylphenidate is NMT 2.0%.

Time span of measurement: About 2 times the retention time of methylphenidate.

Packaging and storage Preserve in well-closed containers.

Methylphenidate Hydrochloride Tablets
메틸페니데이트염산염 정

Methylphenidate Hydrochloride Tablets contains NLT 93.0% and NMT 107.0% of the labeled amount of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$: 269.77).

Method of preparation Prepare as directed under Tablets, with Methylphenidate Hydrochloride.

Identification Weigh the amount of Methylphenidate Hydrochloride Tablets, previously powdered, equivalent to 50 mg of methylphenidate hydrochloride, put in a 40-mL centrifuge tube, add 10 mL of chloroform, shake well, and centrifuge. Filter the clear supernatant through a glass filter to a beaker, and repeat this procedure with 10 mL of chloroform. Combine the extracts, evaporate on a steam bath to dryness. To the residue, add 2 mL of acetonitril, stir, and filter through a small glass filter. Wash the crystals obtained from the above step with 2 mL of acetonitrile, and then dry the crystals in vacuum. Determine the infrared spectra of the resulting crystals and methylphenidate hydrochloride RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Dissolution Take 1 tablet of Methylphenidate Hydrochloride, and perform the test according to Method 1 using 900 mL of water as the dissolution medium at 100 revolutions per minute. After 45 minutes from the start of the dissolution test, take the dissolution medium, filter, and perform the test as directed under the Assay using this solution as the test solution.
It meets the requirements if the dissolution rate of Methylphenidate Hydrochloride Tablets for 45 minutes is NLT 75%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately and powder NLT 20 tables of Methylphenidate Hydrochloride. Weigh accurately a portion of this powder, equivalent to about 20 mg of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$), add 70 mL of the mobile phase, shake vigorously to mix for 15 minutes, cool to room temperature, and add the mobile phase to make exactly 100 mL. Filter the resulting solution, discard the first 10 mL of the filtrate, take exactly 10

mL of the subsequent filtrate, and add exactly 5 mL of the internal standard solution, shake to mix, and use this solution as the test solution. Separately, weigh accurately 20 mg of methylphenidate hydrochloride RS and dissolve in the mobile phase to make exactly 100 mL. Pipet 10 mL of this solution, add 5 mL of the internal standard solution, shake to mix, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the ratios, Q_T and Q_S of the peak area of methylphenidate to that of the internal standard.

Amount (mg) of methylphenidate hydrochloride ($C_{14}H_{19}NO_2 \cdot HCl$) = Amount (mg) of methylphenidate hydrochloride RS $\times \frac{Q_T}{Q_S}$

Internal standard solution—Weigh accurately 10 mg of Phenylephrine Hydrochloride, and dissolve in the mobile phase to make 25 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Dissolve 1.64 g of anhydrous sodium acetate in 900 mL of water, adjust the pH to 4.0 with acetic acid, and add water to make 1000 mL. To 300 mL of the resulting solution, add 300 mL of acetonitrile and 400 mL of methanol, and mix them.

Flow rate: 1.5 mL/min

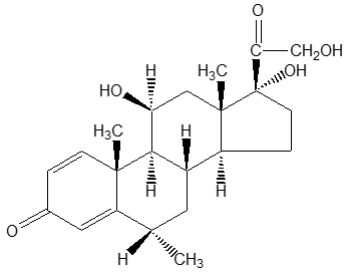
System suitability

System performance: Proceed with 50 μL of the standard solution according to the above conditions; phenylephrine and methylphenidate are eluted in this order with the resolution between their peaks being NLT 2.0.

System repeatability: Repeat the test 6 times with 50 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area ratios is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Methylprednisolone
메틸프레드니솔론



$C_{22}H_{30}O_5$: 374.47

(6*S*,8*S*,9*S*,10*R*,11*S*,13*S*,14*S*,17*R*)-11,17-Dihydroxy-17-(2-hydroxyacetyl)-6,10,13-trimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-3-one [*83-43-2*]

Methylprednisolone, when dried, contains NLT 96.0% and NMT 104.0% of methylprednisolone ($C_{22}H_{30}O_5$).

Description Methylprednisolone occurs as a white, crystalline powder and is odorless.

It is sparingly soluble in methanol or 1.4-dioxane, slightly soluble in ethanol(95) or chloroform, and practically insoluble in water or ether.

Melting point—Between 232 and 260 ℃ (with decomposition).

Identification (1) Add 2 mL of sulfuric acid in about 2 mg of Methylprednisolone; the resulting solution exhibits a red color with no fluorescence. Add 10 mL of water to this solution; the resulting solution bleaches and a gray cotton-shaped precipitate is produced.

(2) Dissolve about 10 mg of Methylprednisolone in 1 mL of methanol, add 1 mL of Fehling's TS, and heat; the resulting solution exhibits a red color and precipitate.

(3) Determine the absorption spectra of Methylprednisolone and methylprednisolone RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Optical rotation $[\alpha]_D^{20}$: Between +96° and +101° (0.1 g, after drying, methanol, 10 mL, 100 mm).

Purity ***Related substances***—Weigh about 50 mg of Methylprednisolone, dissolve in 5 mL of the mixture of chloroform and methanol (9 : 1), and use this solution as the test solution. Pipet 1 mL of this solution, add the mixture of chloroform and methanol (9 : 1) to make exactly 200 mL and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with the mixture of dichloromethane, ether, methanol, and water (385 : 75 : 40 : 6) as the developing solvent to a

distance of about 12 cm and air-dry the plate. Heat the plate at 105 ℃ for 10 minutes, cool, and spray evenly the alkaline blue tetrazolium TS on the plate; the spots other than the principal spot from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 1.0% (0.5 g, 105 ℃, 3 hours).

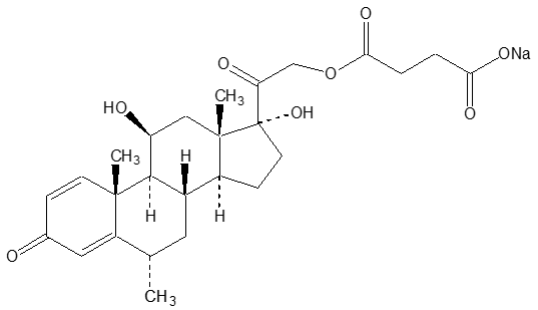
Residue on ignition NMT 0.2% (0.2 g).

Assay Weigh accurately about 10 mg of Methylprednisolone, previously dried, and dissolve in methanol to make exactly 100 mL. Pipet 5 mL of this solution, add methanol to make exactly 50 mL, and determine the absorbance of this solution, at the absorbance maximum wavelength at about 350 nm, as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of methylprednisolone } (C_{22}H_{30}O_5) = \frac{A}{400} \times 10000$$

Packaging and storage Preserve in tight containers.

Methylprednisolone Sodium Succinate
메틸프레드니솔론숙시네이트나트륨



$C_{26}H_{33}NaO_8$: 496.53

Sodium 4-(2-((6*S*,8*S*,9*S*,10*R*,11*S*,13*S*,14*S*,17*R*)-11,17-dihydroxy-6,10,13-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-yl)-2-oxoethoxy)-4-oxobutanoate [*2375-03-3*]

Methylprednisolone Sodium Succinate, contains NLT 97.0% and NMT 103.0% of methylprednisolone sodium succinate ($C_{26}H_{33}NaO_8$), calculated on the dried basis.

Description Methylprednisolone Sodium Succinate occurs as a white amorphous solid material.
It is very soluble in water or ethanol(95), very slightly soluble in acetone, and practically insoluble in chloroform.
It is hygroscopic.

Identification (1) Dissolve Methylprednisolone Sodium Succinate and methylprednisolone sodium RS, previously dried, in methanol and prepare a solution in which each mL contains 20 μg. Determine the absorption spectra of this solution as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Dissolve 0.1 g each of Methylprednisolone Sodium Succinate and methylprednisolone sodium succinate RS in water to make 10 mL. Add 1 mL of 3 mol/L hydrochloric acid and extract immediately with 50 mL of chloroform. Filter the chloroform extraction using absorbent cotton, evaporate to dryness on a steam bath, and dry at 60 ℃ for 3 hours in vacuum. Determine the infrared spectra of the residue as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Methylprednisolone Sodium Succinate responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{25}$: Between +96° and +104° (0.1 g, after drying, ethanol(95), 10 mL, 100 mm).

Purity ***Sodium***—Weigh accurately 1.0 g of Methylprednisolone Sodium Succinate, previously dried, add 75 mL of acetic acid(100), heat lightly, and dissolve. Add 20 mL of 1,4-dioxane and titrate with 0.1 mol/L perchloric acid VS until the solution exhibits a bluish green color (indicator: 1 drop of methylrosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction (between 4.49% and 4.77%).

$$\text{Each mL of 0.1 mol/L perchloric acid VS} = 2.299 \text{ mg of Na}$$

Loss on drying NMT 3.0% (1 g, 105 ℃, 3 hours).

Assay Weigh accurately about 0.1 g of Methylprednisolone Sodium Succinate and dissolve in ethanol(95) to make exactly 200 mL. Pipet 5.0 mL of this solution, add ethanol(95) to make exactly 200 mL, and use this solution as the test solution. Separately, weigh accurately about 12.5 mg of methylprednisolone sodium succinate RS, dissolve in ethanol(95) to make exactly 100 mL. To 0.5 mL of this solution, add ethanol(95) to make exactly 50 mL, and use this solution as the standard solution. Prepare ethanol(95) as the blank test solution. Transfer 20.0 mL each of the blank test solution, the test solution, and the standard solution in a Erlenmeyer flask with a stopper, add 2.0 mL of solution where 50 mg of blue tetrazolium and 10 mL of methanol are dissolved in, add 4.0 mL each of the mixture of ethanol(95) and tetramethylammonium hydroxide (9 : 1), and allow it to stand in the dark for 90 minutes. Add 1.0 mL of acetic acid(100) and determine the absorbance, A_T and A_S, at 525 nm with the solution from the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy using the blank test solution as the control solution.

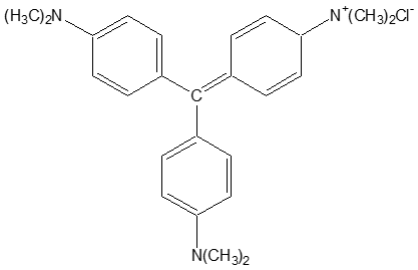
$$\text{Amount (mg) of methylprednisolone sodium succinate } (C_{26}H_{33}NaO_8)$$

$$= 8.37 \times C \times \frac{A_T}{A_S}$$

C: Concentration (μg/mL) of methylprednisolone succinate in the standard solution

Packaging and storage Preserve in light-resistant, tight containers.

Methylrosanilinium Chloride
메틸로사닐린염화물



Crystal Violet
Methylrosaniline Chloride $C_{25}H_{30}ClN_3$: 407.98
[4-[*bis*[4-(Dimethylamino)phenyl]methylidene]cyclohexa-2,5-dien-1-ylidene]-dimethylazanium chloride [*548-62-9*]

Methylrosanilinium Chloride is hexamethyl pararosaniline chloride and usually contains pentamethyl pararosaniline chloride and tetramethyl pararosaniline chloride.

Methylrosanilinium Chloride contains NLT 96.0% and NMT 101.0% of methylrosanilinium chloride [hexamethyl pararosaniline chloride ($C_{25}H_{30}ClN_3$)], calculated on the dried basis.

Description Methylrosanilinium Chloride occurs as a fragment with a green metallic luster or a dark green powder, which has no odor or a slight odor. It is soluble in ethanol(95), sparingly soluble in water and practically insoluble in ether.

Identification (1) Put 1 mg of Methylrosanilinium Chloride in 1 mL of sulfuric acid; Methylrosanilinium Chloride dissolves while the solution exhibits an orange to reddish brown color. To this solution, drop water; the color of the solution changes from brown through green to blue.

(2) Dissolve 20 mg of Methylrosanilinium Chloride in 10 mL of water, add 5 drops of hydrochloric acid, and use this solution as the test solution. To 5 mL of this solution, add tannic acid TS in drops; an dark blue precipitate is produced.

(3) Add 0.5 g of zinc powder to 5 mL of the test solution obtained in (2) and shake to mix; the solution is decolorized. Put 1 drop of this solution into filter paper and add 1 drop of ammonia TS right next to it; a blue color is observed at the parts where two solutions meet.

Purity (1) ***Ethanol-insoluble substances***—Weigh accurately about 1 g of Methylrosanilinium Chloride, previously dried, add 50 mL of ethanol(95), heat on a steam bath for 15 minutes under a reflux condenser, and filter the precipitate through a tared glass filter to collect. Wash with warm ethanol until the washings does not show a violet color and dry at 105 ℃ for 2 hours; the amount is NMT 1.0%.

(2) ***Heavy metals***—Proceed with 1.0 g of Methylrosanilinium Chloride as directed under Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(3) ***Zinc***—Add 0.1 mL of sulfuric acid to 0.10 g of Methylrosanilinium Chloride and incinerate by ignition. After cooling, add 5 mL of dilute hydrochloric acid, 0.5 mL of dilute nitric acid and 4 mL of water, boil, and then add 5 mL of ammonia TS. Boil again, filter, and add 2 to 3 drops of sodium sulfide TS to the filtrate; the resulting is not turbid.

(4) ***Arsenic***—Proceed with 0.40 g of Methylrosanilinium Chloride as directed under Method 3 and perform the test (NMT 5 ppm).

Loss on drying NMT 7.5% (1 g, 105 ℃, 4 hours).

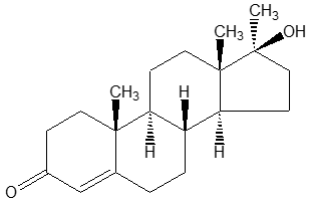
Residue on ignition NMT 1.5% (0.5 g).

Assay Weigh accurately about 0.4 g of Methylrosanilinium Chloride, transfer into a wide-mouth Erlenmeyer flask, and dissolve in 25 mL of water and 10 mL of hydrochloric acid. Then, add 50 mL of 0.1 mol/L titanium(III) chloride, passing through carbon dioxide, and heat to boiling. Boil again over a low heat for 15 minutes with occasionally shaking. Cooling while passing through carbon dioxide, and titrate the excess titanium(III) chloride with 0.1 mol/L ammonium ferric sulfate VS (indicator: 5 mL of ammonium thiocyanate TS). The endpoint of the titration is when the solution slightly exhibits a red color. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L titanium(III) chloride VS
= 20.399 mg of $C_{25}H_{30}ClN_3$

Packaging and storage Preserve in tight containers.

Methyltestosterone
메틸테스토스테론



$C_{20}H_{30}O_2$: 302.45
(8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-17-Hydroxy-10,13,17-

trimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[a]phenanthren-3(2*H*)-one [*58-18-4*]

Methyltestosterone, when dried, contains NLT 98.0% and NMT 102.0% of methyltestosterone ($C_{20}H_{30}O_2$).

Description Methyltestosterone occurs as white to pale yellow crystals or a crystalline powder and is odorless.
It is freely soluble in methanol or ethanol(95), soluble in acetic acid, sparingly soluble in ether, and practically insoluble in water.

Identification (1) Determine the absorption spectra of Methyltestosterone and methyltestosterone RS in ethanol(95) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Methyltestosterone and methyltestosterone RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +79° and +85° (0.1 g, after drying, ethanol(95), 10 mL, 100 mm).

Melting point Between 163 and 168 ℃.

Purity ***Related substances***—Weigh about 40 mg of Methyltestosterone, dissolve in 2 mL of ethanol, and use this solution as the test solution. Pipet 1 mL of the test solution, add ethanol(95) to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with the mixture of chloroform and diethylamine (19 : 1) as the developing solvent to a distance of 15 cm and air-dry the plate. Examine the plate under ultraviolet rays (main wavelength: 366 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 1.0% (0.5 g, in vacuum, phosphorus (V) oxide, 10 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately about 20 mg of Methyltestosterone and methyltestosterone RS, previously dried in a desiccator (in vacuum, phosphorous (V) oxide) for 10 hours, and dissolve each in methanol to make exactly 200 mL. Pipet 5 mL each of this solution, add exactly 5 mL of the internal standard solution to each, add methanol to make 50 mL, and use these solutions as the test solution and the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and calculate the ratios, Q_T and Q_S, of the peak area of methyltestosterone to that of the internal standard for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of methyltestosterone } (C_{20}H_{30}O_2) = \text{Amount of (mg) methyltestosterone RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of propyl paraoxybenzoiate in methanol (1 in 10000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 241 nm).

Column: A stainless steel column 6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of acetonitrile and water (11 : 9).

Flow rate: Adjust the flow rate so that the retention time of methyltestosterone is about 10 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; the internal standard and methyltestosterone are eluted in this order with the resolution between their peaks being NLT 9.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of methyltestosterone to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Methyltestosterone Tablets
메틸테스토스테론 정

Methyltestosterone Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of methyltestosterone ($C_{20}H_{30}O_2$: 302.45).

Method of preparation Prepare as directed under tablets, with Methyltestosterone.

Identification (1) Weigh a portion of Methyltestosterone Tablets, previously powdered, equivalent to 10 mg of methyltestosterone according to the labeled amount, add 50 mL of chloroform, shake for 30 minutes, and filter. Evaporate the filtrate to dryness, dissolve the residue in 10 mL of acetone, and use this solution as the test solution. Separately, dissolve 10 mg of methyltestosterone RS in 10 mL of acetone and use this solution as the standard solution. With these solutions, perform the test as di-

rected under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of chloroform and ethanol (9:1) to a distance of about 12 cm and air-dry the plate. Spray evenly dilute sulfuric acid on the plate, and heat it at 110 ℃ for 10 minutes; the R_f values of the spots obtained from the test and standard solutions are the same.

Disintegration Meets the requirements.

Uniformity of dosage units It meets the requirements when the Content uniformity test is performed according to the following method.

Take 1 tablet of Methyltestosterone Tablets, add 5 mL of water to disintegrate, add 50 mL of methanol, and shake to mix for 30 minutes. Add methanol to exactly 100 mL and centrifuge the solution. Pipet *V* mL of the clear supernatant, add methanol to make exactly *V'* mL so that each mL contains 10 μg of methyltestosterone ($C_{20}H_{30}O_2$), and use this solution as the test solution. Separately, weigh accurately about 10 mg of methyltestosterone RS, previously dried in a desiccator (in vacuum, phosphorus pentoxide) for 10 hours, dissolve in 5 mL of water and 50 mL of methanol, and then add methanol to make exactly 100 mL. Pipet 5 mL of this solution, add methanol to make exactly 50 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength of about 241 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of methyltestosterone } (C_{20}H_{30}O_2) = \text{Amount of (mg) methyltestosterone RS} \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{10}$$

Assay Weigh accurately and powder NLT 20 tables of Methyltestosterone Tablets. Weigh accurately a portion of this powder, equivalent to about 25 mg of methyltestosterone ($C_{20}H_{30}O_2$), add about 70 mL of methanol, shake to mix for about 30 minutes, and add methanol to make exactly 100 mL. Pipet 2 mL of this solution, add exactly 5 mL of the internal standard solution, add methanol to make exactly 50 mL, filter through a membrane filter (not exceeding 0.45 μm in pore size), and use this solution as the test solution. Separately, weigh accurately about 20 mg of methyltestosterone RS, previously dried in a desiccator (in vacuum, phosphorus pentoxide) for 10 hours, and dissolve in methanol to make exactly 200 mL. Pipet 5 mL of this solution, add exactly 5 mL of the internal standard solution, add methanol to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and calculate the ratios, Q_T and Q_S, of the peak area of methyltestosterone to that of the internal standard from the test solution and the standard solution, respectively.

$$\text{Amount (mg) of methyltestosterone } (C_{20}H_{30}O_2) = \text{Amount of (mg) methyltestosterone RS} \times \frac{Q_T}{Q_S} \times \frac{5}{4}$$

Internal standard solution—A solution of propyl p-hydroxybenzoate in methanol (1 in 10000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 241 nm).

Column: A stainless steel column about 6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of acetonitrile and water (11 : 9).

Flow rate: Adjust the flow rate so that the retention time of methyltestosterone is about 10 minutes.

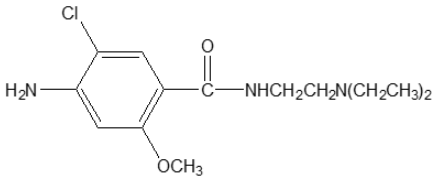
System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; the internal standard solution and methyltestosterone are eluted in this order with the resolution between their peaks being NLT 9.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of methyltestosterone to those of the internal standard is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Metoclopramide
메토클로프라미드



$C_{14}H_{22}ClN_3O_2$: 299.80

4-Amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-methoxybenzamide [*364-62-5*]

Metoclopramide, when dried, contains NLT 99.0% and NMT 101.0% of metoclopramide ($C_{14}H_{22}ClN_3O_2$).

Description Metoclopramide occurs as white crystals or a crystalline powder and is odorless.

It is freely soluble in acetic acid(100), soluble in methanol or in chloroform, sparingly soluble in ethanol(95), acetic anhydride or acetone, very slightly soluble in ether and practically insoluble in water.

It dissolves in dilute hydrochloric acid.

Identification (1) Dissolve 10 mg of Metoclopramide in 1 mL of dilute hydrochloric acid and 4 mL of water; the solution responds to the Qualitative Analysis for primary aromatic amines.

(2) Dissolve 10 mg of Metoclopramide in 5 mL of dilute hydrochloric acid and 20 mL of water, and to 5 mL of this solution, add 1 mL of Dragendorff's TS; an orange precipitate is formed.

(3) Dissolve 0.1 g each of Metoclopramide and metoclopramide RS in 1 mL of 1 mol/L hydrochloric acid TS and add water to make 100 mL. To 1 mL each of these solutions, add water to make 100 mL. Determine the absorption spectra of the resulting solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Melting point Between 146 and 149 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g of Metoclopramide in 10 mL of 1 mol/L hydrochloric acid TS; the solution is colorless and clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Metoclopramide as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Dissolve 1.0 g of Metoclopramide in 5 mL of 1 mol/L hydrochloric acid TS and performed the test using this solution as the test solution (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.10 g of Metoclopramide in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 200 mL, and use it as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel (with a fluorescent indicator) for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol and ammonia water(28) (19 : 1) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Dry the plate further at 80 ℃ for 30 minutes. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than those obtained from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

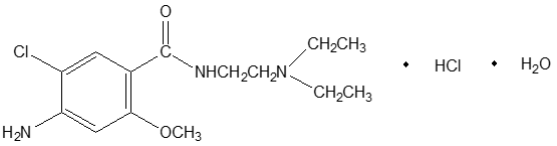
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Metoclopramide, previously dried, dissolve in 50 mL of acetic acid(100), add 5 mL of acetic anhydride, and warm for 5 minutes. After cooling, titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of methylrosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 29.980 mg of $C_{14}H_{22}ClN_3O_2$

Packaging and storage Preserve in well-closed containers.

Metoclopramide Hydrochloride Hydrate
메토클로프라미드염산염수화물



Metoclopramide Hydrochloride
$C_{14}H_{22}ClN_3O_2 \cdot HCl \cdot H_2O$: 354.27
4-Amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-methoxybenzamide hydrate hydrochloride [*54143-57-6*]

Metoclopramide Hydrochloride Hydrate contains NLT 98.0% and NMT 101.0% of metoclopramide hydrochloride ($C_{14}H_{22}ClN_3O_2 \cdot HCl$: 336.26), calculated on the anhydrous basis.

Description Metoclopramide Hydrochloride Hydrate occurs as a white crystalline powder and is odorless or has a faint odor.
It is very soluble in water, freely soluble in ethanol(95), sparingly soluble in chloroform and practically insoluble in ether.

Identification (1) Dissolve 50 mg of Metoclopramide Hydrochloride Hydrate in 5 mL of water and add 5 mL of 1% 4-dimethylaminobenzaldehyde in 1 mol/L hydrochloric acid; the solution turns orange.

(2) Perform the test as directed under the section of Related substances under the Purity; the R_f value of the principal spot in the identification solution corresponds to that of the standard solution (1).

(3) Determine the infrared spectra of Metoclopramide Hydrochloride Hydrate and metoclopramide hydrochloride hydrate RS, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Heavy metals***—Dissolve 2.5 g of Metoclopramide Hydrochloride Hydrate in 25 mL of freshly boiled and cooled water, and use 12 mL of this solution as the test solution. Separately, prepare 2 mL of lead standard solution in the same manner as the test solution. To 10 mL of this solution, add 2 mL of the test solution, and use this solution as the control solution. Separately, add 2 mL of the test solution to 10 mL of water and use this solution as the blank test solution. To 12 mL each of the test solution, the control solution and the blank test solution, add 2 mL of pH 3.5 acetate buffer solution, mix, add 1.2 mL of thioacetamide TS, and mix immediately.

Allow them to stand for 2 minutes; the color of the test solution is no more intense than that of the control solution (NMT 20 ppm).

System suitability—The color of the control solution is faint brown compared to that of the blank test solution.

(2) ***Related substances***—Weigh accurately an appropriate amount of Metoclopramide Hydrochloride Hydrate and dissolve in methanol to make a solution containing 50 mg per mL, and use this solution as the test solution. Take an appropriate amount of the test solution, dissolve in methanol to make a solution containing 0.5 mg per mL, and use this solution as the identification solution. Separately, weigh an appropriate amount of metoclopramide hydrochloride hydrate RS and dissolve in methanol to make a solution containing 1 mg per mL. Add methanol to this solution to dilute quantitatively to make solutions with the concentrations indicated in the table below, and use these solutions as the standard solutions.

Standard solutions	Dilution	Concentration (μg/mL)	Percentage (%) with respect to the test solution
Standard solution (1)	(1 in 4)	250	0.5
Standard solution (2)	(3 in 20)	150	0.3
Standard solution (3)	(1 in 20)	50	0.1

With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution, the identification solution and the standard solutions on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, methanol, toluene and ammonia water (140 : 60 : 20 : 1) to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light; any spot other than the principal spot obtained from the test solution is not larger and is not more intense than the principal spot obtained from the standard solution (1) (NMT 0.5%), and the sum of the intensities of all spots other than the principal spot obtained from the test solution is NMT 1.0%.

Water NLT 4.5% and NMT 6.0% (0.5 g, volumetric titration, direct titration).

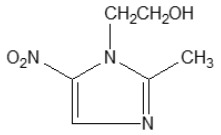
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.25 g of Metoclopramide Hydrochloride Hydrate, add 5 mL of 0.01 mol/L hydrochloric acid TS and 50 mL of ethanol(95), and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry; determine the volume consumed between the two endpoints). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 33.63 mg of $C_{14}H_{22}ClN_3O_2 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Metronidazole
메트로니다졸



$C_6H_9N_3O_3$: 171.15
2-(2-Methyl-5-nitroimidazol-1-yl)ethanol [*443-48-1*]

Metronidazole, when dried, contains NLT 99.0% and NMT 101.0% of metronidazole ($C_6H_9N_3O_3$).

Description Metronidazole occurs as white to pale yellow crystals or a crystalline powder, and is odorless and has a slightly bitter taste.
It is freely soluble in acetic acid(100), sparingly soluble in methanol, in ethanol(95) or in acetone, slightly soluble in water and very slightly soluble in ether.
It dissolves in dilute hydrochloric acid.
It is changed by light.

Identification (1) Determine the absorption spectra of solutions of Metronidazole and metronidazole RS in 0.1 mol/L hydrochloric acid TS as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Metronidazole and metronidazole RS, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 159 and 163 °C.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Metronidazole as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***2-Methyl-5-nitroimidazole***—Dissolve 0.10 g of Metronidazole in acetate to make exactly 10 mL and use this solution as the test solution. Separately, dissolve 20 mg of 2-methyl-5-nitroimidazole RS in acetone to make exactly 20 mL, then pipet 5.0 mL of this solution, add acetone to make exactly 100 mL and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent

indicator). Next, develop the plate with a mixture of acetone, water, and ethyl acetate (8 : 1 : 1) as a developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than those obtained from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, silica gel, 24 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Metronidazole, previously dried, dissolve in 30 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 0.5 mL of 1-naphtholbenzein TS). However, the endpoint of titration is when the orange color of the solution turns into a green color. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 17.115 mg of $C_6H_9N_3O_3$

Packaging and storage Preserve in light-resistant, tight containers.

Metronidazole Tablets
메트로니다졸 정

Metronidazole Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of metronidazole ($C_6H_9N_3O_3$: 171.15).

Method of preparation Prepare as directed under Tablets, with Metronidazole.

Identification (1) Powder Metronidazole Tablets, weigh an amount equivalent to 0.1 g of metronidazole according to the labeled amount, add 0.1 mol/L hydrochloric acid TS to make exactly 100 mL. Shake this solution vigorously to mix, allow to stand for 30 minutes, and centrifuge. Pipet 1 mL of the clear supernatant, and add 0.1 mol/L hydrochloric acid TS to make 100 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 275 nm and 279 nm.

(2) Weigh an amount of Metronidazole Tablets, previously powdered, equivalent to 0.20 g of Metronidazole according to the labeled amount, add 20 mL of acetone, shake and mix for 10 minutes, centrifuge the solution, and use the clear supernatant as the test solution. Separately, dissolve 0.10 g of metronidazole RS in 10 mL of acetone, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of acetone, water, and ethyl acetate (8 : 1 :1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm), and the R_f values of the principal spots obtained from the test solution and the standard solution are the same.

Dissolution Take 1 tablet of Metronidazole Tablets, proceed with 900 mL of water as the test solution at 50 revolutions per minute according to Method 2, and perform the test. Take NLT 20 mL of the dissolved solution after 90 minutes from the start of the dissolution test and filter the solution through a membrane filter with a pore size of NMT 0.45 μm. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add water to obtain a solution having known concentration of about11 μg of metronidazole per mL according to the labeled amount. Make it exactly *V′* mL and use this solution as the test solution. Separately, dry and decompress metronidazole RS with silica gels as a desiccating agent for 24 hours, weigh accurately 22 mg of Metronidazole Tablets, dissolve in water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at 320 nm as directed under Ultraviolet-visible Spectroscopy. Meets the requirements if the dissolution rate of Metronidazole Tablets in 90 minutes is NLT 70%.

The dissolution rate (%) to the labeled amount of metronidazole ($C_6H_9N_3O_3$)

$$= W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 45$$

WS: Amount (mg) of metronidazole RS
C: Labeled amount (mg) of metronidazole in 1 tablet

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following method.
Take a table of Metronidazole Tablets, add 25 mL of a mixture of water and methanol (1 : 1), shake vigorously for 25 minutes to mix, and add the mixture of water and methanol (1 : 1) to make exactly 50 mL. Pipet 5 mL of this solution, and add a mixture of water and methanol (1 : 1) to make exactly 100 mL. Filter the solution through a membrane filter with a pore size of 0.45 μm, discard the first 3 mL of the filtrate, and use the subsequent filtrate as the test solution. Perform the test as directed under the Assay below.

Amount (mg) of metronidazole ($C_6H_9N_3O_3$)

$$= \text{Amount (mg) of metronidazole RS} \times \frac{A_T}{A_S} \times 10$$

Assay Weigh accurately the mass of NLT 20 tables of Metronidazole Tablets, and reduce to powder. Weigh an amount equivalent to about 0.25 g of metronidazole

($C_3H_9N_3O_3$), add 25 mL of a mixture of water and methanol (1 : 1), shake vigorously to mix for 10 minutes, and add a mixture of water and methanol (1 : 1) to make exactly 50 mL. Pipet 5 mL of this solution, and add a mixture of water and methanol (4 : 1) to make exactly 100 mL. Filter the resulting solution through a membrane filter with a pore size of NMT 0.45 μm, discard the first 3 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, dry and decompress metronidazole RS with silica gels as a desiccating agent for 24 hours, weigh accurately 22 mg of Metronidazole Tablets, dissolve in a solution of water and methanol (4 : 1) to make exactly 100 mL, and use this solution as the standard solution. Pipet 10 μL each of the test solution and the standard solution, and perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S of metronidazole in each solution.

$$\text{Amount (mg) of metronidazole } (C_6H_9N_3O_3) = \text{Amount (mg) of metronidazole RS} \times \frac{A_T}{A_S} \times 10$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 320 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of water and methanol (80 : 20).

Flow rate: Adjust the flow rate so that the retention time of metronidazole is about 5 minutes.

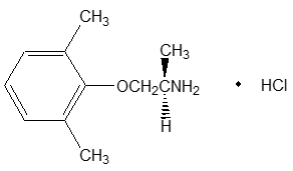
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the number of theoretical plates and the symmetry factor for the metronidazole peak is NLT 3000 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of metronidazole is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Mexiletine Hydrochloride
멕실레틴염산염



and enantiomer

$C_{11}H_{17}NO \cdot HCl$: 215.72

(*RS*)-1-(2,6-Dimethylphenoxy)propan-2-amine hydrochloride [*5370-01-4*]

Mexiletine Hydrochloride, when dried, contains NLT 98.0% and NMT 102.0% of mexiletine hydrochloride ($C_{11}H_{17}NO \cdot HCl$).

Description Mexiletine Hydrochloride occurs as a white powder.

It is freely soluble in water or ethanol(95), slightly soluble in acetonitrile, and practically insoluble in ether.

An aqueous solution of Mexiletine Hydrochloride (1 in 20) shows no optical rotation.

Identification (1) Determine the absorption spectra of the solutions of Mexiletine Hydrochloride and mexiletine hydrochloride RS in 0.01 mol/L hydrochloric acid TS (1 in 2000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Mexiletine Hydrochloride and mexiletine hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the two spectra, dissolve each in ethanol(95), evaporate, and perform the test with the residue in the same manner.

(3) An aqueous solution of Mexiletine Hydrochloride (1 in 100) responds to the Qualitative Analysis (2) for chloride.

Melting point Between 200 and 204 °C.

pH Dissolve 1.0 g of Mexiletine Hydrochloride in 10 mL of water; the pH of this solution is between 3.8 and 5.8.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Mexiletine Hydrochloride in 10 mL of water; the resulting solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 2.0 g of Mexiletine Hydrochloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 20 mg of Mexiletine Hydrochloride in 20 mL of the mobile phase and use this solution as the test solution. Pipet 1 mL of the test solution, add the mobile phase to make exactly 250 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; each peak area other than the major peak obtained from the test solution is not greater than the major peak area from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

Detection sensitivity: Adjust the sensitivity so that the peak height of mexiletine obtained from 20 μL of the standard solution is 5 mm to 10 mm.

Time span of measurement: About 3 times the retention time of mexiletine. However, exclude solvent peaks.

Loss on drying NMT 0.5% (1 g, 105 °C, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 20 mg each of Mexiletine Hydrochloride and mexiletine hydrochloride RS, previously dried, and dissolve in the mobile phase to make exactly 20 mL. Pipet 5 mL each of these solutions, add exactly 5 mL of the internal standard solution, add the mobile phase to make exactly 100 mL, and use these solutions as the test solution and the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of mexiletine to internal standard.

$$\text{Amount (mg) of mexiletine hydrochloride } (C_{11}H_{17}NO\cdot HCl) = \text{Amount (mg) of mexiletine hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of phenethylamine hydrochloride in the mobile phase (3 in 5000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 7 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

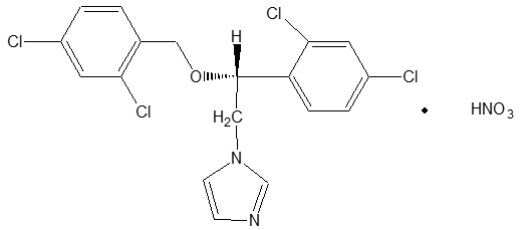
Mobile phase: Dissolve 2.5 g of sodium lauryl sulfate and 3 g of sodium dihydrogen phosphate dihydrate in 600 mL of water and add 420 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of mexiletine is about 6 minutes.

Selection of column: Proceed with 20 μL of the standard solution according to the above conditions; internal standard and mexiletine are eluted in this order with the resolution being NLT 9.

Packaging and storage Preserve in light-resistant, tight containers.

Miconazole Nitrate
미코나졸질산염



and enantiomer

$C_{18}H_{14}Cl_4N_2O\cdot HNO_3$: 479.14

(*RS*)-1-[2-(2,4-Dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]imidazole; nitric acid [*22832-87-7*]

Miconazole Nitrate, when dried, contains NLT 98.5% and NMT 101.0% of miconazole nitrate ($C_{18}H_{14}Cl_4N_2O\cdot HNO_3$).

Description Miconazole Nitrate occurs as a white crystalline powder.

It is freely soluble in *N*,*N*-dimethylformamide, sparingly soluble in methanol, slightly soluble in ethanol(95), acetone, or acetic acid(100), and very slightly soluble in water or ether.

Melting point—About 180 °C (with decomposition).

Identification (1) Add 2 mL of Reinecke salt TS to 2 mL of Miconazole Nitrate in methanol (1 in 100); a pale red precipitate is formed.

(2) Determine the absorption spectra of Miconazole Nitrate and miconazole nitrate RS in methanol (1 in 2500) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Perform the Flame Coloration (2) with Miconazole Nitrate in methanol (1 in 100); it exhibits a green color.

(4) A Miconazole Nitrate in methanol (1 in 100) responds to the Qualitative Analysis for nitrate.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Miconazole Nitrate in 100 mL of methanol; the solution is clear and colorless.

(2) ***Chloride***—Weigh 0.10 g of Miconazole Nitrate, dissolve in 6 mL of dilute nitric acid and *N*,*N*-dimethylformamide to make 50 mL, and perform the test using this solution as the test solution. Separately, add 6 mL of dilute nitric acid and *N*,*N*-dimethylformamide to 0.25 mL of 0.01 mol/L hydrochloric acid to make 50 mL, and use this solution as the control solution (NMT 0.09%).

(3) ***Heavy metals***—Proceed with 1.0 g of Miconazole Nitrate as directed under Method 2 and perform the test. Prepare the control solution with 1.0 mL of the lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Proceed with 1.0 g of Miconazole Nitrate as directed under Method 3 and perform the test

(NMT 2 ppm).

(5) ***Related substances***—Dissolve 0.10 g of Miconazole Nitrate in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution and add methanol to make exactly 20 mL. Pipet 1 mL of this solution and add methanol to make exactly 20 mL. Use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Thin Layer Chromatography. Spot 50 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of *n*-hexane, chloroform, methanol, and ammonia water(28) (60 : 30 : 10 : 1) (as the developing solvent) to a distance of about 12 cm, and air-dry the plate. Allow the plate to stand for 20 minutes in iodine steam; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, silica gel, 60 ℃, 3 hours).

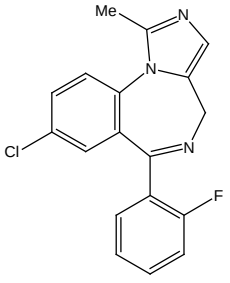
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.35 g of Miconazole Nitrate, previously dried, and add 50 mL of acetic acid(100), warm to dissolve. After cooling, titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 47.91 mg of $C_{18}H_{14}Cl_4N_2O \cdot HNO_3$

Packaging and storage Preserve in light-resistant, tight containers.

Midazolam
미다졸람



$C_{18}H_{13}ClFN_3$: 325.77

8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-a][1,4]benzodiazepine [*59467-70-8*]

Midazolam contains NLT 98.5% and NMT 101.5% of midazolam ($C_{18}H_{13}ClFN_3$), calculated on the dried basis.

Description Midazolam occurs as a white or yellow crystalline powder.
It is freely soluble in acetone or ethanol(95), soluble in methanol and practically insoluble in water.

Identification (1) Determine the infrared spectra of Midazolam and midazolam RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The R_f values of the principal spots obtained from the standard solution (2) and the test solution (2) in Related Substances are the same.

(3) Take 90 mg of Midazolam in a porcelain crucible, add 0.3 g of anhydrous sodium carbonate, mix, and ignite for NMT 5 minutes. After cooling, add 5 mL of dilute nitric acid to the residue, shake to mix, and filter. Add 1.0 mL of the filtrate to a mixture of 0.1 mL of alizarin S TS and 0.1 mL of zirconyl nitrate TS, mix, and allow to stand for 5 minutes; the resulting solution turns yellow and the blank test solution prepared in the same manner tunes red.

(4) Add 1 mL of water to 1 mL of the filtrate in (3); the solution responds to the Qualitative Analysis (2) for chloride.

Melting point Between 161 and 164 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g of Midazolam in 0.1 mol/L hydrochloric acid TS to make 10 mL; the solution is clear.

(2) ***Related substances***—(i) Dissolve 0.2 g of Midazolam in ethanol(95) to make 5 mL, and use this solution as the test solution (1). Add ethanol(95) to 1.0 mL of this solution (the test solution (1)) to make 50 mL and use this solution as the test solution (2). Add ethanol(95) to 1.0 mL of the test solution (1) to make exactly 10 mL, then add ethanol(95) to 1.0 mL of this solution to make exactly 100 mL, and use this solution as the standard solution (1). Dissolve 8 mg of midazolam RS in ethanol(95) to make 10 mL and use this solution as the standard solution (2). Additionally, dissolve 8 mg of midazolam RS and 8 mg of chlordiazepoxide in ethanol(95) to make 10 mL and use this solution as the standard solution (3). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solutions and the standard solutions on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, methanol, water, and acetic acid(100) (80 : 20 : 15 : 2) (as the developing solvent) to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution (1) are not more intense than the spots from the standard solution (1) (NMT 0.1%). This test is valid when two spots from the standard solution (3) are distinctly separated.

(ii) Dissolve 50 mg of Midazolam in methanol to make 50 mL and use this solution as the test solution.

Add methanol to 1 mL of this solution to make 100 mL. Add methanol to 1 mL of this solution to make 10 mL and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area by the automatic integration method; the peak areas of related substance I {(6*RS*)-8-chloro-6-(2-fluorophenyl)-1-methyl-5,6-dihydro-4*H*-imidazo[1.5-α][1,4]benzodiazepine} and related substance II {8-chloro-1-methyl-6-phenyl-4*H*-imidazo[1.5-α][1,4]benzodiazepine} obtained from the test solution are not greater than the area of the major peak from the standard solution (0.1%), and the peak area of related substance III {(6*RS*)-8-chloro-6-(2-fluorophenyl)-1-methyl-6*H*-imidazo[1.5-α][1,4]benzodiazepine} is not greater than 2 times the area of the major peak from the standard solution (0.2%). The peak area of related substances other than related substances I, II and III obtained from the test solution is not greater than the area of the major peak from the standard solution (0.1%). The total area of related substances is not greater than 3 times the area of the major peak obtained from the standard solution (0.3%). Exclude any peaks with an area not greater than 0.5 times the area of the major peak from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Mobile phase: Dissolve 7.7 g of ammonium acetate in 1000 mL of water and dissolve 4 g of tetrabutylammonium hydroxide in 1000 mL of water, respectively. Mix these solutions and adjust the pH to 5.3 with acetic acid. Add 560 mL of methanol to 440 mL of this solution.

Flow rate: 1.0 mL/min

Time span of measurement: About 2.5 times the retention time of midazolam.

Relative retention time: Proceed with 5 μL each of the test solution and the standard solution according to the above conditions; the relative retention times of the peaks of the related substances I, II and III to that of the peak of midazolam are about 0.9, 1.2, and 2.2, respectively.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

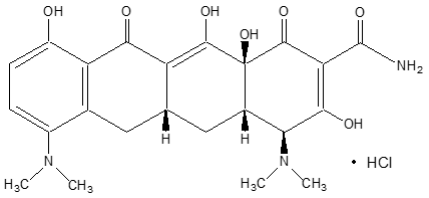
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.12 g of Midazolam, dissolve in 30 mL of acetic acid(100), add 20 mL of acetic anhydride, and mix. Titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 16.29 mg of $C_{18}H_{13}ClFN_3$

Packaging and storage Preserve in light-resistant, well-closed containers.

Minocycline Hydrochloride
미노사이클린염산염



$C_{23}H_{27}N_3O_7 \cdot HCl$: 493.94

(4*S*,4*aS*,5*aR*,12*aS*)-4,7-Bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide hydrochloride [*13614-98-7*]

Minocycline Hydrochloride is the hydrochloride of a derivative of tetracycline.

Minocycline Hydrochloride contains NLT 890 μg (potency) and NMT 950 μg (potency) per mg of minocycline ($C_{23}H_{27}N_3O_7$: 457.48), calculated on the anhydrous basis.

Description Minocycline Hydrochloride occurs as a yellow crystalline powder.
It is freely soluble in *N*,*N*-dimethylformamide, soluble in methanol, sparingly soluble in water and slightly soluble in ethanol(95).

Identification (1) Determine the absorption spectra of solutions (1 in 62500) of Minocycline Hydrochloride and minocycline hydrochloride RS dissolved in hydrochloric acid in methanol (19 in 20000), as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the absorption spectra of solutions of Minocycline Hydrochloride and minocycline hydrochloride RS as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Minocycline Hydrochloride (1 in 100) responds to the Qualitative Analysis (2) for chloride.

Crystallinity Meets the requirements.

pH Dissolve 1.0 g of Minocycline Hydrochloride in 100 mL of water; the pH of this solution is between 3.5 and 4.5.

Absorbance $E_{1cm}^{1\%}$ (358 nm): Between 296 and 328 (8 mg, 0.01 mol/L hydrochloride methanol TS, 500 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Minocycline Hydrochloride in 100 mL of water; the solution is clear. Perform the test as directed under the Ultraviolet-visible Spectroscopy; the absorbance of the solution at 560 nm is NMT 0.06. However, perform the test within 1 hour after preparing this solution.

(2) ***Heavy metals***—Proceed with 0.5 g of Minocycline Hydrochloride and perform the test as directed under Method 2. Prepare the control solution with 2.5 mL of lead standard solution (NMT 50 ppm).

(3) ***Related substances***—Weigh 50 mg of Minocycline Hydrochloride, dissolve it in 100 mL of the mobile phase, and use this solution as the test solution. Perform the test immediately after preparing the test solution. Perform the test with 20 μL of the test solution as directed under the Liquid Chromatography according to the following operating conditions and determine each peak area of each solution by the automatic integration method, and calculate the peak area percentage of each solution by the percentage peak area method; the peak area percentage of epiminocycline is NMT 1.2%, and the peak area percentage of each peak, other than minocycline and epiminocycline, is NMT 1.0%. Additionally, the sum of each peak area, other than minocycline and epiminocycline, is NMT 2.0%.

Operating conditions

For the detector, column, column temperature and mobile phase, comply with the operating conditions under the Assay.

Flow rate: Adjust the flow rate so that the retention time of minocycline is about 12 minutes. The retention time of epiminocycline is about 10 minutes under these conditions.

System suitability

System performance: Proceed as directed under the system suitability under the Assay.

Test for required detectability: Pipet 2 mL of the test solution, add the mobile phase to make exactly 100 mL, and use this solution as the system suitability solution. Pipet 5 mL of the system suitability solution and add the mobile phase to make exactly 100 mL. Confirm that the peak area of minocycline obtained from 20 μL of this solution is equivalent to 3.5% to 6.5% of that from 20 μL of the minocycline suitability solution.

System repeatability: Repeat the test 6 times with 20 μL each of the system suitability solutions according to the above conditions; the relative standard deviation of the ratios of the peak area of minocycline is NMT 2.0%.

Time span of measurement: About 2.5 times the retention time of minocycline beginning after the solvent peak.

Loss on drying NMT 10.0% (1.0 g, in vacuum, 100 ℃, 5 h.).

Water Between 4.3% and 8.0% (0.3 g, volumetric titration, direct titration).

Residue on ignition NMT 0.5% (1.0 g).

Sterility It meets the requirements when Minocycline Hydrochloride is used in a sterile preparation. However, it is excluded in cases where there is a final sterilization process in the manufacturing of a sterile preparation.

Bacterial endotoxins Less than 1.25 EU/mg (potency) when Minocycline Hydrochloride is used in a sterile preparation.

Histamine It meets the requirements when Minocycline Hydrochloride is used in a sterile preparation. Weigh an appropriate amount of Minocycline Hydrochloride, dissolve it in Isotonic Sodium Chloride Injection to prepare a solution containing 5.0 mg (potency) per mL, and use this solution as the test solution. Use 0.6 mL of the solution for the test.

Assay Weigh accurately about 50 mg (potency) each of Minocycline Hydrochloride and minocycline hydrochloride RS, dissolve in the mobile phase to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution under the following conditions as directed under the Liquid Chromatography, and determine the peak areas, A_T and A_S of minocycline in the test solution and the standard solution.

$$\text{Potency (μg) of minocycline } (C_{23}H_{27}N_3O_7) = \text{Potency (μg) of minocycline hydrochloride RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Adjust the pH of a mixture of ammonium oxalate TS, *N*,*N*-dimethylformamide, and disodium dihydrogen ethylenediaminetetraacetate TS (11 : 5 : 4) to 6.5 by adding tetrabutylammonium hydroxide TS.

Flow rate: 1 mL/min

System suitability

System performance: Dissolve 50 mg of Minocycline Hydrochloride in 25 mL of the mobile phase. Heat 5 mL of this solution on a steam bath for 60 minutes and add the mobile phase to make 25 mL. Proceed with 10 μL of this solution according to the above conditions; epiminocycline and minocycline are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions under the above conditions; the relative standard deviation of the peak areas of minocycline is NMT 1.0%.

Ammonium oxalate TS—Dissolve a mixture of water and acetonitrile (13 : 2) in 0.98 g of ammonium oxalate monohydrate to make 100 mL.

Disodium dihydrogen ethylenediaminetetraacetate TS—Dissolve a mixture of water and acetonitrile (13 : 2) in 18.6 g of disodium dihydrogen ethylenediaminetetraacetate hydrate to make 1000 mL.

Packaging and storage Preserve in light-resistant, tight containers.

Minocycline Hydrochloride Capsules
미노사이클린염산염 캡슐

Minocycline Hydrochloride Capsules contain NLT 90.0% and NMT 120.0% of the labeled amount of minocycline ($C_{23}H_{27}N_3O_7$: 457.48).

Method of preparation Prepare Minocycline Hydrochloride Capsules as directed under Capsules, with Minocycline.

Identification Weigh amounts of Minocycline Hydrochloride Capsules equivalent to 50 mg (potency) of minocycline and about 50 mg (potency) of minocycline RS according to the labeled amount, and dissolve in 20 mL of ethanol, respectively, and use each solution as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution to the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with fluorescence indicator), and develop the plate with a mixture of 1-butanol, methanol and 10% citric acid (4 : 1 : 2) as the developing solvent to a distance of about 10 cm. Examine the plate under ultraviolet rays (main wavelength: 254 nm); the R_f values of the spots from the test solution and the standard solution are the same.

Loss on drying NMT 12.0% (1.0 g, NMT 0.7 kPa, 100 ℃, 5 hours)

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Proceed as directed under the Assay under Minocycline Hydrochloride Hydrate. Weigh accurately the contents with 20 capsules of Minocycline Hydrochloride Capsules, powder, weigh accurately about 50 mg (potency) of Minocycline Hydrochloride Capsules according to the marked potency, and dissolve in the mobile phase to make exactly 50 mL. Use this solution as the test solution. Weigh about 50 mg (potency) of minocycline hydrochloride hydrate RS, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the standard solution.

Packaging and storage Preserve in tight containers.

Minocycline Hydrochloride Dental Ointment
미노사이클린염산염 치과용 연고

Minocycline Hydrochloride Dental Ointment is a dental ointment and contains NLT 90.0% and NMT 120.0% of the labeled amount of minocycline ($C_{23}H_{27}N_3O_7$: 457.48).

Method of preparation Prepare as directed under Ointments, with Minocycline Hydrochloride.

Identification The major peaks obtained from the test solution and the standard solution under the Assay are the same in the retention time.

Water NMT 3.0% (0.3 g, volumetric titration, direct titration)

Assay Weigh accurately about 10 mg (potency) of Minocycline Hydrochloride Dental Ointment according to the labeled potency, dissolve with 10 mL each of dimethylformamide, extract 3 times, and combine the extracts. Add water to make exactly 100 mL, then pipet 10 mL of the resulting solution, add the mobile phase to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg (potency) of minocycline hydrochloride RS, dissolve in 30 mL of dimethylformamide, and add water to make exactly 100 mL. Pipet 10 mL of this solution, add the mobile phase to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of minocycline, A_T and A_S, in each solution.

$$\text{Potency (μg) of minocycline } (C_{23}H_{27}N_3O_7) = \text{Potency (μg) of minocycline hydrochloride RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 344 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).

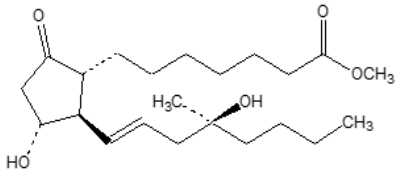
Column temperature: A constant temperature of about 25 °C.

Mobile phase: Adjust the pH of a mixture of 0.2 mol/L ammonium oxalate solution, dimethylformamide and 0.1 mol/L ethylenediaminetetraacetic acid disodium salt solution (11 : 5 : 4) to 6.2 with 0.4 mol/L tetra-*n*-butylammonium hydroxide solution.

Flow rate: Adjust the flow rate so that the retention time of minocycline is about 12 minutes.

Packaging and storage Preserve in tight containers.

Misoprostol
미소프로스톨



$C_{22}H_{38}O_5$: 382.54
(11α,13*E*)-11,16-Dihydroxy-16-methyl -9-oxoprost-13-en-1-oic acid methyl ester

Misoprostol contains NLT 97.0% and NMT 102.0% of misoprostol ($C_{22}H_{38}O_5$), calculated on the anhydrous basis.

Description Misoprostol occurs as a colorless to light yellow viscous oil.
It is freely soluble in ethanol, ether, chloroform or ethyl acetate and very slightly soluble in water or hexane.

Identification Determine the infrared spectra of Misoprostol and misoprostol RS as directed under the liquid film method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. However, the concentration of the test solution should be 30 mg/mL of chloroform.

Purity (1) ***Clarity and color of solution***—Dissolve about 50 mg of Misoprostol in 2.5 mL of methanol; the solution is clear. Perform the test as directed under the Ultraviolet-visible Spectroscopy using methanol as a control solution, and determine the absorbance at a wavelength of 440 nm; the absorbance is NMT 0.1.

(2) ***Related substances (A, B, C, D)***—Weigh accurately about 50 mg of Misoprostol and dissolve it in the mobile phase to make 10.0 mL. Use this solution as the test solution. Separately, weigh accurately 2 mg each of reference standards A, B, C and D, and dissolve in the mobile phase to make 100.0 mL. Use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions; Related substance A is NMT 1.0%, related substance B is NMT 0.2%, related substance C is NMT 0.3%, and related substance D is NMT 0.5%. The total of impurities is NMT 2.5%.

$$\text{X}\,(\%) = \frac{\text{A}_\text{X}}{\text{A}_\text{S}} \times \frac{\text{C}_\text{S}}{\text{C}_\text{X}} \times 100$$

X: A, B, C, D
A_X: Peak area of test solution
A_S: Peak area of standard solution
C_S: Concentration of standard solution (mg/mL)
C_X: Concentration of test solution (mg/mL)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 213 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Flow rate: 1.0 mL/min

Water NMT 1.0%.

Assay Weigh accurately about 10 mg of Misoprostol, add 40 mL of the mobile phase, and extract by shaking in an orbital shaker for 45 minutes. Then, add the mobile phase to make 50 mL, filter this solution, and use the resulting solution as the test solution. Separately, weigh accurately about 10 mg of misoprostol RS and dissolve it in the mobile phase to make 50 mL. Use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution according to the following conditions as directed under the Liquid Chromatography, and determine the peak areas, A_T and A_S, of misoprostol.

$$\text{Amount of misoprostol } (C_{22}H_{38}O_5)\text{ (mg)} = \text{Amount of misoprostol RS (mg)} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 200 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography.

Column temperature: 55 ℃

Mobile phase: A mixture of water, methanol and acetonitrile (35 : 40 : 25).

Packaging and storage Preserve in tight containers.

1% Misoprostol Powder
미소프로스톨 100배산

1% Misoprostol Powder contain NLT 90.0% and NMT 110.0% of the labeled amount of misoprostol ($C_{22}H_{38}O_5$: 382.54).

Method of preparation Prepare as directed under Powders, with 1 g of Misoprostol and 99 g of Hypromellose.

Identification (1) Weigh 40 mg of 1% Misoprostol Powder, add 80% methanol to make 25 mL, and use this solution as the test solution. Separately, weigh 40 mg of hypromellose RS, add 80% methanol to make 25 mL, and use this solution as a control solution. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it does not exhibit a

maximum at a wavelength of about 280 nm. Pipet 10 mL each of the test solution and the control solution, add 10 mL of a mixture of methanol and 1 mol/L sodium hydroxide (4 :1) to each, allow to stand at room temperature for 30 minutes, and determine the absorption spectra as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit maxima near 280 nm.

(2) Weigh 0.1 g of 1% Misoprostol Powder, add 5 mL of ethanol, shake for 10 minutes to mix, then centrifuge. Filter the clear supernatant and use the filtrate as the test solution. Pipet 0.5 mL of the test solution, add 1.5 mL of 1% m-dinitrobenzene, and cool. Add 1.5 mL of 10% sodium hydroxide, and allow to stand under ice solution in the dark for 20 minutes; a reddish purple color is exhibited.

(3) Weigh 0.1 g of 1% Misoprostol Powder, place in 100 mL of hot water, and cool at room temperature while agitating. To 5 mL of this solution, carefully add 5 mL of a solution, prepared by dissolving 35 mg anthrone in 35% sulfuric acid to make 100 mL, and allow to stand; the lower layer exhibits a blue to bluish green color.

Viscosity Between 2.4 cps and 3.6 cps.

Purity (1) ***Clarity and color of solution***—Add 1 g of hypromellose to 100 mL of boiling water and mix; a suspension is formed, and the residue does not dissolve. Cool the suspension to 20 ℃ and mix; the liquid becomes a clear or milky, sticky colloid mixture.

(2) ***Arsenic***—Proceed with 2.0 g of 1% Misoprostol Powder according to Method 3 and perform the test (NMT 1 ppm).

(3) ***Heavy metals***—Proceed with 2.0 g of 1% Misoprostol Powder according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

Water NMT 1.5%.

Residue on ignition NMT 3.0% (1 g).

Assay Weigh accurately about 0.2 g of 1% Misoprostol Powder, dissolve in the mobile phase to make 10 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of misoprostol RS, dissolve in the mobile phase to make 50 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of misoprostol, A_T and A_S, in each solution.

$$\text{Amount (mg) of misoprostol } (C_{22}H_{38}O_5) = \text{Amount (mg) of misoprostol RS} \times \frac{A_T}{A_S} \times \frac{1}{5}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 200 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm - 10 μm in particle diameter).

Mobile phase: A mixture of methanol, water and acetonitrile (40 : 35 : 25).

Flow rate: 2.0 mL/min

Packaging and storage Preserve in tight containers.

1% Misoprostol Powder Tablets
미소프로스톨배산 정

1% Misoprostol Powder Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of misoprostol ($C_{22}H_{38}O_5$: 382.54).

Method of preparation Prepare as directed under Tablets, with 1% Misoprostol Powder.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Uniformity of dosage units Perform the Content uniformity test with 1% Misoprostol Powder Tablets as directed under the Assay; it meets the requirements.

Dissolution Take 1 tablet of 1% Misoprostol Powder Tablets and perform the test at 50 revolutions per minute according to Method 2 under the Dissolution, using 500 mL of water as the dissolution medium. Take the medium 20 minutes after starting the test, filter through a membrane filter, and use this solution as the test solution. Separately, weigh accurately about 6 mg of misoprostol RS, and add acetonitrile to make 100 mL. Take 2.0 mL of this solution, add water to make 250 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions; NLT 75% of the labeled amount of misoprostol ($C_{22}H_{38}O_5$) is dissolved in 20 minutes.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 200 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: 52% acetonitrile solution

Flow rate: 1.5 mL/min

Assay Weigh accurately the mass of NLT 20 tablets of 1% Misoprostol Powder Tablets, and powder. Weigh accurately an amount, equivalent to about 2 mg of misoprostol ($C_{22}H_{38}O_5$), add 80 mL of 50% acetonitrile solution, shake to mix, add 50% acetonitrile solution to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about10 mg of misoprostol RS,

and dissolve in 50% acetonitrile solution to make 50 mL. Take 5.0 mL of this solution, add 50% acetonitrile solution to make 50 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of misoprostol for each solution.

$$\text{Amount (mg) of misoprostol } (C_{22}H_{38}O_5) = \text{Amount (mg) of misoprostol RS} \times \frac{A_T}{A_S} \times \frac{1}{5}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 200 nm).

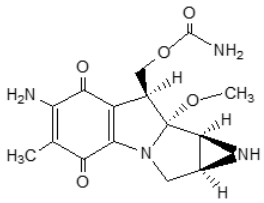
Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of methanol, water and acetonitrile (40 : 35 : 25).

Flow rate: 1.5 mL/min

Packaging and storage Preserve in tight containers.

Mitomycin C
미토마이신C



$C_{15}H_{18}N_4O_5$: 334.33

(1a*S*,8*S*,8a*R*,8b*S*)-6-Amino-4,7-dioxo-8a-methoxy-5-methyl-1,1a,2,8,8a,8bhexahydroazirino[2 ′, 3 ′: 3,4]pyrrolo[1,2-*a*]indol-8-ylmethyl carbamate [*50-07-7*]

Mitomycin C is a compound with antitumor activity obtained by culturing *Streptomyces caespitosus*.

Mitomycin C contains NLT 970 μg and NMT 1030 μg (potency) of mitomycin C ($C_{15}H_{18}N_4O_5$: 334.33) per mg, calculated on the dried basis.

Description Mitomycin C occurs as bluish purple crystals or a crystalline powder.

It is freely soluble in *N*,*N*-dimethylacetamide, slightly soluble in water or methanol and very slightly soluble in ethanol(99.5).

Identification (1) Determine the absorption spectra of aqueous solutions of Mitomycin C and mitomycin C RS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Mitomycin C and mitomycin C RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Crystallinity Meets the requirements.

pH Dissolve 1.0 g of Mitomycin C in 10 mL of water; the pH of this solution is between 5.5 and 7.5.

Absorbance $E_{1cm}^{1\%}$ (362 nm): Between 650 and 750 (1.0 mg, water, 100 mL).

Purity ***Related substances***—Perform this test rapidly after the test solution and the standard solution are prepared. Dissolve 50 mg of Mitomycin C in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution and add methanol to make exactly 100 mL. Use this solution as the standard solution. Pipet 10 μL each of the test solution and the standard solution and perform the test as directed under the Liquid Chromatography according to the following conditions, and determine peak areas of each solution by the automatic integration method; each area of the peak other than that of mitomycin C obtained from the test solution is not greater than the peak area of mitomycin C from the standard solution. In addition, the total area of the peaks other than that of mitomycin C from the test solution is not greater than 3 times the peak area of mitomycin C from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 ℃.

Mobile phase: Adjust the mixing ratio of mobile phases A and B to control the gradient elution as follows.

Mobile phase A: Add water to 20 mL of 0.5 mol/L ammonium acetate TS to make 1000 mL. Add 200 mL of methanol to 800 mL of this solution.

Mobile phase B: Add water to 20 mL of 0.5 mol/L ammonium acetate TS to make 1000 mL. Add 1000 mL of methanol to this solution.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 10	100	0
10 - 30	100 → 0	0 → 100
30 - 45	0	100

Flow rate: 1.0 mL/min

System suitability

Test for required detectability: Pipet 10 mL of the standard solution and add methanol to make exactly 100 mL. Confirm that the peak area of mitomycin C obtained

from 10 μL of this solution is equivalent to 7% to 13% of the peak area of mitomycin C from 10 μL of the standard solution.

System performance: Dissolve 25 mg of Mitomycin C and 40 mg of 3-ethoxy-4-hydroxybenzaldehyde in 50 mL of methanol. Proceed with 10 μL of this solution under the above conditions, mitomycin C and 3-ethoxy-4-hydroxybenzaldehyde are eluted in this order with the resolution between these peaks being NLT 15.

System repeatability: Repeat the test 3 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of mitomycin C is NMT 3.0%.

Time span of measurement: About 2 times the retention time of mitomycin C after the solvent peak.

Loss on drying NMT 1.0% (0.1 g, NMT 0.67 kPa, 60 ℃, 3 h.).

Sterility It meets the requirements when used in a sterile preparation.

Bacterial endotoxins Less than 50 EU per mg (potency) of mitomycin C when used in a sterile preparation.

Assay Weigh accurately about 25 mg (potency) each of Mitomycin C and mitomycin C RS, dissolve in *N*,*N*-Dimethylacetamide to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution according to the following conditions as directed under the Liquid Chromatography, and determine the peak areas, A_T and A_S, of mitomycin C.

$$\text{Potency (μg) of mitomycin C } (C_{15}H_{18}N_4O_5) = \text{Potency (μg) of mitomycin C RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 365 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with phenyl silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: Add 5 mL of diluted acetic acid(100) (1 in 20) to 40 mL of 0.5 mol/L ammonium acetate TS, and then add water to make 1000 mL. Add 200 mL of methanol to 600 mL of this solution.

Flow rate: Adjust the flow rate so that the retention time of mitomycin C is about 7 minutes.

System suitability

System performance: Dissolve about 25 mg of mitomycin C RS and 0.375 g of 3-ethoxy-4-hydroxybenzaldehyde in 50 mL of *N*,*N*-dimethylacetamide. Proceed with 10 μL of this solution according to the above conditions; mitomycin C and 3-ethoxy-4-hydroxybenzaldehyde are eluted in this order with the resolution of the two peaks being NLT 5.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of mitomycin C is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Mitomycin C for Injection
주사용 미토마이신C

Mitomycin C for Injection is an injection to be dissolved before use, and contains NLT 90.0% and NMT 110.0% of the labeled amount of mitomycin C. ($C_{15}H_{18}N_4O_5$: 334.33).

Method of preparation Prepare as directed under Injections, with Mitomycin C.

Description Mitomycin C for Injection occurs as a bluish purple powder.

Identification Weigh an amount equivalent to 2 mg (potency) of mitomycin C according to the labeled amount of Mitomycin C for Injection, and dissolve in 200 mL of water. Determine the absorption spectra of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 216 and 220 nm and between 362 and 366 nm.

pH Take exactly an amount of Mitomycin C for Injection, equivalent to 0.25 g (potency) of mitomycin C, and dissolve in 20 mL of water; the pH of the solution is 5.5 to 8.5.

Loss on drying NMT 1.0% (0.4 g, in vacuum, NMT 0.67 kPa, phosphorus pentoxide, 60 °C, 3 hours).

Sterility Meets the requirements.

Bacterial endotoxins Less than 10 EU per mg (potency) of mitomycin C.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units It meets the requirements when the Content uniformity test is performed according to the following procedure. Add exactly *V* mL of *N*,*N*-dimethylacetamide to 1 unit of Mitomycin C for Injection to contain about 0.5 mg (potency) of mitomycin C per mL, shake well to mix, centrifuge, and use the clear supernatant as the test solution. Separately, weigh accurately an amount equivalent to about 25 mg (potency) of mitomycin C RS, add *N*,*N*-dimethylacetamide to make ex-

actly 50 mL, and use this solution as the standard solution. Perform the test as directed in under the Assay of Mitomycin C as follows.

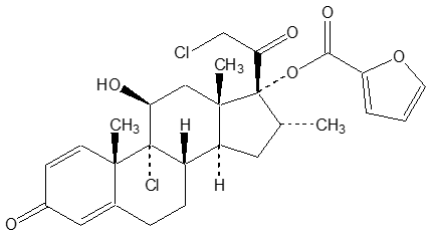
$$\text{Potency (mg) of mitomycin C } (C_{15}H_{18}N_4O_5) = \text{Potency (mg) of mitomycin C RS} \times \frac{A_T}{A_S} \times \frac{V}{50}$$

Assay Perform the test as directed under the Assay of Mitomycin C. However, take NLT 10 units of Mitomycin C for Injection, weigh accurately the mass of the contents; weigh accurately an amount equivalent to about 10 mg (potency) according to the labeled potency of Mitomycin C for Injection, and add exactly 20 mL of *N*,*N*-dimethylacetamide, shake well to mix, centrifuge, and use the clear supernatant as the test solution. Separately, weigh accurately an amount equivalent to about 25 mg (potency) of mitomycin C RS, dissolve in *N*,*N*-dimethylacetamide to make exactly 50 mL, and use this solution as the standard solution.

$$\text{Potency (mg) of mitomycin C } (C_{15}H_{18}N_4O_5) = \text{Potency (mg) of mitomycin C RS} \times \frac{A_T}{A_S} \times \frac{2}{5}$$

Packaging and storage Preserve in hermetic containers.

Mometasone Furoate
모메타손푸로에이트



$C_{27}H_{30}Cl_2O_6$: 521.43

(8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*R*,17*R*)-9-Chloro-17-(2-chloroacetyl)-11-hydroxy-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-yl furan-2-carboxylate [*83919-23-7*]

Mometasone Furoate contains NLT 97.0% and NMT 102.0% of mometasone furoate ($C_{27}H_{30}Cl_2O_6$), calculated on the dried basis.

Description Mometasone Furoate occurs as a white powder.
It is freely soluble in acetone or dichloromethane, slightly soluble in ethanol(95) and practically insoluble in water.

Identification (1) Determine the infrared spectra of Mometasone Furoate and mometasone furoate RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Proceed as directed under the Assay; the retention time of the major peak obtained from the test solution corresponds to that from the standard solution.

Optical rotation $[\alpha]_D^{25}$: Between +50° and +55° (50 mg, previously dried, ethanol(95), 10 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Mometasone Furoate according to Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(2) ***Related substances***—Weigh accurately 0.10 g of Mometasone Furoate, dissolve in dichloromethane to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately 0.1 g of mometasone furoate RS and dissolve in dichloromethane to make exactly 10 mL. Dilute portions of this solution with dichloromethane to obtain solutions having known concentrations of 0.5, 0.2, 0.1, 0.02 and 0.01 mg of mometasone furoate per mL, and use these solutions as the standard solutions of (1), (2), (3), (4) and (5), respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 40 μL each of the test solution and the standard solutions of (1), (2), (3), (4) and (5) on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate using a mixture of chloroform and ethyl acetate (3 : 1) (as the developing solvent) to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the principal spot obtained from the standard solution (3) (NMT 0.1%), and the sum of the intensities of the spots other than the principal spot obtained from the test solution is NMT 2.0%.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg each of Mometasone Furoate and mometasone furoate RS and dissolve each in ethanol(95) to make exactly 50 mL. Pipet 5.0 mL each of these solutions and add a mixture of methanol, water and acetic acid(31) (65 : 35 : 0.2) to make exactly 50 mL. Pipet 10 mL each of these solutions and 10 mL of the internal standard solution into a 50 mL-volumetric flask, add a mixture of methanol, water and acetic acid(31) (65 : 35 : 0.2) to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of mometasone furoate to the internal standard, respectively.

$$\text{Amount (mg) of mometasone furoate } (C_{27}H_{30}Cl_2O_6) = \text{Amount (mg) of mometasone furoate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh 40 mg of beclomethasone dipropionate and dissolve in a mixture of methanol, water and acetic acid(31) (65 : 35 : 0.2) to make 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of methanol and water (65 : 35).

Flow rate: 1.7 mL/min

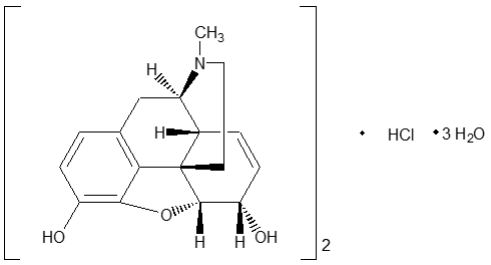
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the relative retention times are about 1.6 for beclomethasone dipropionate and 1.0 for mometasone furoate with the resolution between these peaks being NLT 4.0, and the symmetry factor for the mometasone furoate peak is NMT 1.8.

System repeatability: Repeat the test 5 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the ratios of the peak area of mometasone furoate to that of the internal standard is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Morphine Hydrochloride Hydrate
모르핀염산염수화물



Morphine Hydrochloride

$C_{17}H_{19}NO_3 \cdot HCl \cdot 3H_2O$: 375.84

(4*R*,4*aR*,7*S*,7*aR*,12*bS*)-3-Methyl-2,3,4,4a,7,7a-hexahydro-1*H*-4,12-methanobenzofuro[3,2-e]-isoquinoline-7,9-diol trihydrate hydrochloride [*6055-06-7*]

Morphine Hydrochloride Hydrate contains NLT 98.0% and NMT 102.0% of morphine hydrochloride ($C_{17}H_{19}NO_3 \cdot HCl$: 321.80), calculated on the anhydrous basis.

Description Morphine Hydrochloride Hydrate occurs as white crystals or a crystalline powder.

It is freely soluble in formic acid, soluble in water, sparingly soluble in methanol, and slightly soluble in ethanol(95).

It gradually turns yellowish brown by light.

Identification (1) Determine the absorption spectra of solutions of Morphine Hydrochloride Hydrate and morphine hydrochloride hydrate RS (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths. Also, determine the absorption spectra of solutions of Morphine Hydrochloride Hydrate and morphine hydrochloride hydrate RS in dilute sodium hydroxide TS (1 in 10000); both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Morphine Hydrochloride Hydrate and morphine hydrochloride hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) The aqueous solution of Morphine Hydrochloride Hydrate (1 in 50) responds to the Qualitative Analysis (2) for chloride.

Optical rotation $[\alpha]_D^{20}$: Between –111° and –116° (0.5 g, calculated on the anhydrous basis, water, 25 mL, 100 mm).

pH Dissolve 0.1 g of Morphine Hydrochloride Hydrate in water; the pH of this solution is between 4.0 and 6.0.

Purity (1) ***Clarity and color of solution***—Dissolve 0.40 g of Morphine Hydrochloride Hydrate in 10 mL of water; the resulting solution is clear. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at 420 nm is NMT 0.12.

(2) ***Sulfate***—Dissolve 0.20 g of Morphine Hydrochloride Hydrate in 5 mL of water and add 2 to 3 drops of barium chloride TS; the solution has no turbidity.

(3) ***Meconic acid***—Dissolve 0.20 g of Morphine Hydrochloride Hydrate in 5 mL of water, add 5 mL of dilute hydrochloric acid, and 2 drops of iron(III) chloride TS; the resulting solution does not exhibit a red color.

(4) ***Related substances***—Dissolve 0.1 g of Morphine Hydrochloride Hydrate in 10 mL of diluted ethanol(99.5) (1 in 2) and use this solution as the test solution. Pipet 1 mL of this solution, add diluted ethanol(99.5) (1 in 2) to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel (with a fluorescent indicator) for thin-layer chromatography. Next, develop the plate with a mixture of ethanol(99.5), toluene, acetone and ammonia water(28) (14 : 14 : 7 : 1) (as the developing solvent) to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from

the standard solution.

Water Between 13.0% and 15.0% (0.1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately about 0.5 g of Morphine Hydrochloride Hydrate, dissolve in 3.0 mL of formic acid, add 100 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), mix, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 32.180 mg of $C_{17}H_{19}NO_3 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Morphine Hydrochloride Injection
모르핀염산염 주사액

Morphine Hydrochloride Injection is an aqueous solution for injection. Morphine Hydrochloride Injection contains NLT 93.0% and NMT 107.0% of the labeled amount of morphine hydrochloride hydrate ($C_{17}H_{19}NO_3 \cdot HCl \cdot 3H_2O$: 375.84).

Method of preparation Prepare as directed under Injections, with Morphine Hydrochloride Hydrate.

Description Morphine Hydrochloride Injection occurs as a colorless to pale yellowish brown and clear liquid.
It gradually turns yellowish brown by light.
pH—Between 2.5 and 5.0.

Identification According to the labeled amount of Morphine Hydrochloride Injection, take an amount equivalent to 40 mg of Morphine Hydrochloride Hydrate, add water to make 20 mL, and use this solution as the test solution. Add water to 5 mL of the test solution to make 100 mL and determine the absorption spectrum as directed under Ultraviolet-visible Spectrophotometry: it exhibits a maximum between 283 nm and 287 nm. Add dilute sodium hydroxide TS to 5 mL of the test solution to make 100 mL and determine the absorption spectrum: it exhibits a maximum between 296 nm and 300 nm.

Sterility Meets the requirements.

Bacterial endotoxins Less than 1.5 EU per mg of morphine hydrochloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements

Extractable volume of injections Meets the requirements.

Assay Take exactly an amount of Morphine Hydrochloride Injection equivalent to about 20 mg of morphine hydrochloride hydrate ($C_{17}H_{19}NO_3 \cdot HCl \cdot 3H_2O$) according to the labeled amount, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of morphine hydrochloride hydrate RS, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of the test solution and the standard solution, respectively.

Amount (mg) of morphine hydrochloride hydrate ($C_{17}H_{19}NO_3 \cdot HCl \cdot 3H_2O$)
= Amount (mg) of morphine hydrochloride hydrate RS $\times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 284 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 0.73 g of sodium 1-heptanesulfonate in 720 mL of water, add 280 mL of methanol and 10 mL of acetic acid(100), mix, and filter.

Flow rate: 1.5 mL/min

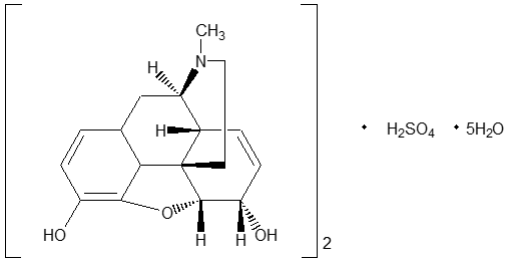
System suitability

System performance: Proceed with 25 μL of the standard solution under the above operating conditions; the symmetry factor is NMT 2.0.

System repeatability: Repeat the test 6 times according to the above conditions with 25 μL each of the standard solution; the relative standard deviation of the peak area is NMT 2.0%.

Packaging and storage Preserve in light-resistant, hermetic containers.

Morphine Sulfate Hydrate
모르핀황산염수화물



Morphine Sulfate $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$: 758.83
(4*R*,4*aR*,7*S*,7*aR*,12*bS*)-3-Methyl-2,3,4,4a,7,7a-hexahydro-1*H*-4,12-methanobenzofuro[3,2-e]-isoquinoline-7,9-diol pentahydrate sulfuric acid [*6211 -15 -0*]

Morphine Sulfate Hydrate contains NLT 98.0% and NMT 102.0% of morphine sulfate [$(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4$: 668.75], calculated on the anhydrous basis.

Description Morphine Sulfate Hydrate occurs as white lustrous crystals like hair or silk, columnar crystals, or a white crystalline powder. It is odorless and gradually loses its water of crystallization when left in the air.
It is freely soluble in hot water, soluble in water, sparingly soluble in ethanol(95) or warmed ethanol and practically insoluble in chloroform or ether.
It turns dark by light.

Identification (1) Take 1 mg of Morphine Sulfate Hydrate in a porcelain crucible or a watch glass, add 0.5 mL of sulfuric acid containing 1 drop of formaldehyde solution TS per mL of sulfuric acid; the resulting solution exhibits a deep violet color at once, which quickly changes to a deep bluish purple color (distinction from codeine, which turns deep purplish blue right away, and from hydromorphone, which turns at first yellowish brown, changing to reddish purple, and then to purple).

(2) Dissolve 5 mg of Morphine Sulfate Hydrate in 5 mL of sulfuric acid, add 1 drop of iron(III) chloride TS, mix, and heat in boiling water for 2 minutes; the resulting solution exhibits a blue color. Thereto, add 1 drop of nitric acid; the solution turns dark reddish brown (codeine and ethylmorphine give the same color reactions, while hydromorphone and papaverine do not produce the same color reactions).

(3) Determine the infrared spectra of Morphine Sulfate Hydrate and morphine sulfate hydrate RS, previously dried 1 hour at 145 ℃, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit maxima at the same wavenumbers.

(4) The aqueous solution of Morphine Sulfate Hydrate (1 in 50) responds to the Qualitative Analysis for sulfate.

Optical rotation $[\alpha]_D^{25}$: Between –107° and –109.5° (0.2 g, calculated on the anhydrous basis, water, 10 mL, 100 mm).

Purity (1) ***Acid***—Dissolve 0.5 g of Morphine Sulfate Hydrate in 15 mL of water, add 1 drop of methyl red TS, and titrate with 0.02 mol/L sodium hydroxide VS until a yellow color appears; the volume consumed is NMT 0.50 mL.

(2) ***Chloride***—Add 1 mL of 2 mol/L nitric acid TS or 1 mL of silver nitrate TS to 10 mL of the aqueous solution (1 in 100) of Morphine Sulfate Hydrate; no precipitate or turbidity is formed immediately.

(3) ***Ammonium salt***—Transfer 0.2 g of Morphine Sulfate Hydrate in 5 mL of 1 mol/L sodium hydroxide TS and heat on a steam bath for 1 minute; no odor of ammonia is perceptible.

(4) ***Related substances***—Transfer 1.0 g of Morphine Sulfate Hydrate into a separatory funnel containing 10 mL of 1 mol/L sodium hydroxide TS, shake well with three successive portions of 15 mL, 10 mL and 10 mL of chloroform for extraction, and filter the chloroform layer through a filter paper previously moistened with chloroform. Add 5 mL of water to this chloroform extract, shake to mix, and evaporate the chloroform layer to dryness on a steam bath. To the residue, add 10.0 mL of 0.01 mol/L sulfuric acid and heat gently until it is dissolved. After cooling, add 2 drops of methyl red TS and titrate excess acid with 0.02 mol/L sodium hydroxide VS; the volume consumed is NLT 7.5 mL (1.5%).

Water Between 10.4% and 13.4% (0.2 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately about 24 mg of Morphine Sulfate Hydrate, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately a suitable amount of morphine sulfate hydrate RS (measure the water content in advance), dissolve in the mobile phase to obtain a solution having a known concentration of 0.24 mg of anhydrous morphine sulfate per mL, and use this solution as the standard solution. Prepare the standard solution immediately before use. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of morphine sulfate for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of morphine sulfate } [(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4] = 100 \times C \times \frac{A_T}{A_S}$$

C: Concentration (mg/mL) of anhydrous morphine sulfate in the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 284 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 30 cm in length, packed with

octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: Dissolve 0.73 g of sodium 1-heptanesulfonate in 720 mL of water, add 280 mL of methanol and 10 mL of acetic acid(100), mix, and filter.

Flow rate: 1.5 mL/min

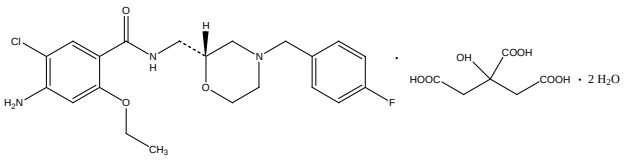
System suitability

System performance: Proceed with 25 μL of the standard solution according to the above conditions; the symmetry factor is NMT 2.0.

System repeatability: Repeat the test 6 times with 25 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Mosapride Citrate Hydrate
모사프리드시트르산염수화물



and enantiomer

$C_{21}H_{25}ClFN_3O_3 \cdot C_6H_8O_7 \cdot 2H_2O$: 650.05

4-Amino-5-chloro-2-ethoxy-*N*-{[(2*RS*)-4-(4-fluorobenzyl)morpholin-2-yl]methyl}-benzamide monocitrate dihydrate [*636582-62-2*]

Mosapride Citrate Hydrate contains NLT 98.5% and NMT 101.0% of mosapride citrate ($C_{21}H_{25}ClFN_3O_3 \cdot C_6H_8O_7$: 614.02), calculated on the anhydrous basis.

Description Mosapride Citrate Hydrate occurs as a white to yellowish white crystalline powder.

It is freely soluble in *N*,*N*-dimethylformamide or acetic acid(100), sparingly soluble in methanol, slightly soluble in ethanol(99.5) and practically insoluble in water.

A solution of Mosapride Citrate Hydrate in *N*,*N*-dimethylformamide (1 in 20) shows no optical rotation.

Identification (1) Determine the absorption spectra of solutions of Mosapride Citrate Hydrate and mosapride citrate hydrate RS in methanol (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Mosapride Citrate Hydrate and mosapride citrate hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) A solution of Morphine Hydrochloride Hydrate in *N*,*N*-dimethylformamide (1 in 10) responds to the Qualitative Analysis (1) for citrate.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Mosapride Citrate Hydrate in a platinum crucible according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 0.10 g of Mosapride Citrate Hydrate in 50 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution and add methanol to make exactly 50 mL. Pipet 1 mL of this solution, add methanol to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area from each solution by the automatic integration method; the peak area of the relative retention time of about 0.47 for mosapride in the test solution is not greater than 3 times the peak area of mosapride in the standard solution, and each peak area other than that of mosapride and mentioned above is not greater than the peak area of mosapride in the standard solution. Also, the total peak areas other than that of mosapride in the test solution is not greater than 5 times the peak area of mosapride in the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 274 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Use mobile phases A and B to control a step or gradient elution as follows.

Mobile phase A: Dissolve 8.82 g of trisodium citrate dihydrate in 800 mL of water, adjust the pH to 4.0 with dilute hydrochloric acid, and add water to make 1000 mL.

Mobile phase B: Acetonitrile

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 35	80 → 45	20 → 55

Flow rate: 1.0 mL/min

System suitability

Test for required detectability: Pipet 4 mL of the standard solution and add methanol to make exactly 20 mL. Confirm that the peak area of mosapride obtained from 5 μL of this solution is equivalent to 15% to 25% of the peak area of mosapride from the standard solution.

System performance: Proceed with 5 μL of the standard solution according to the above conditions; the number of theoretical plates and the symmetry factor of the peak of mosapride are NLT 40000 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of mosapride is NMT 5.0%.

Time span of measurement: For 35 minutes beginning after the solvent peak.

Water Between 5.0% and 6.5% (0.5 g, volumetric titration, back titration).

Residue on ignition NMT 0.1% (1 g, platinum crucible).

Assay Weigh accurately about 0.5 g of Mosapride Citrate Hydrate, dissolve it in 70 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 61.40 mg of $C_{21}H_{25}ClFN_3O_3 \cdot C_6H_8O_7$

Packaging and storage Preserve in well-closed containers.

Mosapride Citrate Tablets
모사프리드시트르산염 정

Mosapride Citrate Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of mosapride citrate ($C_{21}H_{25}ClFN_3O_3 \cdot C_6H_8O_7$: 614.02).

Method of preparation Prepare as directed under Tablets, with Mosapride Citrate Hydrate.

Identification (1) Weigh an amount of powdered Mosapride Citrate Tablets, equivalent to 10 mg of mosapride citrate ($C_{21}H_{25}ClFN_3O_3 \cdot C_6H_8O_7$) according to the labeled amount, and add 10 mL of dilute acetic acid, shake to mix for 10 minutes, and filter. To 5 mL of the filtrate, add 0.3 mL of Dragendorff's TS; orange precipitates are formed.

(2) Determine the absorption spectrum of the test solution obtained from the Assay as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima at wavelengths of 271 nm to 275 nm and 306 nm to 310 nm.

Purity ***Related substances*—**Powder NLT 20 tablets of Mosapride Citrate Tablets. Weigh an amount of this powder, equivalent to 10 mg of mosapride citrate ($C_{21}H_{25}ClFN_3O_3 \cdot C_6H_8O_7$) according to the labeled amount, wet with 1 mL of water. Add 9 mL of methanol, shake to mix for 20 minutes, centrifuge, and use the clear supernatant as the test solution. Pipet 1 mL of this solution and add methanol to make exactly 20 mL. Take 2 mL of this solution, add methanol to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of each solution as directed in the automatic integration method; the peak area having the relative retention time of about 0.60 and 0.85 with respect to mosapride obtained from the test solution is not larger than the peak area of mosapride obtained from the standard solution, and the peak areas other than mosapride peak and the above mentioned peaks from the test solution are not larger than 2/5 of the peak area of mosapride from the standard solution. Also, the total area of the peaks other than the peak of mosapride obtained from the test solution is not larger than 2 times the peak area of mosapride from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase A, mobile phase B and flow rate, proceed according to the operating conditions under the Purity (2) of Mosapride Citrate Hydrate.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 40	85 → 45	15 → 55

System suitability

Test for required detectability: Pipet 1 mL of the standard solution, and add methanol to make exactly 25 mL. Confirm that the peak area of mosapride obtained from 10 μL of this solution is equivalent to 3.0% to 5.0% of the peak area of mosapride from the standard solution.

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the number of theoretical plates and the symmetry factor of the peak of mosapride are NLT 40000 plates and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of mosapride is NMT 3.0%.

Time span of measurement: For 40 minutes beginning after the solvent peak.

Dissolution Perform the test with 1 tablet of Mosapride Citrate Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of Solution 2 as the dissolution medium. Take NLT 20 mL of the dissolved solution after 45 minutes from the start of the dissolution test, and filter through a membrane filter with a pore size of NMT 0.45 μm. Discard the first 10 mL of the filtrate, take exactly V mL of the subsequent filtrate, add the dissolution medium to make exactly V' mL so that the solution contains about 2.8 μg of mosapride citrate ($C_{21}H_{25}ClFN_3O_3 \cdot C_6H_8O_7$), according to the labeled amount, per mL, and use this solution as the test solution. Separately, weigh accurately about 30 mg of the mosapride citrate RS (previously determined the water content in the same manner as for Mosapride Citrate Hydrate),

and dissolve in the mobile phase to make exactly 100 mL. Pipet 2 mL of this solution, add the mobile phase to it make exactly 200 mL, and use this solution as the standard solution. Take exactly 50 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas A_T and A_S of mosapride for each solution. The dissolution rate of Mosapride Citrate Tablets for 45 minutes is NLT 80%.

$$\text{Dissolution rate (\%) for the labeled amount of mosapride citrate } (C_{21}H_{25}ClFN_3O_3\cdot C_6H_8O_7) = W_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 9$$

W_S: Amount (mg) of mosapride citrate RS, calculated on the anhydrous basis

C: Labeled amount (mg) of mosapride citrate ($C_{21}H_{25}ClFN_3O_3\cdot C_6H_8O_7$) per tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 274 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 8.82 g of trisodium citrate dihydrate in 800 mL of water, adjust the pH to 3.3 with dilute hydrochloric acid, and add water to make 1000 mL. To 240 mL of this solution. add 90 mL of methanol and 70 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of mosapride is about 9 minutes.

System suitability

System performance: Proceed with 50 μL of the standard solution according to the above conditions; the number of theoretical plates and the symmetry factor of the peak of mosapride are NLT 4000 plates and NMT 2.0, respectively.

System repeatability: Repeat the test 6 times with 50 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of mosapride is NMT 2.0%.

Uniformity of dosage units Meets the requirements.

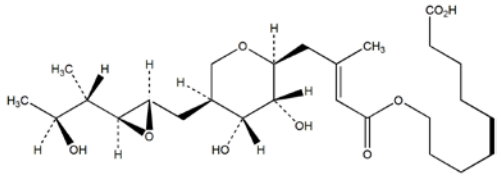
Assay Weigh exactly and powder NLT 20 tablets of Mosapride Citrate Tablets. Weigh accurately a portion of this powder, equivalent to about 10 mg of mosapride citrate ($C_{21}H_{25}ClFN_3O_3\cdot C_6H_8O_7$), and wet with 2 mL of water. Next, add 70 mL of methanol, shake to mix for 20 minutes, add methanol to make exactly 100 mL, and centrifuge. Pipet 10 mL of the clear supernatant, add methanol to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 53 mg of mosapride citrate RS (previously determined the water content in the same manner as for Mosapride Citrate Tablets), dissolve in methanol to make exactly 100 mL. Pipet 2 mL of this solution, add methanol to make exactly 50 mL, and use this solution as the standard solution. Determine the absorbances of the test solution and the standard solution, A_T and A_S, at the wavelength of 273 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of mosapride citrate } (C_{21}H_{25}ClFN_3O_3\cdot C_6H_8O_7) = W_S \times \frac{A_T}{A_S} \times \frac{1}{5}$$

W_S: Amount (mg) of mosapride citrate RS, calculated on the dried basis

Packaging and storage Preserve in tight containers.

Mupirocin
무피로신



$C_{26}H_{44}O_9$: 500.62

9-[(*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-3,4-Dihydroxy-5-[[(2*S*,3*S*)-3-[(2*S*,3*S*)-3-hydroxybutan-2-yl]-oxiran-2-yl]methyl]oxan-2-yl]-3-methylbut-2-enoyl]oxynonanoic acid [*12650-69-0*]

Mupirocin is a compound prepared by culturing *Peudomonas fluorescens* and has an antibacterial activity. Mupirocin contains NLT 920 μg (potency) and NMT 1020 μg ($C_{26}H_{44}O_9$: 500.62), calculated on the anhydrous basis.

Description Mupirocin occurs as a white powder.
It is freely soluble in methanol, in ethanol(95), in acetone or in chloroform, slightly soluble in ether and very slightly soluble in water.

Identification Determine the infrared spectra of Mupirocin and mupirocin RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

pH The pH of a saturated solution of Mupirocin is between 3.5 and 4.5.

Purity ***Total related substances***—Weigh accurately about 0.1 g of Mupirocin, dissolve in a mixture of 0.1 mol/L sodium acetate buffer (pH 4.0) and methanol (1 : 1), make exactly 10 mL, and use this solution as the test solution A. Then, pipet 5 mL of the test solution A, add the mixture of 0.1 mol/L sodium acetate buffer (pH 4.0)

and methanol (1 : 1) to make exactly 200 mL, and use this solution as the test solution B. Perform the test with 20 μL of the test solution B as directed under the Liquid Chromatography according to the following conditions and calculate the peak area of mupirocin. Separately, perform the test with 20 μL of the test solution A as directed under the Liquid Chromatography according to the following conditions and calculate the areas of peaks for each related substance other than the peak of the solvent. (NMT 8.0%)

$$\text{Total content (\%) of related substances} = \frac{A_2}{A_1 + A_2} \times 100$$

$$A_1: \frac{Peak\ area\ of\ mupirocin}{Amount\ (mg) of\ mupirocin\ in\ 1\ mL\ of\ test\ solution\ B}$$

$$A_2: \frac{Total\ area\ of\ peaks\ of\ related\ substances - total\ area\ of\ peak\ of\ solvent}{Amount\ (mg) of\ mupirocin\ in\ 1\ mL\ of\ test\ solution\ A}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (6 μm in particle diameter).

Mobile phase: A mixture of 0.1 mol/L ammonium acetate buffer solution (pH 5.7) and tetrahydrofuran (75 : 25).

Flow rate: 2.0 mL/min

Water NMT 1.0% (1.0 g, volumetric titration, direct titration).

Assay Weigh accurately about 11 mg (potency) each of Mupirocin and mupirocin lithium RS, dissolve each in 25 mL of acetonitrile, add phosphate buffer (pH 6.3) to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of mupirocin from each solution.

$$\text{Potency (μg) of mupirocin } (C_{26}H_{44}O_9) = \text{Potency (μg) of mupirocin lithium RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 229 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of phosphate buffer (pH 6.3) and acetonitrile (3 : 1).

Flow rate: 2.0 mL/min

System suitability

System performance: Pipet 10 mL of the standard solution, adjust the pH to 2.0 with 6 mol/L hydrochloric acid, allow to stand for 2 hours, adjust the pH to 6.3 ± 0.2 with 5 mol/L sodium hydroxide, and use this solution as the system suitability solution. Proceed with this solution according to the above conditions; the relative retention times of the mupirocin acid hydrolysate and mupirocin are 0.7 and 1.0, respectively, with the resolution between these peaks being NLT 2.0. Proceed with the standard solution according to the above conditions; the number of theoretical plates and the symmetry factor of the peak of mupirocin are NLT 1500 and NMT 2.0, respectively.

System repeatability: Repeat the test 5 times with the standard solution according to the above conditions; the relative standard deviation of the mupirocin peak area is NMT 2.0%.

Phosphate buffer solution, pH 6.3—Adjust the pH of solution containing 0.05 mol/L sodium dihydrogen phosphate monohydrate to 6.3 ± 0.2 with 10 mol/L sodium hydroxide.

Packaging and storage Preserve in tight containers.

Mupirocin Ointment
무피로신 연고

Mupirocin Ointment contains NLT 90.0% and NMT 120.0% of the labeled amount of mupirocin ($C_{26}H_{44}O_9$: 500.62).

Method of preparation Prepare as directed under Ointments, with Mupirocin.

Identification Perform the test as directed under the Assay; the retention time of the major peak from the test solution is the same as that of the major peak from the standard solution in the obtained chromatogram.

Assay Perform the test according to the Assay under Mupirocin. However, weigh accurately an amount of Mupirocin Ointment, equivalent to about 10 mg (potency) according to the labeled potency, dissolve in 25 mL of acetonitrile, add phosphate buffer solution, pH 6.3, to make exactly 100 mL, and use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Mupirocin Calcium Cream
무피로신칼슘 크림

Mupirocin Calcium Cream contains NLT 90.0% and NMT 120.0% of the labeled amount of mupirocin

($C_{26}H_{44}O_9$: 500.62).

Method of preparation Prepare as directed under Creams, with Mupirocin Calcium Hydrate.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

pH Dissolve an amount of Mupirocin Calcium Cream, equivalent to 0.1 g (potency) of mupirocin, in 10 mL of water; the pH of this solution is between 6.0 and 8.0.

Purity ***Related substances*****—**Perform the test as directed under the Assay. However, weigh accurately an amount of Mupirocin Calcium Cream, equivalent to about 50 mg (potency), add 5 mL of tetrahydrofuran, and mix well. Add 5 mL of 0.1 mol/L sodium acetate TS, centrifuge, filter the lower layer, and use this filtrate as the test solution. If a preservative is included, prepare a standard solution of the preservative and determine the position of the preservative peak in the test solution (NMT 8.5%).

$$\text{Content (\%) of related substances} = \frac{A_R}{A_T} \times (100)$$

A_T: Sum of all peak areas other than the preservative peak from the test solution

A_R: Sum of peak areas of all related substances

Assay Weigh accurately an amount of Mupirocin Calcium Cream, equivalent to about 20 mg (potency) according to the labeled potency, dissolve in 75 mL of a mixture of 0.5 mol/L sodium phosphate buffer solution, pH 6.3, and tetrahydrofuran (2 : 1), add 0.5 mol/L phosphate buffer solution, pH 6.3, to make exactly 200 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of mupirocin RS, dissolve in 75 mL of a mixture of 0.5 mol/L sodium phosphate buffer solution, pH 6.3, and tetrahydrofuran (2 : 1), add 0.5 mol/L phosphate buffer solution, pH 6.3, to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S of mupirocin.

$$\text{Potency (μg) of mupirocin } (C_{26}H_{44}O_9) = \text{Potency (μg) of mupirocin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octylsilane silica gel for liquid chromatography (10 μm in particle diameter).

Flow rate: 1.0 mL/min

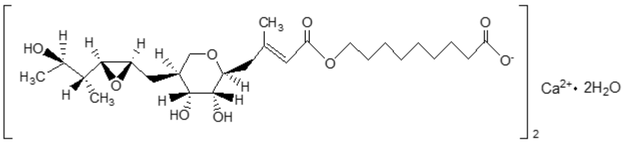
Mobile phase: Maintain for 10 minutes with solution A, then increase solution B concentration linearly to 100% in 35 minutes, and maintain solution B for 20 minutes.

Solution A: A mixture of 0.1 mol/L ammonium acetate buffer solution, pH 5.7, and tetrahydrofuran (3 : 1).

Solution B: A mixture of 0.1 mol/L ammonium acetate buffer solution, pH 5.7, and tetrahydrofuran (7 : 2).

Packaging and storage Preserve in tight containers.

Mupirocin Calcium Hydrate
무피로신칼슘수화물



$C_{52}H_{86}O_{18}Ca \cdot 2H_2O$: 1075.34

Calcium 9-[(*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-[[(2*S*,3*S*)-3-[(2*S*,3*S*)-3-hydroxybutan-2-yl]oxiran-2-yl]methyl]oxan-2-yl]-3-methylbut-2-enoyl]oxynonanoate dihydrate [*115074-43-6*]

Mupirocin Calcium Hydrate is the calcium salt of a compound prepared by culturing *Pseudomonas fluorescens*, which has an antibacterial activity.

Mupirocin Calcium Hydrate contains NLT 895 μg (potency) and NMT 970 μg (potency) per mg of mupirocin ($C_{26}H_{44}O_9$: 500.62), calculated on the anhydrous basis.

Description Mupirocin Calcium Hydrate occurs as a white powder and has a bitter taste.

It is freely soluble in methanol and slightly soluble in water or ethanol(95).

Identification (1) To 1 mL of a solution of Mupirocin Calcium Hydrate in methanol (1 in 200), add 4 mL of hydroxylamine perchlorate-ethanol (99.5) TS and 1 mL of *N*,*N'*-dicyclohexylcarbodiimide-ethanol (99.5) TS, shake well to mix, and allow to stand in lukewarm water for 20 minutes. After cooling, add 1 mL of iron(III) perchlorate-ethanol (99.5) TS and shake to mix; the resulting solution exhibits a deep violet color.

(2) Determine the absorption spectrum of a solution of Mupirocin Calcium Hydrate (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 219 nm and 224 nm.

(3) Determine the absorption spectrum of Mupirocin Calcium Hydrate as directed in the paste method under the Mid-infrared Spectroscopy; it exhibits absorption at the wavenumbers about 1708 cm^{-1}, 1648 cm^{-1}, 1558 cm^{-1}, 1231 cm^{-1}, 1151 cm^{-1} and 894 cm^{-1}.

(4) A solution of Mupirocin Calcium Hydrate (3 in

1000) responds to the Qualitative Analysis (3) for calcium salt.

Optical rotation $[\alpha]_D^{20}$: Between -16° and -20° (1 g, calculated on the anhydrous basis, methanol, 20 mL, 100 mm).

Purity (1) ***Chloride***—Weigh accurately about 50 mg of Mupirocin Calcium Hydrate, dissolve in a mixture of 1 mL of 2 mol/L nitric acid and 15 mL of methanol, use this solution as the test solution, and perform the test. Prepare the control solution by adding a mixture of 1 mL of 2 mol/L nitric acid and 15 mL of methanol to 0.7 mL of 0.02 mol/L hydrochloric acid (NMT 0.5%).

(2) ***Related substances***—Dissolve about 50 mg of Mupirocin Calcium Hydrate in a mixture of 0.1 mol/L acetic acid-sodium acetate buffer (pH 4.0) and tetrahydrofuran solution (3 in 4) (1 : 1) to make 10 mL and use this solution as the test solution (1). Pipet 2 mL of this solution, add a mixture of 0.1 mol/L acetic acid-sodium acetate buffer (pH 4.0) and tetrahydrofuran solution (3 in 4) (1 : 1) to make exactly 100 mL and use this solution as the test solution (2). Preserve these test solutions at a temperature between 4 and 8 °C. Perform the test with exactly 20 μL each of the test solutions (1) and (2) as directed under the Liquid Chromatography according to the following conditions. Determine the areas of each peak obtained from the test solutions (1) and (2) by the automatic integration method; the amount of the principal related substance having a relative retention time of about 0.7 with respect to mupirocin is NMT 4.0%, and the total amount of related substances other than the solvent and mupirocin is NMT 6.0%.

$$\text{Content (\%) of the principal related substance} = \frac{A_\mathrm{i}}{A + A_\mathrm{m}} \times 100 \times \frac{\mathrm{P} \times 100}{100 - \dfrac{A \times 100}{A + A_\mathrm{m}}}$$

$$\text{Total content (\%) of related substances} = \frac{A}{A + A_\mathrm{m}} \times 100 \times \frac{\mathrm{P} \times 100}{100 - \dfrac{A \times 100}{A + A_\mathrm{m}}}$$

A: Total area of peaks other than the peaks for the solvent and mupirocin obtained from the test solution (1)

A_i: Area of the peak having the relative retention time of about 0.7 with respect to mupirocin obtained from the test solution (1)

A_m: A value obtained by multiplying the peak area of mupirocin obtained from the test solution (2) by 50

P: Potency of mupirocin ($C_{26}H_{44}O_9$) per mg of Mupirocin Calcium Hydrate, obtained as directed under the Assay

Operating conditions

Detector, column, column temperature, mobile phase and flow rate: Proceed as directed under the operating conditions under the Assay.

System suitability

System performance: Proceed as directed under the system suitability under the Assay.

Test for required detectability: Pipet 1 mL of the test solution (2) and add a mixture of 0.1 mol/L acetic acid-sodium acetate buffer (pH 4.0) and tetrahydrofuran solution (3 in 4) (1 : 1) to make exactly 20 mL. Confirm that the peak area of mupirocin obtained from 20 μL of this solution is equivalent to 4% to 6% of the peak area of mupirocin obtained from 20 μL of the test solution (2).

System repeatability: Repeat the test 6 times with 20 μL each of the test solutions (2) according to the above conditions; the relative standard deviation of the peak areas of mupirocin is NMT 2.0%.

Time span of measurement: About 3 times the retention time of mupirocin beginning after the solvent peak.

0.1 mol/L acetic acid-sodium acetate buffer solution (pH 4.0)—Dissolve 13.61 g of sodium acetate trihydrate in about 750 mL of water, adjust the pH to 4.0 with acetic acid(100), and add water to make 1000 mL.

Water Between 3.0% and 4.5% (0.5 g, volumetric titration, direct titration).

Assay Weigh accurately about 20 mg (potency) each of Mupirocin and mupirocin lithium RS, dissolve each in a mixture of 0.1 mol/L acetic acid-sodium acetate buffer (pH 4.0) and tetrahydrofuran solution (3 in 4) (1 : 1) to make exactly 200 mL, and use these solutions as the test solution and the standard solution, respectively. Preserve these solutions at a temperature between 4 and 8 °C. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of mupirocin from each solution.

$$\text{Potency (μg) of mupirocin } (C_{26}H_{44}O_9) = \text{Potency (μg) of mupirocin lithium RS} \times \frac{A_\mathrm{T}}{A_\mathrm{S}}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase A: Dissolve 7.71 g of ammonium acetate in 750 mL of water, adjust the pH to 5.7 with acetic acid(100), and add water to make 1000 mL. To 300 mL of this solution, add 100 mL of tetrahydrofuran.

Flow rate: Adjust the flow rate so that the retention time of mupirocin is about 12.5 minutes.

System suitability

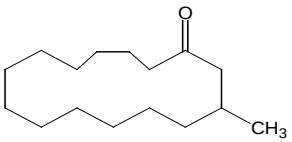
System performance: Dissolve about 20 mg of mupirocin lithium RS and about 5 mg of ethyl p-hydroxybenzoate in a mixture of 0.1 mol/L acetic acid-sodium acetate buffer (pH 4.0) and tetrahydrofuran solu-

tion (3 in 4) (1 : 1) to make 200 mL. Proceed with 20 μL of this solution according to the above conditions; mupirocin and ethyl p-hydroxybenzoate eluted in this order with the resolution between these peaks being NLT 12.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of mupirocin is NMT 1.0%.

Packaging and storage Preserve in tight containers.

l-Muscone
l-무스콘



$C_{16}H_{30}O$: 238.41

(3*R*)-3-Methyl-cyclopentadecanone, [*10403-00-6*]

l-Muscone contains NLT 98.0% of *l*-muscone ($C_{16}H_{30}O$).

Description *l*-Muscone occurs as a colorless to pale yellow oily liquid and has a slight characteristic odor.
It is very soluble in chloroform, in ether, in *n*-hexane or in ethanol(95) and very slightly soluble in water.

Identification (1) Determine the infrared spectrum of *l*-Muscone as directed under the liquid film method under the Mid-infrared Spectroscopy; it exhibits absorption at the wavenumbers of about 2928 cm^{-1}, 1713 cm^{-1}, 1460 cm^{-1} and 1368 cm^{-1}.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Optical rotation $[\alpha]_D^{20}$: Between -11° and -14° (110 mg, methanol, 10 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 50 mg of *l*-Muscone in 10 mL of ethanol(95); the resulting solution is colorless to pale yellow and clear.

(2) ***Heavy metals***—Proceed with 1.0 g of *l*-Muscone according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve 50 mg of *l*-Muscone in 5 mL of ethanol(95) and use this solution as the test solution. Pipet 2 mL of this solution, add ethanol(95) to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of petroleum ether and ether (19 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly *p*-anisaldehyde-sulfuric acid TS on the dried plate and heat it at 110 ℃ for 5 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Assay Weigh accurately about 20 mg of *l*-Muscone, add 10.0 mL of the internal standard solution, dissolve in chloroform to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of *l*-muscone RS, add 10.0 mL of the internal standard solution, dissolve in chloroform to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 3 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of *l*-muscone to that of the internal standard, respectively.

$$\text{Amount of } l\text{-muscone } (C_{16}H_{30}O) \text{ (mg)} = \text{Amount of } l\text{-muscone RS (mg)} \times (Q_T / Q_S)$$

Internal standard solution—A solution of cyclopentadecanone in chloroform (1 in 500).

Operating conditions

Detector: A hydrogen flame-ionization detector

Column: A fused silica column about 0.32 mm in internal diameter and about 30 m in length, coated inside with dimethylpolysiloxane for gas chromatography, 0.25 μm in thickness.

Column temperature: A constant temperature of about 180 °C.

Sample injection port temperature: 250 ℃

Detector temperature: 260 ℃

Carrier gas: Nitrogen

Flow rate: 1.0 mL/min

Split ratio: 10 : 1

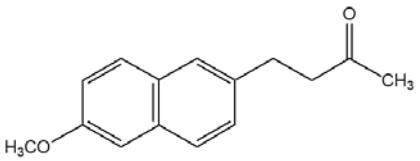
System suitability

System performance: Proceed with 3 μL of the standard solution according to the above conditions; the internal standard and *l*-muscone are eluted in this order with the resolution between these peaks being NLT 1.5.

System repeatability: Repeat the test 6 times with 3 μL each of the standard solution according to the above conditions; the relative standard deviation of the ratios of the peak area of *l*-muscone to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Nabumetone
나부메톤



$C_{15}H_{16}O_2$: 228.29

4-(6-Methoxynaphthalen-2-yl)butan-2-one [*42924-53-8*]

Nabumetone contains NLT 98.0% and NMT 101.0% of nabumetone ($C_{15}H_{16}O_2$), calculated on the anhydrous basis.

Description Nabumetone occurs as white to pale yellow crystals or a crystalline powder.

It is freely soluble in acetone, sparingly soluble in methanol and ethanol(95) and practically insoluble in water.

Melting point—Between 79 and 84 ℃.

Identification (1) Determine the infrared spectra of Nabumetone and nabumetone RS, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Nabumetone as directed under Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Weigh accurately about 0.1 g of Nabumetone, dissolve in acetonitrile to make exactly 100 mL, and use this solution as the test solution. Perform the test with 10 μL of the test solution as directed under the Liquid Chromatography according to the following conditions, and calculate the amount of related substances; the related substances with the relative retention time of 2.7 is NMT 0.3%, the amount of the other individual related substances is NMT 0.1%, and the amount of the total related substances is NMT 0.8%.

$$\text{Amount of related substances (\%)} = 100FA_i/(A_N+\sum FA_i)$$

F: Relative correction factor (related substances with the relative retention time of 0.73 is 0.12, related substances with the relative retention time of 2.7 is 0.10, related substances with the relative retention time of 0.93 is 0.25, related substances with the relative retention time of 1.2 is 0.42, related substances with the relative retention time of 0.85 is 0.94, related substances with the relative retention time of 1.9 is 1.02, and related substances with the relative retention time of 2.6 is 0.91.)

A_i: Peak area of each related substance

A_N: Peak area of Nabumetone

Operating conditions

Follow the operating conditions in Assay for the detector, column, mobile phase and flow rate.

System suitability

System performance: Weigh each of Nabumetone RS and nabumetone related substance I RS, dissolve in acetonitrile, and dilute suitably to make the concentration of the solution of about 1 mg/mL and 1 μg/mL, respectively. Use this solution as the test solution for system suitability. Proceed with 10 μL of this solution according to the above conditions; the relative retention time of the peaks of nabumetone and related substances I are 1.0 and about 0.9, respectively, and the resolution between the two peaks is NLT 1.5.

System repeatability: Repeat the test 5 times with each 10 μL of the system suitability solution; the relative standard deviation of the peak area of nabumetone is NMT 2.0%.

Water NMT 0.2% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.1 g of Nabumetone, dissolve in acetonitrile to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of nabumetone RS, dissolve in acetonitrile to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak areas, A_T and A_S, of nabumetone.

$$\text{Amount of nabumetone } (C_{15}H_{16}O_2) \text{ (mg)} = \text{Amount of nabumetone RS (mg)} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (4 μm in particle diameter).

Mobile phase: Control the step or gradient elution by mixing the mobile phases A and B as directed under the following table.

Mobile phase A: A mixture of water and acetic acid(100) (999 : 1).

Mobile phase B: A mixture of acetonitrile and tetrahydrofuran (7 : 3).

Time (min)	Mobile Phase A (vol%)	Mobile Phase B (vol%)
0	60	40
0 - 12	60	40
12 - 28	60 → 20	40 → 80
28 - 29	20 → 60	80 → 40
29 - 30	60	40

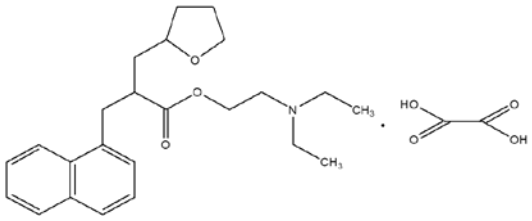
Flow rate: 1.3 mL/min

System suitability

System repeatability: Repeat the test 5 times according to the above conditions with 10 μL each of the standard solution; the relative standard deviation of the peak area of nabumetone is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Nafronyl Oxalate
나프로닐옥살산염



$C_{24}H_{33}NO_3 \cdot C_2H_2O_4$: 473.56

Tetrahydro-α-(1-naphthylmethyl)-2-furanpropionic acid 2-(diethylamino)ethyl ester oxalate (1 : 1), [*3200-06-4*]

Nafronyl Oxalate, when dried, contains NLT 98.0% and NMT 100.5% of nafronyl oxalate ($C_{24}H_{33}NO_3 \cdot C_2H_2O_4$).

Description Nafronyl Oxalate occurs as a white crystalline powder, and it is odorless.

It is freely soluble in water, methanol and chloroform, sparingly soluble in acetone and practically insoluble in ether.

Melting point—Between 107 and 109 ℃.

Identification (1) Add calcium chloride TS to the aqueous solution of Nafronyl Oxalate; a white precipitate is produced and it is insoluble in acetic acid but soluble in hydrochloric acid. The oxalate dissolved in the hydrochloric acid bleaches potassium permanganate TS.

(2) Determine the infrared spectra of Nafronyl Oxalate and nafronyl oxalate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Sulfate***—Proceed with about 10 g of Nafronyl Oxalate as directed under the Sulfate. Prepare the control solution with 0.4 mL of 0.005 mol/L sulfuric acid (NMT 0.002%).

(2) ***Heavy metals***—Weigh about 4 g of Nafronyl Oxalate, add 2 mL of 0.1 mol/L hydrochloric acid and 25 mL of water to make 25 mL, and perform the test according to Method 1. Prepare the control solution with 2.0 mL of lead standard solution (NMT 5 ppm).

(3) ***Arsenic***—Proceed with about 1.3 g of Nafronyl Oxalate after dissolving in 35 mL of water according to Method 1 and perform the test (NMT 1.5 ppm).

Loss on drying NMT 0.5% (1 g, 80 ℃, in vacuum, 5 hours).

Residue on ignition NMT 0.05% (4 g).

Assay Weigh accurately about 1 g of Nafronyl Oxalate, previously dried, dissolve in 50 mL of acetic acid(100) for non-aqueous titration, add 1 drop of methylrosaniline chloride TS, and titrate with 0.1 mol/L perchloric acid VS. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 47.35 mg of $C_{24}H_{33}NO_3 \cdot C_2H_2O_4$

Packaging and storage Preserve in tight containers.

Nafronyl Oxalate Capsules
나프로닐옥살산염 캡슐

Nafronyl Oxalate Capsules contains NLT 95.0% and NMT 105.0% of the labeled amount of nafronyl oxalate ($C_{24}H_{33}NO_3 \cdot C_2H_2O_4$: 473.56).

Method of preparation Prepare as directed under Capsules, with Nafronyl Oxalate.

Identification Weigh the amount equivalent to 0.1 g of nafronyl oxalate according to the labeled amount of Nafronyl Oxalate Capsules, dissolve in 10 mL of ethanol, and use this solution as the test solution. Weigh 0.1 g of nafronyl oxalate RS, dissolve in 10 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, acetic acid(100) and water (50 : 25 : 10) as the developing solvent, and air-dry the plate. Spray Dragendorff's TS onto the plate; the R_f value and color from the spots of the test solution and the standard solution are the same.

Dissolution Perform the test with 1 capsule of Nafronyl Oxalate Capsules at 100 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of the second solution as the dissolution solution. Take the dissolved solution 45 minutes after the start of the Dissolution and filter it. Discard the first 10 mL of the filtrate, take exactly *V mL* of the next filtrate, add the second solution in the Dissolution so that 1 mL contains about 100 μg of nafronyl oxalate according to the labeled amount to make exactly *V' mL*, and use this solution as the test solution. Separately, weigh accurately about 20 mg of nafronyl oxalate RS, dissolve in the second solution in the Dissolution to make 200 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test and standard solutions as directed under the Liq-

uid Chromatography according to the following conditions. Calculate the peak areas A_T and A_S of nafronyl oxalate ($C_{24}H_{33}NO_3$) for each solution. It is suitable when the dissolution rate of Nafronyl Oxalate Capsules in 45 minutes is NLT 80%.

$$\text{Dissolution rate for the labeled amount of Nafronyl Oxalate } (C_{24}H_{33}NO_2)\ (\%) = W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 45$$

W_S: Amount (mg) of nafronyl oxalate RS

C: Labeled amount of nafronyl oxalate ($C_{24}H_{33}NO_3$) in 1 capsule (mg)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 283 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with 5 μm of octadecylsilanized silica gel for liquid chromatography.

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of Acetonitrile, tetrabutylammonium buffer (pH 7.0) and methanol (790 : 150 : 60).

Flow rate: 1.0 mL/min

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT about 20 Nafronyl Oxalate Capsules. Weigh accurately an amount, equivalent to about 20 mg of nafronyl oxalate ($C_{24}H_{33}NO_3 \cdot C_2H_2O_4$), transfer to a 100-mL volumetric flask, dissolve it by putting water, and add water to the gauge line. Filter it, and use the filtrate as the test solution. Separately, weigh accurately about 200 mg of nafronyl oxalate RS, dissolve in water to make exactly 100 mL. Take exactly 10 mL of the solution, add water to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and calculate the peak areas A_T and A_S from the test solution and the standard solution.

$$\text{Amount of Nafronyl Oxalate } (C_{24}H_{33}NO_3 \cdot C_2H_2O_4)\ (\text{mg}) = \text{Amount of nafronyl oxalate RS (mg)} \times \frac{A_T}{A_S} \times \frac{1}{10}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 283 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with 5 μm of octadecylsilanized silica gel for liquid chromatography.

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of acetonitrile, tetrabutylammonium buffer (pH 7.0) and methanol (790 : 150 : 60).

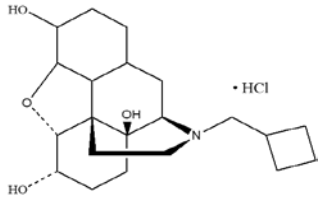
Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of nafronyl oxalate is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Nalbuphine Hydrochloride
날부핀염산염



$C_{21}H_{27}NO_4 \cdot HCl$: 393.90

(5α,6α)-17-(Cyclobutylmethyl)-4,5-epoxymorphinan-3,6,14-triol hydrochloride, [23277-43-2]

Nalbuphine Hydrochloride contains NLT 98.0% and NMT 102.0% of nalbuphine hydrochloride ($C_{21}H_{27}NO_4 \cdot HCl$: 393.90), calculated on the anhydrous basis.

Description Nalbuphine Hydrochloride occurs as a white powder.

Identification (1) Add iron(III) chloride TS to an aqueous solution of Nalbuphine Hydrochloride; the resulting solution exhibits a bluish purple color.

(2) Weigh about 0.1 g each of Nalbuphine Hydrochloride and nalbuphine hydrochloride RS, dissolve each in 5 mL of ethanol, and use these solutions as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 L each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for Thin-layer chromatography (fluorescent indicator added). Develop the plate with a mixture of saturated ammonia butanol and methanol (100 : 5) to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light(main wavelength 254 nm); the color and the R_f value of the spots obtained from the test solution and the standard solution are the same.

(3) Dissolve about 0.15 g of Nalbuphine Hydrochloride in 25 mL of water and transfer to a separatory funnel. Add 2 to 3 drops of ammonia TS and extract the precipitate 3 times with three 5 mL portions of chloroform. Filter the extract each time through a glass wool layer previously wet with chloroform, evaporate the filtrate to dryness, and dry at 105 ℃ for 1 hour. Dissolve 0.15 g of Nalbuphine Hydrochloride, previously dried, 0.15 g of nalbuphine hydrochloride RS in 5 mL of chloroform.

Determine the infrared spectra, using the chloroform layer as the control solution, as directed under the solution method under the Mid-infrared Spectroscopy; the spectra exhibit similar intensity of absorption at the same wavenumber as nalbuphine RS.

Melting point Dissolve about 0.15 g of Nalbuphine Hydrochloride in 25 mL of water, transfer to a separatory funnel, add 2 to 3 drops of ammonia TS, and extract the precipitate 3 times with 5 mL of chloroform each. Filter the extract each time through a glass wool layer previously wet with chloroform, evaporate the filtrate to dryness, dry at 105 ℃ for 1 hour, and determine the melting point; the melting point is between 227 and 232 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve about 1.0 g of Nalbuphine Hydrochloride in 30 mL of water; the resulting solution is clear and the absorbance at 460 nm is NMT 0.1.

(2) ***Noroxymorphine hydrochloride and oxymorphine hydrochloride***—Dissolve about 0.1 g of Nalbuphine Hydrochloride in methanol to make 5 mL and use this solution as the test solution. Separately, dissolve noroxymorphine and oxymorphine RS in methanol to make the concentration 20 mg/100 mL each and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution onto a plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of saturated ammonia butanol and methanol (100 : 5) to a distance of about 15 cm in the darkroom, and air dry the plate. Spray a detecting agent on the plate; the spots other than the principal spot obtained from the test solution are not more intense than the spot from the standard solution (NMT 1.0%).

(3) ***Ketone***—Dissolve about 0.1 g of Nalbuphine Hydrochloride in 1 mL of low carbonyl methanol and use this solution as the test solution (1). Separately, transfer N,O-bis (cyclobutyl carbonyl) noroxymorphine into a 50-mL volumetric flask and add low carbonyl methanol to make the concentration 1.0 mg/mL (correspond to 1.0% of ketone content in the sample). With this solution, make the standard solution for calibration curve with the concentration in the following table.

Ketone content in the sample (%)	mL/pith of 1.0% standard solution	final volume mL	Factor
1.0	-	0	1.0
0.7	7.0	10.0	0.7
0.5	5.0	10.0	0.5
0.3	15.0	50.0	0.3
0.	5.0	50.0	0.1

Take 1 mL each of the test solution (1) and the standard solution for calibration curve, transfer to a 50-mL volumetric flask, add 1 mL of low carbonyl methanol 2,4-dinitrophenylhydrazine solution, saturated, TS and 1 drop of hydrochloric acid, and cover the 10-mL beaker. Heat on a steam bath at between 70 and 80 ℃ for 15 minutes and allow it to cool for 15 minutes. Add 4 mL of 20% potassium hydroxide solution and 4 mL of water, stir well, and add 80% low carbonyl methanol solution to the gauge line. Use this solution as the test solution and the standard solution. Separately, take 1 mL of low carbonyl methanol, proceed in the same manner as in preparation of the test solution, and use this solution as the blank test solution. With the test solution, the standard solution, and the blank test solution, perform the test using 1 cm cell and air as the control solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance at the wavelength of maximum between 360 nm and 680 nm. When determining with the standard solution, the test solution and the blank test solution, the times required for determining the absorbances after adding 20% sodium hydroxide solution should be same. Plot a calibration curve from the absorbance of the standard solution and determine the content of ketone in the sample (NMT 1.0%).

$$\text{Total ketone (\%) in standard solution} = \frac{\text{Amount (mg) of standard solution}}{50} \times \text{Factor of standard solution}$$

$$\text{Total ketone (\%) in sample} = \frac{\text{Ketone (\%) in calibration curve} \times 100}{\text{Amount of sample (mg)} \times \text{factor of solvent}}$$

If it is difficult to purchase low carbonyl methanol, prepare as follows. To 500 mL of methanol, add 5 g of 2,4-Dinitrophenylhydrazine and 2 to 3 drops of hydrochloric acid. Reflux for 2 hours, pass through a short vigreux column, and distill. It can be used between 2 and 3 months if stored in hermetic containers.

(4) ***Non-amine***—Put about 1 g of Nalbuphine Hydrochloride to a 125 mL separatory funnel, add 50 mL of 0.1 mol/L hydrochloric acid, and shake hard to mix until completely dissolved. Extract 3 times with 10 mL of chloroform each, filter the extract each time through a wool layer previously wet with chloroform, transfer the combined filtrate to a 50-mL volumetric flask, and add chloroform to make 50 mL. Use this solution as the control solution and determine the absorbance at around wavelength of 280 nm as directed under the Ultraviolet-visible Spectroscopy; the absorbance is NMT 0.80 (NMT 1%).

(5) ***β-nalbuphine hydrochloride***—Dissolve about 0.1 g of Nalbuphine Hydrochloride in methanol to make 10 mL and use this solution as the test solution. Separately, dissolve 50 mg of β-nalbuphine hydrochloride RS in methanol to make 50 mL and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution onto a plate made of silica gel for thin-layer chromatog-

raphy. Develop the plate with a mixture of acetone and trimethylamine (70 : 30) to a distance of about 15 cm in the darkroom and air dry the plate. Spray iron(III) chloride-potassium ferricyanide TS on the plate; the spots other than the principal spot obtained from the test solution is not more intense than the spot from the standard solution (NMT 10%).

Water NMT 5.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.25% (1 g).

Assay Weigh accurately an amount of Nalbuphine Hydrochloride, equivalent to 10 mg of nalbuphine hydrochloride ($C_{21}H_{27}NO_4 \cdot HCl$) and add the mobile phase to make exactly 100 mL. Take 2.0 mL of this solution and add the mobile phase to make 10 mL and use this solution as the test solution. Separately, weigh accurately about 10 mg of nalbuphine hydrochloride RS and add the mobile phase to make exactly 100 mL. Take about 2.0 mL of this solution, add the mobile phase to make 10 mL, and use this solution as the standard solution. With 10 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography, and determine nalbuphine hydrochloride peak areas A_T and A_S of each solution.

Amount of nalbuphine hydrochloride ($C_{21}H_{27}NO_4 \cdot HCl$)
= Amount (mg) of nalbuphine hydrochloride RS $\times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25cm in length, packed with cyano silyl silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Dissolve 6.80 g of potassium dihydrogen phosphate in 980 mL of water, adjust the pH to 2.5 by adding phosphoric acid, and add water to make 1000 mL. To 800 mL of this solution add 200 mL of methanol.

Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL of the test solution according to the above conditions; the relative standard deviation of peak areas of nalbuphine hydrochloric acid is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Nalbuphine Hydrochloride Injection
날부핀염산염 주사액

Nalbuphine Hydrochloride Injection contains NLT 95.0% and NMT 105.0% of the labeled amount of nalbuphine hydrochloride ($C_{21}H_{27}NO_4 \cdot HCl$: 393.90).

Method of preparation Prepare as directed under injections, with Nalbuphine Hydrochloride.

Identification Use Nalbuphine Hydrochloride Injection as the test solution. Separately, weigh 20 mg of nalbuphine hydrochloride RS, dissolve in 2 mL of water, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of heptane, tetrahydrofuran, ethanol and ammonia water (50 : 40 : 15 : 3) to a distance of about 15 cm and air-dry the plate. Examine under ultraviolet light (main wavelength 254 nm); the spots obtained from the test solution and the standard solution have the same color and the same R_f value.

pH Between 3.0 and 4.2.

Safety With 5 healthy and well-nourished white mice weighing about 20 g, inject intraperitoneally about 0.4 mL of Nalbuphine Hydrochloride Injection to each mouth, and observe; the mice do not die within 72 hours. If even 1 mouse dies within 72 hours after the injection, perform the test again with 10 white mice weighing between 19.5 g and 20.5 g; all the mice are alive within 72 hours.

Sterility Meets the requirements.

Pyrogen Meets the requirements. However, to 5 mL of Nalbuphine Hydrochloride Injection, add 75 mL of isotonic sodium chloride injection and about 1 mL of 1 mol/L sodium hydroxide solution to adjust the pH to 7.0, add isotonic sodium chloride injection to make 100 mL, and use the solution as the test solution. Inject the test solution to a rabbit by 5 mL per kg of the rabbit weight.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Weigh accurately an amount of Nalbuphine Hydrochloride Injection, equivalent to 10 mg of nalbuphine hydrochloride ($C_{21}H_{27}NO_4 \cdot HCl$), and add the mobile phase to make exactly 100 mL. Take 2.0 mL of this solution, add the mobile phase to make 10 mL, and use this solution as the test solution Separately, weigh accurately 10 mg of nalbuphine hydrochloride RS and add the mobile phase to make exactly 100 mL. Take 2.0 mL of this

solution, add the mobile phase to make 10 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and determine the peak areas A_T and A_S of nalbuphine hydrochloride for each solution.

$$\text{Amount of nalbuphine hydrochloride } (C_{21}H_{27}NO_4 \cdot HCl) = \text{Amount (mg) of nalbuphine hydrochloride RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with cyano silyl silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Dissolve 6.80 g of potassium dihydrogen phosphate in 980 mL of water, adjust the pH to 2.5 by adding phosphoric acid, and add water to make 1000 mL. To 800 mL of this solution, add 200 mL of methanol.

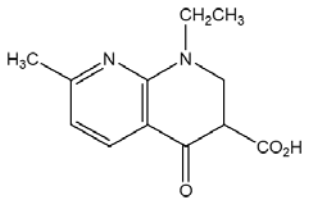
Flow rate: 1.0 mL/min

System suitability

System repeatability: Perform the test 6 times according to the above conditions with 10 μL of the test solution; the relative standard deviation of the peak areas of nalbuphine hydrochloride is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Nalidixic Acid
날리딕스산



$C_{12}H_{12}N_2O_3$: 232.24

1-Ethyl-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid [*389-08-2*]

Nalidixic Acid, when dried, contains NLT 99.0% and NMT 101.0% of nalidixic acid ($C_{12}H_{12}N_2O_3$).

Description Nalidixic Acid occurs as white to pale yellow crystals or a crystalline powder.

It is sparingly soluble in *N,N*-Dimethylformamide, very slightly soluble in ethanol(99.5), and practically insoluble in water.

It is soluble in sodium hydroxide TS.

Identification (1) Determine the absorption spectra of Nalidixic Acid and 0.01 mol/L sodium hydroxide TS (1 in 200000) of nalidixic acid RS as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Nalidixic Acid and nalidixic acid RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 225 and 231 °C.

Purity (1) ***Chloride***—To 2.0 g of Nalidixic Acid add 50 mL of water, warm at 70 °C for 5 minutes, cool quickly, and filter. To 25 mL of the filtrate, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.35 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.012%).

(2) ***Heavy metals***—Proceed with 1.0 g of Nalidixic Acid according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve about 20 mg of Nalidixic Acid in 20 mL of 0.01 mol/L sodium hydroxide TS. Pipet 5 mL of this solution, add water to make exactly 10 mL, and use this solution as the test solution. Pipet 2 mL of the test solution, add water to make exactly 1000 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution as directed in the automatic integration method; the peak area other than the peak of nalidixic acid from the test solution is not greater than the peak area of nalidixic acid from the standard solution. The total area of the peaks other than the peak of nalidixic acid from the test solution is not greater than 2.5 times the peak area of nalidixic acid from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 260 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 6.24 g of sodium dihydrogen phosphate dihydrate in 950 mL of water, adjust the pH to 2.8 using phosphoric acid, and add water to make 1000 mL. To 300 mL of this solution add 200 mL of methanol.

Flow rate: Adjust so the retention time of nalidixic acid is about 19 minutes.

System suitability

Test for required detectability: Pipet 5 mL of the

standard solution and add water to make exactly 10 mL. Confirm that the peak area of nalidixic acid from 10 μL of this solution is NLT 40% and NMT 60% of the peak area of nalidixic acid from the standard solution.

System performance: Dissolve 25 mg of methyl *p*-hydroxybenzoate in a mixture of water and methanol (1 : 1). To 1 mL of this solution, add water to make 10 mL. To 5 mL of this solution, add 5 mL of the standard solution. Proceed 10 μL of this solution according to the above conditions; methyl *p*-hydroxybenzoate and nalidixic acid are eluted in this order with the resolution being NLT 13.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of nalidixic acid is NMT 2.0%.

Loss on drying NMT 0.2% (1 g, 105 ℃, 3 hours).

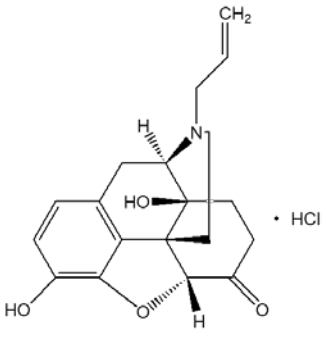
Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.3 g of Nalidixic Acid, previously dried, dissolve in 50 mL of *N*,*N*-Dimethylformamide, and titrate with 0.1 mol/L tetramethylammonium hydroxide VS (potentiometric titration under the Titrimetry). Separately, add 13 mL of a mixture of water and methanol (89 : 11) to 50 mL of *N*,*N*-Dimethylformamide, perform a blank test in the same manner, and make any necessary correction.

Each mL of 0.1 mol/L tetramethylammonium hydroxide VS
= 23.22 mg of $C_{12}H_{12}N_2O_3$

Packaging and storage Preserve in tight containers.

Naloxone Hydrochloride
날록손염산염



$C_{19}H_{21}NO_4 \cdot HCl$: 363.84

(1*S*,5*R*,13*R*,17*S*)-10,17-Dihydroxy-4-(prop-2-en-1-yl)-12-oxa-4-azapentacyclo[9.6.1.01,13.05,17.07,18]octadeca-7(18),8,10-trien-14-one hydrochloride [*357-08-4*]

Naloxone Hydrochloride contains NLT 98.5% and NMT 101.0% of naloxone hydrochloride ($C_{19}H_{21}NO_4 \cdot HCl$), calculated on the dried basis.

Description Naloxone Hydrochloride occurs as white to yellow crystals or a crystalline powder.
It is freely soluble in water, soluble in methanol, slightly soluble in ethanol(99.5) and acetic acid(100), and very slightly soluble in acetic anhydride.
It is hygroscopic.
It is colored by light.

Identification (1) Determine the absorption spectra of Naloxone Hydrochloride and aqueous solution (1 in 10000) of naloxone hydrochloride RS as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Naloxone Hydrochloride and naloxone hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous of Naloxone Hydrochloride (1 in 50) responds to the Qualitative Analysis (2) for chloride.

Optical rotation $[\alpha]_D^{25}$: Between -170° and -181° (0.25 g, calculated on the dried basis, water, 10 mL, 100 mm).

pH Dissolve 0.10 g of Naloxone Hydrochloride in 10 mL of newly boiled and cooled water; the pH of the solution is between 4.5 and 5.5.

Purity ***Related substances***—Perform the test as rapidly as possible without exposure to light, using a light-resistant container. Dissolve 80 mg of Naloxone Hydrochloride in 10 mL of methanol, and use this solution as the test solution. Pipet 1 mL of the test solution, add methanol to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of ammonia*1*-butanol and methanol (20 : 1) to a distance of about 12 cm, and air dry the plate. Spray evenly iron(III) chloride-potassium hexacyanoferrate(III) TS on the plate; the number of the spots other than the principal spot obtained from the test solution are NMT 1 and they are not more intense than the spots from the standard solution.

Ammonia1-butanol—To 100 mL of 1-butanol, add 60 mL of ammonia water (1 in 100), shake well to mix, and use *1*-butanol layer.

Loss on drying NMT 2.0% (0.1 g, 105 ℃, 5 hours, cool in a desiccator (phosphorus pentoxide)).

Residue on ignition NMT 0.2% (0.1 g).

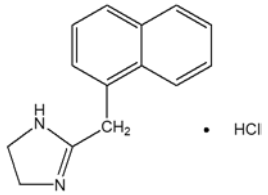
Assay Weigh accurately about 0.3 g of Naloxone Hydrochloride, and dissolve in 80 mL of acetic acid(100) by

warming. After cooling, add 80 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each 1 mL of 0.1 mol/L perchloric acid VS
= 36.384 mg of $C_{19}H_{21}NO_4 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Naphazoline Hydrochloride
나파졸린염산염



$C_{14}H_{14}N_2 \cdot HCl$: 246.74
2-(Naphthalen-1-ylmethyl)-4,5-dihydro-1*H*-imidazole hydrochloride [*550-99-2*]

Naphazoline Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of naphazoline hydrochloride ($C_{14}H_{14}N_2 \cdot HCl$).

Description Naphazoline Hydrochloride occurs as a white crystalline powder. It is odorless and tastes bitter.
It is freely soluble in water, soluble in ethanol(95) and acetic acid(100), very slightly soluble in acetic anhydride and practically insoluble in ether.

Melting point—Between 255 and 260 ℃ (with decomposition).

Identification (1) Add 5 mL of bromine TS to the aqueous solution (1 in 100) of Naphazoline Hydrochloride and boil; the resulting solution exhibits an intense violet color.

(2) Add 2 mL of sodium hydroxide TS to 30 mL of the aqueous solution (1 in 100) of Naphazoline Hydrochloride, and extract twice with 25 mL of ether. Add the extracts of ether and evaporate to dryness with the aid of a current of air. Dry the residue at 80 ℃ for 1 hour; the residue melts between 117 and 120 ℃.

(3) Dissolve the residue of (2) by adding 2 to 3 drops of dilute hydrochloric acid and 5 mL of water, and add 2 mL of Reinecke salt TS; a purple crystalline precipitate is produced.

(4) An aqueous solution of Naphazoline Hydrochloride (1 in 10) responds to the Qualitative Analysis for chloride.

pH Dissolve about 0.10 g of Naphazoline Hydrochloride in 10 mL of newly boiled and cooled water; the pH of the resulting solution is NLT 5.0 and NMT 7.0.

Purity (1) ***Clarity and color of solution***—Dissolve about 1.0 g of Naphazoline Hydrochloride in 10 mL of water; the resulting solution is colorless and clear.

(2) ***Heavy metals***—Proceed with about 1.0 g of Naphazoline Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Loss on drying NMT 0.5% (1 g, 105 °C, 2 hours).

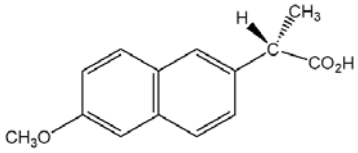
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Naphazoline Hydrochloride, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 24.674 mg of $C_{14}H_{14}N_2 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Naproxen
나프록센



$C_{14}H_{14}O_3$: 230.26
(*S*)-2-(6-Methoxynaphthalen-2-yl) propanoic acid [*22204-53-1*]

Naproxen, when dried, contains NLT 98.5% and NMT 101.0% of naproxen ($C_{14}H_{14}O_3$).

Description Naproxen occurs as white crystals or a crystalline powder, and it is odorless.
It is freely soluble in acetone, soluble in methanol, ethanol(99.5) or chloroform, sparingly soluble in ether and practically insoluble in water.
It dissolves in sodium hydroxide TS.

Identification (1) Dissolve 10 mg of Naproxen in 5 mL of methanol, put 5 mL of water, add 2 mL of potassium iodide TS and 5 mL of potassium iodate solution (1 in 100), and shake to mix; the resulting solution exhibits a yellow to pale brown color. Add 5 mL of chloroform to this solution and shake to mix; the chloroform layer exhibits a pale purple color.

(2) Pipet 1 mL of the ethanol(99.5) solution (1 in 300) of Naproxen, add 4 mL of perchloric acid hydroxylamine-ethanol (99.5) TS and 1 mL of *N,N'*-Dicyclohexylcarbodiimide-ethanol (99.5) TS, shake well

to mix, and allow to stand in lukewarm water for 20 minutes. After cooling, add 1 mL of iron(III) perchlorate hexahydrate-ethanol (99.5) TS and shake to mix; the resulting solution exhibits a purple color.

(3) Determine the absorption spectra of solutions of Naproxen and ethanol(99.5) solution (1 in 50000) of naproxen RS, as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared spectra of Naproxen and Naproxen RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{25}$: Between +63.0° and +68.5° (after drying, 0.1 g, chloroform, 10 mL, 100 mm).

Melting point Between 154 and 158 °C.

Purity (1) ***Clarity and color of solution***—Dissolve 2.0 g of Naproxen in 20 mL of acetone; the resulting solution is clear. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at 400 nm is NMT 0.070.

(2) ***Heavy metals***—Proceed with 2.0 g of Naproxen according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Proceed with 2.0 g of Naproxen according to Method 3 and perform the test (NMT 1 ppm).

(4) ***Related substances***—Perform this test without exposure to daylight, using a light-resistant container. Dissolve about 0.10 g of Naproxen in 10 mL of a mixture of ethanol(95) and chloroform (1 : 1), and use this solution as the test solution. Pipet 2 mL of this solution and add a mixture of ethanol(95) and chloroform (1 : 1) to make exactly 100 mL. Pipet 5 mL of this solution, add a mixture of ethanol(95) and chloroform (1 : 1) to make exactly 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of hexane, dichloromethane, tetrahydrofuran, and acetic acid(100) (50 : 30 : 17 : 3) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine under ultraviolet rays (principal wavelength: 254 nm); the spots other than the principal spot and the spot of the starting point from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 °C, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Naproxen, previously dried, add 100 mL of diluted methanol (4 in 5), dissolve by gentle warming, if necessary, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of phenolphthalein TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 23.026 mg of $C_{14}H_{14}O_3$

Packaging and storage Preserve in light-resistant, well-closed containers.

Naproxen Tablets
나프록센 정

Naproxen Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of naproxen ($C_{14}H_{14}O_3$: 230.26).

Method of preparation Prepare as directed under Tablets, with Naproxen.

Identification Perform the test as directed under the Assay with a mixture of the test solution and the standard solution (1 : 1) from the Assay; it exhibits two peaks corresponding to naproxen and the internal standard.

Dissolution Perform the test with 1 tablet of Naproxen Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of 0.1 mol/L phosphate buffer (pH 7.4) as the dissolution medium. Take the dissolved solution 45 minutes after starting the test, filter, dilute with the dissolution medium, if necessary, and perform the test as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as the control. Determine the absorbance at the absorbance maximum wavelength (λmax) around 332 nm. Separately, weigh accurately an appropriate amount of naproxen RS to make the same concentration as the test solution, and determine the absorbance in the same wavelength.
The dissolution rate of Naproxen Tablets in 30 minutes should be NLT 80%.

0.1 mol/L phosphate buffer solution, pH 7.4— Weigh 2.62 g of sodium dihydrogen phosphate dihydrate and 11.50 g of potassium monohydrogen phosphate, and dissolve in water to make 1000 mL.

Uniformity of dosage units Meets the requirements.

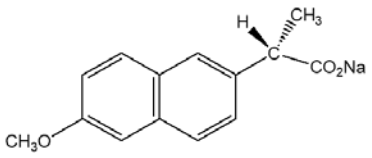
Assay Weigh accurately the mass of NLT 20 tablets of Naproxen Tablets, and powder. Weigh accurately an amount, equivalent to 0.25 g of naproxen ($C_{14}H_{14}O_3$), and perform the test as directed under the Assay of Naproxen sodium tablets. However, weigh accurately an appropriate amount of naproxen RS instead of naproxen sodium RS and add a mixture of acetonitrile and water (90 : 10) to make a solution containing 2.5 mg in 1 mL.

Amount (mg) of naproxen ($C_{14}H_{14}O_3$)
$$= 10\times C \times \frac{Q_T}{Q_S}$$

C: Concentration of the standard solution (μg/mL)

Packaging and storage Preserve in tight containers.

Naproxen Sodium
나프록센나트륨



$C_{14}H_{13}NaO_3$: 252.24
Sodium (*S*)-2-(6-methoxynaphthalen-2-yl)propanoate
[*26159-34-2*]

Naproxen Sodium, when dried, contains NLT 98.0% and NMT 102.0% of naproxen sodium ($C_{14}H_{13}NaO_3$).

Description Naproxen Sodium occurs as a white to milky white crystalline powder.
It is soluble in water or methanol, sparingly soluble in ethanol(95), very slightly soluble in acetone and practically insoluble in chloroform or toluene.

Melting point—About 255 °C (with decomposition).

Identification (1) Determine the absorption spectra of solutions Naproxen Sodium and naproxen sodium RS in methanol (1 in 40000) as directed under the Ultraviolet-visible Spectroscopy; both exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Naproxen Sodium and naproxen sodium RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{25}$: Between -15.3° and -17.0° (after drying, 0.5 g, 0.1 mol/L sodium hydroxide TS, 10 mL, 100 mm).

Purity (1) ***Heavy metals***—Weigh 1.0 g of Naproxen Sodium, dissolve in 20 mL of water, add 5 mL of 1 mol/L hydrochloric acid, and extract three times with 20 mL, 20 mL, and 10 mL of dichloromethane. Discard the dichloromethane layer, proceed with the aqueous layer as directed under Method 1, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Weigh accurately about 0.1 g of Naproxen Sodium, dissolve in methanol to make 5.0 mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of naproxen sodium RS, dissolve in methanol to make a solution containing 20 mg in 1 mL, and use this solution as the standard stock solution. Pipet 1 mL, 3 mL and 5 mL of this solution, and add methanol to make exactly 100 mL each. Pipet 1 mL each of these solutions, add methanol to make exactly 10 mL, and use these solutions as the standard solutions (1), (2) and (3). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solutions (1), (2) and (3) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of toluene, tetrahydrofuran, and acetic acid(100) (30 : 3 : 1) to a distance of about 15 cm, and air-dry the plate. Examine under the ultraviolet rays (principal wavelength 254 nm); the R_f value of the principal spot obtained from the test solution is equivalent to the R_f value of the spot from the standard solution, and the spots other than the principal spot from the test solution are not more intense than the spot from the standard solution (3). The spots other than the principal spot obtained from the test solution are NMT 2.0% of total spots, as compared to those obtained from the standard solutions (1), (2) and (3) (0.1%, 0.3% and 0.5%, respectively).

(3) ***Glass naproxen***—Weigh about 5.0 g of Naproxen Sodium, transfer to a separatory funnel, dissolve by adding 25 mL of water, and extract with 15 mL of chloroform each three times. Evaporate the chloroform extract on a steam bath to dryness, dissolve the residue in 10 mL of a mixture of methanol and water (3 : 1), previously neutralized with 0.1 mol/L sodium hydroxide using the phenolphthalein TS as an indicator, add phenolphthalein TS, and titrate with 0.1 mol/L sodium hydroxide VS; the consumption is NMT 2.2 mL (NMT 1.0%).

Loss on drying NMT 1.0% (1 g, in vacuum, 105 ℃, 3 hours).

Assay Weigh accurately about 0.2 g of Naproxen Sodium, add 2 drops of *p*-Naphtholbenzein TS, dissolve with 50 mL of acetic acid(100), previously neutralized with 0.1 mol/L perchloric acid, if necessary, and titrate with 0.1 mol/L perchloric acid VS.

Each mL of 0.1 mol/L perchloric acid VS
= 25.224 mg of $C_{14}H_{13}NaO_3$

Packaging and storage Preserve in tight containers.

Naproxen Sodium Tablets
나프록센나트륨 정

Naproxen Sodium Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of naproxen sodium ($C_{14}H_{13}NaO_3$: 252.25).

Method of preparation Prepare as directed under Tablets, with Naproxen Sodium.

Identification (1) Weigh a portion of powdered Naproxen Sodium Tablets, equivalent to about 0.25 g of naproxen sodium according to the labeled amount, transfer to a centrifuge tube, and add 12 mL of water and 1 mL of hydrochloric acid; a white precipitate develops. Centrifuge the mixture; the clear supernatant responds to the Qualitative Analysis for sodium salt.

(2) Prepare a mixture of the standard solution and the test solution (1 : 1) and perform the test as directed under the Assay; it exhibits two major peaks, corresponding to naproxen sodium and the internal standard.

Dissolution Perform the test with 1 tablet of Naproxen Sodium Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of 0.1 mol/L phosphate buffer (pH 7.4) as the dissolution medium. Take the dissolved solution 45 minutes after starting the test, filter, dilute with the dissolution medium, if necessary, and prepare a solution containing 50 μg of naproxen sodium ($C_{14}H_{13}NaO_3$) in 1 mL. Perform the test as directed under the Ultraviolet-visible Spectroscopy, use the dissolution medium as the control solution, and determine the absorbance at the absorbance maximum wavelength (λmax) around 332 nm. Separately, weigh accurately an appropriate amount of naproxen sodium RS, dissolve in the dissolution medium to prepare a solution containing 50 μg in 1 mL, and determine the absorbance in the same wavelength.

The dissolution rate of Naproxen Sodium Tablets in 45 minutes should be NLT 80%.

0.1 mol/L phosphate buffer (pH 7.4)—Weigh 2.62 g of sodium dihydrogen phosphate dihydrate and 11.50 g of potassium monohydrogen phosphate, and dissolve in water to make 1000 mL.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Naproxen Sodium Tablets, and powder. Weigh accurately an amount, equivalent to about 0.275 g of naproxen sodium ($C_{14}H_{13}NaO_3$), transfer to a volumetric flask, add 10 mL of water, and shake until it is completely dispersed. Then add acetonitrile to fill up to the mark, and mix. Allow the precipitate to settle, pipet 1 mL of the clear supernatant, and put 2.0 mL of internal standard solution. Add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of naproxen sodium RS, and add a mixture of acetonitrile and water (90 : 10) to prepare a solution containing 2.75 mg in 1 mL. Pipet 1 mL of this solution, put 2.0 mL of the internal standard solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of naproxen sodium to the internal standard.

$$\text{Amount (mg) of naproxen sodium } (C_{14}H_{13}NaO_3) = 10 \times C \times \frac{Q_T}{Q_S}$$

C: Concentration of the standard solution (μg/mL)

Internal standard solution—Acetonitrile solution of butyrophenone (1 in 2000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile, water and acetic acid(100) (50 : 49 : 1).

Flow rate: 1.2 mL/min

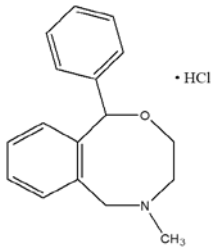
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the naproxen sodium and the internal standard are eluted in this order with the resolution being NLT 5.

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio is NMT 1.5%.

Packaging and storage Preserve in tight containers.

Nefopam Hydrochloride
네포팜염산염



$C_{17}H_{19}NO \cdot HCl$: 289.80

3,4,5,6-Tetrahydro-5-methyl-1-phenyl-1*H*-2,5-benzoxazocine hydrochloride (1:1), [*23327-57-3*]

Nefopam Hydrochloride, when dried, contains NLT 98.5% and NMT 101.5% of nefopam hydrochloride ($C_{17}H_{19}NO \cdot HCl$).

Description Nefopam Hydrochloride occurs as almost white crystalline powder.

It is soluble in hot water and ethanol(95) and practically insoluble in toluene, heptane and ether.

Melting point—Between 248 and 255 ℃ (with decomposition).

Identification (1) Use 1% methanol VS of Nefopam

Hydrochloride as the test solution. Use 1% methanol VS of Nefopam Hydrochloride RS as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test and standard solutions on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethanol, ethyl acetate and ammonia water(28) (5:5:1) and air-dry it. Spray Dragendorff's TS onto the plate; the R_f value and the color of the spots obtained from the test and standard solutions are identical.

(2) Determine the absorption spectrum with 0.01 mol/L hydrochloric acid VS (1 in 10000) of Nefopam Hydrochloride as directed under the Ultraviolet-visible Spectroscopy. Then, it exhibits maximum absorption at 264-268 nm and at 272-276 nm.

(3) Determine the infrared spectra of Nefopam Hydrochloride and Nefopam Hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

Purity ***Heavy metals*—**Test with 1 g of Nefopam Hydrochloride according to Method 2 of the Heavy Metals. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Loss on drying NMT 0.5% (1 g, 105 °C, constant mass).

Residue on ignition NMT 0.1% (1 g)

Assay Weigh accurately about 0.3 g of Nefopam Hydrochloride, dissolves in 50 mL acetic acid(100), add 10 mL of 6% Mercury(II) acetate TS, for non-aqueous determination, and perform potentiometric titration with 0.1 mol/L perchloric acid. Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid
= 28.98 mg of $C_{17}H_{19}NO{\cdot}HCl$

Packaging and storage Preserve in tight containers.

Nefopam Hydrochloride Capsules
네포팜염산염 캡슐

Nefopam Hydrochloride Capsules contains NLT 95.0% and NMT 105.0% of the labeled amount of nefopam hydrochloride ($C_{17}H_{19}NO{\cdot}HCl$: 289.80).

Method of preparation Prepare as directed under Capsules, with Nefopam Hydrochloride.

Identification (1) Dissolve about 1 capsule of Nefopam Hydrochloride Capsule in 20 mL of water, filter, and add Dragendorff's TS slowly in the filtrate; a reddish brown precipitate is formed.

(2) Dissolve about 2 capsules of Nefopam Hydrochloride Capsules in 30 mL water, filter, and use the filtrate as the test solution. Weigh about 20 mg of nefopam hydrochloride RS, dissolve in 10 mL of water, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, ethanol(95) and ammonia water(28) (5 : 5 : 1) as the developing solvent, and air-dry the plate. Spray evenly Dragendorff's TS on the plate; the R_f value and the color of the spots obtained from the test are identical with those from the standard solution.

Disintegration Meet requirements.

Uniformity of dosage units Meet requirements.

Assay Weigh accurately the mass of NLT 20 capsules of Nefopam Hydrochloride Capsules and powder. Weigh accurately an amount of Nefopam Hydrochloride Capsules, equivalent to about 40 mg of nefopam hydrochloride ($C_{17}H_{19}NO{\cdot}HCl$), and add water to make exactly 250 mL. Filter this solution, discard the first 20 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately about 40 mg of nefopam hydrochloride RS, add water to make exactly 250 mL, and use this solution as the standard solution. With the test and standard solutions, determine the absorbance, A_T and A_S at 268 nm, using water as a control solution as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of nefopam hydrochloride ($C_{17}H_{19}NO{\cdot}HCl$)
= Amount (mg) of nefopam hydrochloride RS × (A_T/ A_S)

Packaging and storage Preserve in well-closed containers.

Nefopam Hydrochloride Injection
네포팜염산염 주사액

Nefopam Hydrochloride Injection contains NLT 95.0% and NMT 105.0% of the labeled amount of nefopam hydrochloride ($C_{17}H_{19}NO{\cdot}HCl$: 289.80).

Method of preparation Prepare as directed under Injections, with Nefopam Hydrochloride.

Identification (1) Spot 3 to 4 drops of Dragendorff's TS in 5 mL of Nefopam Hydrochloride Injection; a reddish brown precipitate is formed.

(2) Use this solution as the test solution. Separately, weigh 20 mg of nefopam hydrochloride RS and add water to make 1 mL. Use this solution as the standard solution. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chro-

matography. Next, develop the plate with a mixture of ethanol, ethyl acetate and ammonia water(28) (5 : 5 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly Dragendorff's TS on the plate; the R_f value and the color of the spots obtained from the test are identical with those from the standard solution.

Sterility Meets requirements.

Bacterial endotoxins Less than 15 EU/mg of nefopam hydrochloride.

Particulate contamination: Visible particles Meets requirements.

Insoluble particulate matter in injections Meets requirements.

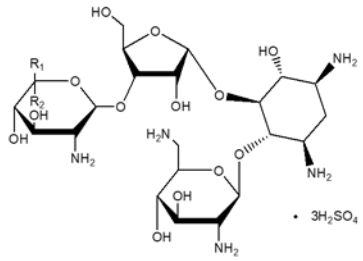
Extractable volume of injections Meets requirements.

Assay Weigh an amount of Nefopam Hydrochloride Injection, equivalent to about 40 mg of nefopam hydrochloride ($C_{17}H_{19}NO \cdot HCl$), and add water to make exactly 250 mL. Use this solution as the test solution. Separately, weigh accurately about 40 mg of nefopam hydrochloride RS, dissolve in water, and make exactly 250 mL. Use this solution as the standard solution. Determine the absorbance of the test solution and the standard solution, A_T and A_S at 268 nm using water as a control solution as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of nefopam hydrochloride ($C_{17}H_{19}NO \cdot HCl$) = Amount (mg) of nefopam hydrochloride RS × (A_T/ A_S)

Packaging and storage Preserve in hermetic containers.

Neomycin Sulfate
네오마이신황산염



Neomycin B : R_1 = H R_2 = CH_2NH_2
Neomycin C : R_1 = CH_2NH_2 R_2 = H

Neomycin Sulfate $C_{23}H_{46}N_6O_{13} \cdot 3H_2SO_4$: 908.88
(2*R*,3*S*,4*R*,5*R*,6*R*)-5-Amino-2-(aminomethyl)-6-[(1*R*,2*R*,3*S*,4*R*,6*S*)-4,6-diamino-2-[(2*S*,3*R*,4*S*,5*R*)-4-[(2*R*,3*R*,4*R*,5*S*,6*S*)-3-amino-6-(aminomethyl)-4,5-dihydroxyoxan-2-yl]oxy-3-hydroxy-5-(hydroxymethyl)oxolan-2-yl]oxy-3-hydroxycyclohexyl]oxyoxane-3,4-diol; sulfuric acid [*1405-10-3*]

Neomycin Sulfate is a sulfate of a mixture of aminoglycoside substances having antibacterial activity produced by the growth of *Streptomyces fradiae*.
Neomycin Sulfate, when dried, contains NLT 623 μg and NMT 740 μg (potency) of neomycin ($C_{23}H_{46}N_6O_{13}$: 614.65).

Description Neomycin Sulfate occurs as a white to light yellow powder.
It is freely soluble in water and practically insoluble in ethanol(95).
It is hygroscopic.

Identification (1) Dissolve 50 mg each of Neomycin Sulfate and neomycin sulfate RS in 1 mL of water and use each solution as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of methanol, ammonia water(28) and dichloromethane (3 : 2 : 1) to a distance of about 10 cm, and air-dry the plate. Spray evenly the ninhydrin acetone solution (1 in 50), and heat at 110 ℃ for 15 minutes; the R_f values of principal spots obtained from the test solution and the standard solution are the same.

(2) The aqueous solution of Netilmicin Sulfate (1 in 20) responds to the Qualitative Analysis (1) for sulfate.

Optical rotation $[\alpha]_D^{20}$: Between +53.5° and 59.0° (1 g, calculated on the dried basis, water, 10 mL, 100 nm).

pH Dissolve 1.0 g of Neomycin Sulfate in 10 mL of water; the pH of this solution is between 5.0 and 7.5.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Neomycin Sulfate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Neomycin Sulfate according to Method 1 and perform the test (NMT 2 ppm).

(3) ***Related substances***—Dissolve about 0.63 g of Neomycin Sulfate in 5 mL of water and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 1 μL each of the test solutions and the standard solution onto the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of methanol, ammonia water(28), and dichloromethane (3 : 2 : 1) to a distance of about 10 cm, and air-dry the plate. Spray evenly ninhydrin acetone solution (1 in 50), heat at 110 ℃ for 15 minutes; the spot with R_f value 0.4 obtained from the test solution is not more intense than the spot from the standard solution.

Sterility It meets the requirements when Neomycin Sulfate is used for manufacturing sterile preparations. But it is exempt from the requirements when there is a final sterilization process in the manufacturing process of sterile preparations.

Loss on drying NMT 8.0% (0.2 g, in vacuum, 60 ºC, 3 hours).

Residue on ignition NMT 0.3% (1 g).

Assay ***Cylinder plate method*** (1) Medium: (a) Agar medium for seed and base layer

Peptone	6.0 g	Sodium chloride	2.5 g
Yeast extract	3.0 g	Glucose	1.0 g
Meat extract	1.5 g	Agar	15.0 g

Weigh the above materials, add purified water to make 1000 mL, and adjust the pH after sterilization to 7.8 to 8.0 using 1 mol/L sodium hydroxide TS.

(2) Test organism and test organism suspension: Use *Staphylococcus aureus* ATCC 6538 P as the test organism. Prepare the test organism suspension so that the transmission of the suspension becomes 80% when determining the transmission using a absorption photometer at the wavelength of 650 nm.

(3) Weigh accurately about 50 mg (potency) of Neomycin Sulfate, previously dried, dissolve in 0.1 mol/L phosphate buffer solution, pH 8.0 to prepare a solution containing 1 mg (potency) per mL, and use this solution as the test stock solution. Take exactly an appropriate amount of this test stock solution, dilute with 0.1 mol/L phosphate buffer solution, pH 8.0 to make two solutions containing each 80.0 μg and 20.0 μg (potency) per mL, and use these solutions as the high concentration test solution and the low concentration test solution, respectively. Separately, take an appropriate amount of neomycin sulfate RS, weigh accurately about 50 mg (potency) after drying, and dissolve in 0.1 mol/L phosphate buffer solution, pH 8.0 to make the standard stock solution containing 1 mg (potency) per mL. Keep the standard stock solution at below 5 °C and use it within 14 days. Take exactly an appropriate amount of this standard stock solution, dilute with 0.1 mol/L phosphate buffer solution, pH 8.0 two solutions containing each 80.0 μg and 20.0 μg (potency) per mL, and use these solutions as the high concentration standard solution and the low concentration standard solution. With these solutions, perform the test as directed under the Microbial Assays for Antibiotics (A) (8).

Packaging and storage Preserve in light-resistant, tight containers.

Neomycin Sulfate Ointment
네오마이신황산염 연고

Neomycin Sulfate Ointment contains NLT 90.0% and NMT 120.0% of the labeled amount of neomycin ($C_{23}H_{46}N_6O_{13}$: 614.65).

Method of preparation Prepare as directed under Ointments, Neomycin Sulfate.

Identification Weigh an amount of Neomycin Sulfate Ointment, equivalent to about 35 mg of neomycin sulfate, according to the labeled potency, transfer it to a separatory funnel, add 50 mL of ether, and shake hard to mix. Extract with 30 mL of 0.1 mol/L phosphate buffer solution, pH 8.0, add 1 mL of ninhydrin TS and 0.5 mL of pyridine to 5 mL of the extract, and boil for 10 minutes; the resulting solution exhibits bluish purple color.

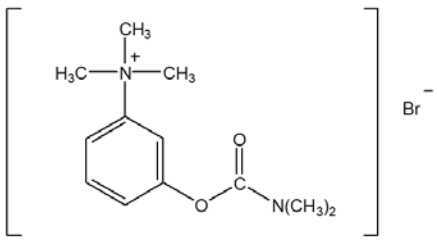
Water NMT 1.0% (1 g, volumetric titration, direct titration).

Assay Perform the test as directed under the Assay under Neomycin Sulfate. However, prepare the test solution as the following method.

Weigh accurately about 0.1 g (potency) of Neomycin Sulfate Ointment, transfer to a separatory funnel, add 50 mL of ether, and shake well to mix. Extract three times each with 25 mL of 0.1 mol/L phosphate buffer solution, pH 8.0, and add 0.1 mol/L phosphate buffer solution, pH 8.0, to the combined extract to make the solution at an appropriate concentration. Take exactly an appropriate amount of this solution, dilute with 0.1 mol/L phosphate buffer solution, pH 8.0 to make the concentration of (3), and use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Neostigmine Bromide
네오스티그민브롬화물



$C_{12}H_{19}BrN_2O_2$: 303.20

3-{[(Dimethylamino)carbonyl]oxy}-*N*,*N*,*N*-trimethylbenzenaminium bromide [*114-80-7*]

Neostigmine Bromide contains NLT 98.0% and NMT 102.0% of neostigmine bromide ($C_{12}H_{19}BrN_2O_2$), calculated on the dried basis.

Description Neostigmine Bromide occurs as a white crystalline powder. It is odorless and tastes bitter.

It is very soluble in ethanol(95) and practically insoluble in ether.

An aqueous solution of Neostigmine Bromide is neutral.

Identification (1) Determine the infrared spectra of Neostigmine Bromide and neostigmine bromide RS as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Neostigmine Bromide (1 in 50) responds to the Qualitative Analysis for bromide.

Melting point Between 171 and 176 ℃ (with decomposition).

Purity *Sulfate*—Dissolve about 0.25 g of Neostigmine Bromide in 10 mL of water, add 1 mL of 3 mol/L hydrochloric acid, and add 1 mL of barium sulfate TS; the solution is not turbid.

Loss on drying NMT 2.0% (1 g, 105 °C, 3 hours).

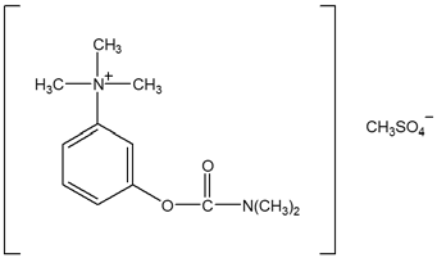
Residue on ignition NMT 0.15% (1 g).

Assay Weigh accurately about 0.225 g of Neostigmine Bromide, dissolve in 2 mL of formic acid, add 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry).

Each mL of 0.1 mol/L perchloric acid VS
= 30.320 mg of $C_{12}H_{19}BrN_2O_2$

Packaging and storage Preserve in tight containers.

Neostigmine Methylsulfate
네오스티그민메틸황산염



$C_{13}H_{22}N_2O_6S$: 334.39

3-{[(Dimethylamino)carbonyl]oxy}-*N*,*N*,*N*-trimethylbenzenaminium; methyl sulfate [*51-60-5*]

Neostigmine Methylsulfate, when dried, contains NLT 98.0% and NMT 102.0% of neostigmine methylsulfate ($C_{13}H_{22}N_2O_6S$).

Description Neostigmine Methylsulfate occurs as a white crystalline powder.
It is very soluble in water and freely soluble in ethanol(95) and acetonitrile.

Identification (1) Determine the absorption spectra of solutions of Neostigmine Methylsulfate and neostigmine methylsulfate RS (1 in 2,000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Neostigmine Methylsulfate and neostigmine methylsulfate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 145 and 149 °C.

pH Dissolve 1.0 g of Neostigmine Methylsulfate in 10 mL of newly boiled and cooled water; the pH of this solution is between 3.0 and 5.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Neostigmine Methylsulfate in 10 mL of water; the resulting solution is clear and colorless.

(2) ***Sulfate***—Dissolve 0.20 g of Neostigmine Methylsulfate in 10 mL of water and add 1 mL of dilute hydrochloric acid and 1 mL of barium chloride TS; no turbidity is produced immediately.

(3) ***Dymethylaminophenol***—Dissolve 0.1 g of Neostigmine Methylsulfate in 5 mL of water, add 1 mL of sodium hydroxide TS, and while cooling with ice, add 1 mL of diazobenzenesulfonic acid TS; no color develops.

Loss on drying NMT 1.0% (1 g, 105 °C, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 25 mg each of Neostigmine Methylsulfate and neostigmine methylsulfate RS, previously dried, and dissolve each in the mobile phase to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Take exactly 10 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas A_T and A_S of neostigmine for each solution.

Amount (mg) of neostigmine methylsulfate ($C_{13}H_{22}N_2O_6S$)
= Amount (mg) of neostigmine methylsulfate RS
× (A_T / A_S)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 259 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 3.12 g of sodium dihydrogen phosphate dihydrate in 1000 mL of water and add phosphoric acid to adjust the pH to 3.0. Dissolve 0.871 g of sodium 1-pentane sulfonate in this solution. To 890 mL of this solution, add 110 mL of acetonitrile.

Flow rate: Adjust the flow rate to make the retention time of neostigmine about 9 minutes.

System suitability

System performance: Dissolve 4 mg of dimethylaminophenol and 25 mg of neostigmine methylsulfate in 50 mL of the mobile phase. Proceed with 10 μL of this solution according to the above conditions; dimethylaminophenol and neostigmine are eluted in this order with the resolution between these peaks being NLT 6.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of neostigmine peak areas is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Neostigmine Methylsulfate Injection
네오스티그민메틸황산염 주사액

Neostigmine Methylsulfate Injection is an aqueous solution for injection. Neostigmine Methylsulfate Injection contains NLT 93.0% and NMT 107.0% of the labeled amount of neostigmine methylsulfate ($C_{13}H_{22}N_2O_6S$: 334.39).

Method of preparation Prepare as directed under Injections, with Neostigmine Methylsulfate.

Description Neostigmine Methylsulfate Injection occurs as a clear and colorless liquid.
It is gradually affected by light.

pH—Between 5.0 and 6.5.

Identification Weigh an amount of Neostigmine Methylsulfate Injection, equivalent to 0.5 mg of neostigmine methylsulfate, according to the labeled amount, and add water, if necessary, to make 10 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 257 nm and 261 nm.

Sterility Meets the requirements.

Bacterial endotoxins Neostigmine Methylsulfate Injection is less than 5 EU per mg of neostigmine methylsulfate.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

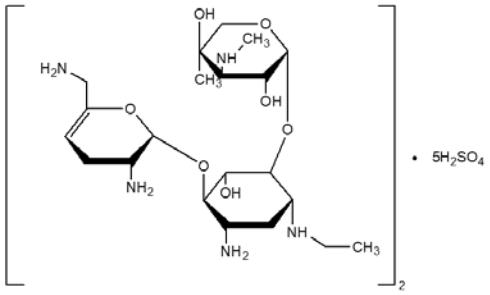
Extractable volume of injections Meets the requirements.

Assay Use Neostigmine Methylsulfate Injection as the test solution. Separately, weigh accurately about 25 mg of neostigmine methylsulfate RS, previously dried at 105 ℃ for 3 hours, and dissolve in the mobile phase to make exactly 50 mL. Use this solution as the standard solution. Perform the test as directed under the Assay of neostigmine methylsulfate.

Amount (mg) of neostigmine methylsulfate ($C_{13}H_{22}N_2O_6S$)
= Amount (mg) of neostigmine methylsulfate RS

Packaging and storage Preserve in light-resistant, hermetic containers.

Netilmicin Sulfate
네틸마이신황산염



$(C_{21}H_{41}N_5O_7)_2 \cdot 5H_2SO_4$: 1441.55

(2*R*,3*R*,4*R*,5*R*)-2-[(1*S*,2*S*,3*R*,4*S*,6*R*)-4-Amino-3-[[(2*S*,3*R*)-3-amino-6-(aminomethyl)-3,4-dihydro-2*H*-pyran-2-yl]oxy]-6-(ethylamino)-2-hydroxycyclohexyl]oxy-5-methyl-4-(methylamino)oxane-3,5-diol; sulfuric acid [*56391-57-2*]

Netilmicin Sulfate is a sulfate of sisomicin derivatives.

Netilmicin Sulfate contains NLT 595 μg and NMT 720 μg (potency) of netilmicin ($C_{21}H_{41}N_5O_7$: 475.58) per mg, calculated on the dried basis.

Description Netilmicin Sulfate occurs as a white to pale yellow powder.
It is very soluble in water and practically insoluble in ethanol(95) and ether.
It is hygroscopic.

Identification (1) Dissolve 30 mg of Netilmicin Sulfate in 3 mL of water, and add 0.2 mL of bromine TS; the color of the solution disappears immediately.

(2) Dissolve 5 mg each of Netilmicin Sulfate and netilmicin sulfate RS in 5 mL of water, respectively, and use these solutions as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol, chloroform, ammonia water(28) and acetone (2 : 2 : 1 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray

0.2% ninhydrin-water saturated 1-butanol TS evenly and heat at about 100 ℃ for about 5 minutes; the principal spots obtained from the test solution and the standard solution are purple to reddish brown, and the R_f values are the same.

(3) The aqueous solution of Netilmicin Sulfate (1 in 100) responds to the Qualitative Analysis (1) for sulfate.

Optical rotation $[\alpha]_D^{20}$: Between +88° and +96° (0.3 g, calculated on the dried basis, water, 10 mL, 100 mm).

pH Dissolve 0.2 g of Netilmicin Sulfate in 5 mL of water; the pH of this solution is between 3.5 and 5.5.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Netilmicin Sulfate in 5 mL of water; the solution is clear and colorless to light yellow.

(2) ***Heavy metals***—Proceed with 1.0 g of Netilmicin Sulfate as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Weigh an amount equivalent to 50 mg of Netilmicin Sulfate, calculated on a dried basis, dissolve in 5 mL of water, and use this solution as the test solution. Pipet 0.5 mL, 1 mL, 1.5 mL, and 3 mL of the test solution, add water to make exactly 50 mL respectively, and use these solutions as the standard solution (1), (2), (3), and (4). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solutions, the standard solution (1), the standard solution (2), the standard solution (3), and the standard solution (4) each on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol, chloroform, ammonia water(28) and acetone (2 : 2 : 1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray 0.2% ninhydrin-water saturated 1-butanol TS and heat at about 100 ℃ for 5 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots obtained from the standard solution (3). The total intensity of spots other than the principal spot obtained from the test solution is not more intense than the spots from the standard solution (4) (NMT 6%).

Sterility It meets the requirements when used for the manufacturing of sterile preparations. However, it is not applied when the manufacturing process of sterile preparations has a final sterilization process.

Bacterial endotoxins It is less than 0.50 EU per mg of netilmicin (potency) when used for the manufacturing of sterile preparations.

Loss on drying NMT 15.0% (0.15 g, NMT 0.67 kPa, 110 ℃, 3 hours). Avoid hygroscopicity when taking the sample.

Residue on ignition NMT 1.0% (1 g).

Assay Weigh accurately about 50 mg (potency) of Netilmicin Sulfate and netilmicin sulfate RS, and dissolve in the mobile phase to make exactly 50 mL, respectively. Use these solutions as the test solution and the standard solution. Perform the test with 20 μL each of the test solution and the standard solution, as directed under the Liquid Chromatography according to the following conditions, and calculate the peak areas, A_T and A_S, of netilmicin from the test solution and the standard solution.

$$\text{Potency (μg) of netilmicin } (C_{16}H_{17}N_3O_5S) = \text{Potency of netilmicin sulfate RS (μg)} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of 1000 mL of a solution, made by adding diluted phosphoric acid (5 in 1000) to 20.22 g of sodium 1-heptanesulfonate, and acetonitrile (620 : 380).

Flow rate: 1 mL/min

System suitability

System performance: Weigh accurately an appropriate amount of Netilmicin Sulfate and sisomicin sulfate RS, prepare each solution containing 1 mg per mL, and use these solutions as the system suitability solution. Proceed with 20 μL of system suitability solution according to the above conditions; the resolution between sisomicin and netilmicin is NLT 1. Proceed with 20 μL of the standard solution according to the above conditions; the number of theoretical plates is NLT 3000, and the symmetry factor is NMT 2.

System repeatability: Repeat the test 5 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of netilmicin is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers, filled with nitrogen or argon (NMT 5 ℃).

Netilmicin Sulfate Injection
네틸마이신황산염 주사액

Netilmicin Sulfate Injection contains NLT 90.0% and NMT 120.0% of labeled amount of netilmicin ($C_{21}H_{41}N_5O_7$: 475.58).

Method of preparation Prepare as directed under Injections, with Netilmicin Sulfate.

Description Netilmicin Sulfate Injection occurs as a clear, colorless to pale yellow liquid.

Identification Perform the test according to the Identification (2) of Netilmicin sulfate.

pH Between 3.5 and 6.0.

Sterility Netilmicin Sulfate Injection meets the requirements of the Sterility.

Bacterial endotoxins Less than 0.50 EU/mg per mg (potency) of netilmicin.

Particulate contamination: Visible particles in injections and ophthalmic solutions Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Proceed as directed under the Assay under Netilmicin sulfate. However, pipet a volume of Netilmicin Sulfate Injection, equivalent to about 0.100 g (potency) according to the labeled potency, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution.

Each mL of potency of netilmicin ($C_{16}H_{17}N_3O_5S$) (μg)
= Potency of netilmicin sulfate RS (μg)× $\frac{A_T}{A_S}$ ×2

Packaging and storage Preserve in hermetic containers.

Newlase
뉴라제

Newlase is a powdered digestive enzyme obtained by extracting and purifying enzymes produced by culturing filamentous fungi of the genus *Rhyzopus*, which contains, when dried, NLT 50000 units and NMT 66000 units of protein digestibility (pH 3.0) and 3000 to 4000 units of fat digestibility (pH 7.0) in 1g.

Description Newlase occurs as a pale yellow powder.
It is sparingly soluble in water and insoluble in ethanol(95).

Identification Perform the test according to the Assay; Newlase shows a positive reaction.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Newlase according to Method 2 and perform the test. Prepare the control solution with 5.0 mL of lead standard solution (NMT 50 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Newlase according to Method 3 and perform the test (NMT 2 ppm).

Loss on drying NMT 1.0% (1 g, 105 °C, 4 hours).

Residue on ignition NMT 25% (1 g).

Assay (1) ***Protein digestion activity***—Weigh accurately 0.5 g of Newlase and dissolve in 0.002 mol/L hydrochloric acid to make 250 mL. Take 10.0 mL of this solution, add 0.002 mol/L hydrochloric acid to make 50 mL, and use it as the test solution. Separately, take 5.0 mL of casein solution (pH 3.0), allow to stand at 37 ± 0.5 ℃ for 10 minutes, add 1.0 mL of the test solution, and shake to mix. After allowing this solution to stand at 37 ± 0.5 ℃ for 10 minutes, add 5 mL of 7.2% trichloroacetic acid solution, shake to mix, and let it stand at 37 ± 0.5 ℃ for 30 minutes, and filter. Take 2.0 mL of the filtrate, add 5.0 mL of 0.55 mol/L sodium carbonate solution and 1 mL of dilute Folin TS (1 in 3), allow to stand at 37 ± 0.5 ℃ for 30 minutes, and measure the absorbance A_T at a wavelength of 660 nm by testing this solution as directed under the Ultraviolet-visible Spectroscopy. Separately, take 1.0 mL of the test solution, add 5 mL of 7.2% trichloroacetic acid solution, shake to mix, add 5 mL of casein solution, allow it to stand it at 37 ± 0.5 °C for 30 minutes, and proceed as above to measure the absorbance A_B as directed under the Ultraviolet-visible Spectroscopy.

Protein digestion activity (unit/g)
$$= (AT - AB) \times F \times \frac{11}{2} \times \frac{1}{10} \times 2500$$

F: Amount of tyrosine for an absorbance difference of 1.000. It is obtained from the tyrosine calibration curve.

Preparation of tyrosine calibration curve: Weigh accurately 0.5 g of tyrosine RS, previously dried at 105 °C for 3 hours, dissolve in 0.2 mol/L hydrochloric acid TS to make 500 mL. Take 1.0 mL, 2.0 mL, 3.0 mL, and 4.0 mL of this solution and add 0.2 mol/L hydrochloric acid solution to make 100 mL, respectively. Take 2.0 mL each of this solution, add 5 mL of 0.55 mol/L sodium carbonate solution and 1 mL of dilute Folin TS (1 in 3), allow to stand at 37 ± 0.5 °C for 30 minutes, and measure the absorbance A_1, A_2, A_3, and A_4 at a wavelength of 660 nm by performing the test as directed under the Ultraviolet-visible Spectroscopy. Separately, use 2 mL of 0.2 mol/L hydrochloric acid solution and measure the absorbance A_0 by performing the test as directed under the Ultraviolet-visible Spectroscopy by proceeding as above. Prepare a calibration curve with the absorbance difference on the vertical axis and the amount of tyrosine (μg) on the horizontal axis to determine the amount of tyrosine for the absorbance difference of 1.000.

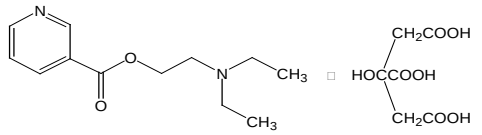
(2) ***Fat digestion activity***— (i) Test solution: Weigh accurately about 0.5 g of Newlase and dissolve in water to make 10 mL. Take exactly 5.0 mL of this solution, add water to make 10 mL, and use this solution as the test solution.

(ii) Procedure: Proceed according to the Fat digestion activity as directed under the Digestive Power. However, use olive oil as the substrate solution and 0.1 mol/L

phosphate buffer (pH 7.0) as the buffer.

Packaging and storage Preserve in tight containers.

Nicametate Citrate
니카메테이트시트르산염



$C_{12}H_{18}N_2O_2 \cdot C_6H_8O_7$: 414.14
2-Diethylaminoethyl pyridine-3-carboxylate 2-hydroxypropane-1,2,3-tricarboxylic acid, [*1641-74-3*]

Nicametate Citrate, when dried, contains NLT 97.0% and NMT 103.0% of nicametate citrate ($C_{12}H_{18}N_2O_2 \cdot C_6H_8O_7$).

Description Nicametate Citrate occurs as a white crystalline powder.
It has a unique aroma and a slightly acidic taste.
It is freely soluble in water and acetic acid(100), sparingly soluble in methanol and practically insoluble in ethanol(95), acetone or chloroform.

Identification (1) A solution of Nicametate Citrate (1 in 100) responds to the Qualitative Analysis for citrate.

(2) Add 5 drops of Reinecke salt TS to 5 mL of the aqueous solution of Nicametate Citrate (1 in 100); a pale red precipitate is produced.

(3) Mix 5 mg of Nicametate Citrate and 0.1 g of 2,4-dinitrochlorobenzene, heat gently to dissolve for 5 to 6 seconds. After cooling, add 4 mL of potassium hydroxide-ethanol TS; the resulting solution exhibits a dark red color.

(4) Dissolve 0.1 g of Nicametate Citrate in water to make 100 mL. Take 5 mL of this solution and add water to make 100 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 262 nm and 265 nm.

Absorbance $E_{1cm}^{1\%}$ (263 nm): Between 72.4 and 77.6 (After drying, 5 mg, water, 100 mL).

pH Between 3.0 and 5.0 (2% aqueous solution).

Purity (1) ***Chloride***—Proceed with 0.5 g of Nicametate Citrate as directed under the Chloride and perform the test. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.028%).

(2) ***Sulfate***—Proceed with 0.5 g of Nicametate Citrate and perform the test. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid VS (NMT 0.096%).

(3) ***Oxalate***—Dissolve 0.5 g of Nicametate Citrate in 3 mL of water, add 4 mL of ethanol and 0.2 mL of calcium chloride TS, and allow it to stand for 1 hour; the solution is clear.

(4) ***Heavy metals***—Proceed with 1.0 g of Nicametate Citrate according to Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(5) ***Arsenic***—Proceed with 1.0 g of Nicametate Citrate according to Method 1 and perform the test (NMT 2 ppm).

Loss on drying NMT 1.0% (1 g, in vacuum, phosphorus pentoxide, 5 hours).

Residue on ignition NMT 0.20% (1 g)

Assay Weigh accurately about 0.4 g of Nicametate Citrate, previously dried, dissolve in 50 mL of acetic acid(100) for non-aqueous titration, and titrate with 0.1 mol/L perchloric acid VS (indicator: 10 drops of α-naphtholbenzein TS). The endpoint of the titration is when the yellowish brown color of this solution turns yellow to green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 20.721 mg of $C_{12}H_{18}N_2O_2 \cdot C_6H_8O_7$

Packaging and storage Preserve in tight containers.

Nicametate Citrate Tablets
니카메테이트시트르산염 정

Nicametate Citrate Tablet contains NLT 95.0% and NMT 105.0% of labeled amount of nicametate citrate ($C_{18}H_{26}N_2O_9$: 414.14)

Method of preparation Prepare as directed under Tablets, with Nicametate Citrate.

Identification Use the powdered 2 tablets of Nicametate Citrate Tablets. Extract with two 20 mL portions of mixture of methanol and water (8 : 2), and filter it. Put the filtrate into a 100-mL volumetric flask, add mixture of methanol and water (8 : 2) to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of nicametate citrate RS and dissolve in the mixture of methanol and water (8 : 2) to make 100 mL. Use this solution as the standard solution. Perform the test with these solutions using the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of acetone, acetic acid(100) and water (10 : 5 : 3) to a distance of about 10 cm, and air-dry the plate. Spray Dragendorff's TS evenly onto the plate; the R_f value and the color of the spots obtained from the sample and the standard solutions are the same.

Dissolution Perform the test with 1 tablet of Nicametate

Citrate Tablets at 100 revolutions per minutes according to Method 2, using 900 mL of 0.05 mol/L of sodium acetate buffer (pH 4.0) as the dissolution medium. Filter the medium 45 minutes after starting the dissolution test, and use this solution as the test solution. Separately, weigh accurately about 11 mg of nicametate citrate RS and dissolve it in 0.05 mol/L sodium acetate buffer (pH 4.0) to make exactly 100 mL. Use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography and determine, A_T and A_S, of the peak area of nicametate citrate. The dissolution rate of Nicametate Citrate Tablets in 45 minutes is NLT 80%.

Dissolution rate (%) for the labeled amount of nicametate citrate ($C_{12}H_{18}N_2O_2 \cdot C_6H_8O_7$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 900$$

*W*s: Amount (mg) of nicametate citrate RS

C: Labeled amount (mg) of nicametate citrate ($C_{12}H_{18}N_2O_2 \cdot C_6H_8O_7$) in 1 tablet

Operating Conditions

Detector: An ultraviolet absorption photometer (wavelength: 263 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of methanol and 0.005 mol/L sodium octanesulfonate solution (45 : 55).

Flow rate: 1.2 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of nicametate citrate is NMT 2.0%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately NLT 20 tablets of Nicametate Citrate Tablets and powder. Weigh accurately an amount, equivalent to about 100 mg of nicametate citrate ($C_{12}H_{18}N_2O_2 \cdot C_6H_8O_7$), and add the mixture of acetic acid and sodium acetate buffer (pH 4.0) to make 100mL. Pipet 10 mL of this solution, add the mixture of acetic acid and sodium acetate buffer (pH 4.0) to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 100 mg of nicametate citrate RS, and add the mixture of acetic acid and sodium acetate buffer (pH 4.0) to make 100mL. Pipet 10 mL of this solution, add the mixture of acetic acid and sodium acetate buffer (pH 4.0) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography and determine, A_T and A_S, of the peak area of nicametate.

Amount (mg) of nicametate citrate ($C_{12}H_{18}N_2O_2 \cdot C_6H_8O_7$)

$$= \text{Amount (mg) of nicametate citrate RS} \times \frac{A_T}{A_S}$$

Operating Conditions

Detector: An ultraviolet absorption photometer (wavelength: 263 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μ*m* in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile Phase: Dissolve 1.08 g of sodium 1-octanesulfonate in water 1000 mL. To 550 mL of this solution, add 450 mL of methanol.

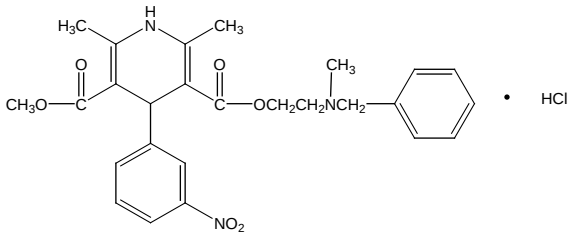
Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of nicametate is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Nicardipine Hydrochloride
니카르디핀염산염



and enantiomer

$C_{26}H_{29}N_3O_6 \cdot HCl$: 515.99

3-(2-(Benzyl(methyl)amino)ethyl) 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate hydrochloride [*54527-84-3*]

Nicardipine hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of nicardipine hydrochloride ($C_{26}H_{29}N_3O_6 \cdot HCl$).

Description Nicardipine Hydrochloride occurs as a slightly greenish yellow crystalline powder.
It is freely soluble in methanol or acetic acid(100), sparingly soluble in ethanol(95) and insoluble in water, acetonitrile or acetic anhydride.
A solution of Nicardipine Hydrochloride in methanol (1 in 20) shows no optical rotation.
It is gradually affected by light.

Identification (1) Determine the absorption spectra of Nicardipine Hydrochloride and a solution of nicardipine

hydrochloride RS in ethanol(99.5) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Nicardipine Hydrochloride and nicardipine hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 20 mg of Nicardipine Hydrochloride in 10 mL of water and 3 mL of nitric acid; the solution responds to the Qualitative Analysis for chloride.

Melting point Between 167 and 171 °C.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Nicardipine Hydrochloride as directed under Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Perform the test using light-resistant container. Dissolve 0.10 g of Nicardipine Hydrochloride in 50 mL of the mobile phase and use this solution as the test solution. Pipet 1.0 mL of this solution and add the mobile phase to make exactly 50 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by automatic integration method; each peak area other than the peak of nicardipine is not greater than the peak area of nicardipine from the standard solution. Also, the sum of each peak area is not greater than 2 times the peak area of nicardipine from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of a solution of perchloric acid (43 in 50000) and acetonitrile (3 : 2).

Flow rate: Adjust the flow rate so that the retention time of nicardipine is about 6 minutes.

System suitability

Detection sensitivity: Pipet 2.0 mL of the standard solution and add the mobile phase to make exactly 20 mL. Adjust the peak area of nicardipine obtained from 20 μL of this solution to 8% to 12% of the peak area of nicardipine obtained from the standard solution.

System performance: Dissolve 2 mg each of Nicardipine Hydrochloride and nifedipine in 50 mL of the mobile phase. Proceed with 10 μL of this solution according to the above conditions; nicardipine and nifedipine are eluted in this order with the resolution being NLT 3.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of nicardipine is NMT 3.0%.

Time span of measurement: About four times the retention time of nicardipine after the solvent peak.

Loss on drying NMT 1.0% (1 g, 105 °C, 2 hours).

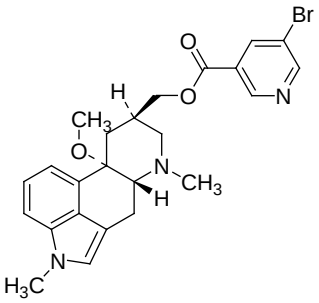
Residue on ignition NMT 0.1% (1 g).

Assay Perform the test using light-resistant containers. Weigh accurately about 0.9 g of Nicardipine Hydrochloride, previously dried, dissolve in 100 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 51.60 mg of $C_{26}H_{29}N_3O_6 \cdot HCl$

Packaging and storage Preserve in light-resistant, well-closed containers.

Nicergoline
니세르골린



$C_{24}H_{26}BrN_3O_3$: 484.39

[(6a*R*,9*R*,10a*S*)-10a-Methoxy-4,7-dimethyl-6a,8,9,10-tetrahydro-6*H*-indolo[4,3-fg]quinoline-9-yl]methyl-5-bromopyridine-3-carboxylate [*27848-84-6*]

Nicergoline, when dried, contains NLT 98.5% and NMT 101.0% of nicergoline ($C_{24}H_{26}BrN_3O_3$).

Description Nicergoline occurs as white to light yellow crystals or a crystalline powder.
It is sparingly soluble in ethanol(99.5), acetonitrile and acetic anhydride, and practically insoluble in water.
It is gradually changed to pale brown by light.

Melting point—About 136 ℃ (with decomposition).

Identification (1) Determine the absorption spectra of the solutions of Nicergoline and nicergoline RS in ethanol(99.5) (1 in 100000) as directed under the Ultraviolet-

visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infra spectra of Nicergoline and nicergoline RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +5.2° and +6.2° (after drying, 0.5 g, ethanol(95), 10 mL, 100 mm).

Purity (1) ***Heavy metals*—**Weigh 2.0 g of Nicergoline and perform the test according to Method 2. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances*—**Dissolve 25 mg of Nicergoline in 25 mL of acetonitrile and use it as the test solution. Pipet 1.0 mL of this solution and add acetonitrile to make exactly 100 mL. Pipet 10 mL of this solution, add acetonitrile to make exactly 50 mL, and use it as the standard solution. Take 20 μL each of the test solution and the standard solution and perform the test according to the Liquid Chromatography under the following conditions. Determine the peak area of each solution according to the automatic integration method; the peak area of a related substance with a retention time relative to nicergoline of about 0.5 is not greater than 4 times the peak area of nicergoline in the standard solution, and the peak area of other individual related substances is not greater than 2.5 times the peak area of nicergoline in the standard solution, and among the standard solutions of the peak area, there are NMT 2 peak areas greater than the peak area of nicergoline. In addition, the sum of peak areas other than nicergoline in the test solution is not greater than 7.5 times the peak area of nicergoline in the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 288 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with 5 μm octadecylsilanized silica gel for liquid chromatography.

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of 0.05 mol/L potassium dihydrogen phosphate TS (pH 7.0), methanol and acetonitrile (350 : 350 : 300).

Flow rate: Adjust the flow rate so that the retention time of nicergoline is about 25 minutes.

System suitability

Test for required detectability: Add acetonitrile to 1 mL of the test solution to make exactly 50 mL, and use it as the system suitability solution. Take exactly 5 mL of this solution and add acetonitrile to make exactly 100 mL. Confirm that the peak area of nicergoline obtained from 20 μL of this solution is 3 to 7% of the peak area of nicergoline obtained from 20 μL of system suitability solution.

System performance: Proceed with 20 μL of the test solution under the above conditions; the number of theoretical plates of nicergoline is NLT 8000 and the coefficient of symmetry is NMT 2.0.

System reproducibility: Repeat the test 6 times with 20 μL each of the standard solution under the above conditions; the relative standard deviation of the peak area of nicergoline is NMT 4.0%.

Time span of measurement: About 2 times the retention time of nicergoline after the solvent peak.

Loss on drying NMT 0.5% (2 g, in vacuum, 60 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Nicergoline, after drying, add 10 mL of acetic anhydride, dissolve it by heating. After cooling, add 40 mL of nitrobenzene and titrate with 0.1 mol/L perchloric acid VS (indicator: 10 drops of neutral red TS). However, the endpoint of the titration is when the solution changes from red to bluish purple to bluish green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 24.22 mg of $C_{24}H_{26}BrN_3O_3$

Packaging and storage Preserve in light-resistant, tight containers.

Nicergoline Tablets
니세르골린 정

Nicergoline Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of nicergoline ($C_{24}H_{26}BrN_3O_3$: 484.39).

Method of preparation Prepare as directed under Tablets, with Nicergoline.

Identification Powder Nicergoline Tablets, weigh an amount equivalent to 10 mg of nicergoline according to the labeled amount, add 20 mL of ethanol(99.5), shake strongly for 10 minutes to mix, and filter using a membrane filter with a pore size of NMT 0.45 μm. Add ethanol(99.5) to 2 mL of the filtrate to make 100 mL. Determine the absorption spectra of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 226 nm and 230 nm and a minimum between 286 nm and 290 nm.

Purity (1) ***Related substances***—With 20 mL of the test solution obtained from the Assay, perform the test according to the Liquid Chromatography under the following conditions. Measure each peak area of the test solution according to the automatic integration method and obtain each amount by the percentage peak area method;

the total area of the peaks other than nicergoline is NMT 2.0%.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, comply with the operating conditions in the Assay.

System suitability

System performance: Proceed as directed under the system suitability under the Assay.

Test for required detectability: Add a mixture of acetonitrile and water (17 : 3) to 1 mL of the standard solution obtained from the Assay to make 50 mL and use it as the system suitability solution. Pipet 5 mL of this solution and add a mixture of acetonitrile and water (17 : 3) to make exactly 100 mL. Confirm that the peak area of nicergoline obtained from 20 μL of this solution is 3 to 7% of the peak area of nicergoline obtained from 20 μL of the system suitability solution.

System reproducibility: Repeat the test 6 times with each 20 μL of the system suitability solution under the above conditions; the relative standard deviation of the peak area of nicergoline is NMT 1.5%.

Time span of measurement: About 2 times the retention time of nicergoline from the solvent peak.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements when the content uniformity test is perform as follows: Add exactly 25 mL of diluted ethanol (4 in 5) to 1 Nicergoline Tablet, sonicate to disperse the particles into smaller pieces, and shake vigorously for 5 minutes to mix. Centrifuge this solution for 10 minutes, take exactly 4 mL of the clear supernatant, add diluted ethanol (4 in 5) to this solution to make exactly 25 mL, and use this solution as the test solution. Separately, dry nicergoline RS under reduced pressure at 60 °C for 2 hours, and dissolve exactly 10 mg of this drug in 25 mL of diluted ethanol (4 in 5). Pipet 4 mL of this solution, add diluted ethanol (4 in 5) to make exactly 50 mL, and use this solution as the standard solution. With the test solution and the standard solution, determine the absorbance A_{T1} and A_{S1} at 288 nm and absorbances A_{T2} and A_{S2} at 340 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of nicergoline } (C_{24}H_{26}BrN_4O_3) = \text{Amount (mg) of nicergoline RS} \times \frac{A_{T1}-A_{T2}}{A_{S1}-A_{S2}} \times \frac{1}{2}$$

Assay Take NLT 20 tablets of Nicergoline Tablets and weigh accurately the mass, powder them. Weigh accurately an amount equivalent to about 20 mg of nicergoline ($C_{24}H_{26}BrN_3O_3$), add exactly 20 mL of a mixture of acetonitrile and water (17 : 3), shake strongly for 10 minutes, centrifuge for 10 minutes, and use the clear liquid at the top layer as the test solution. Separately, weigh accurately about 20 mg of nicergoline RS, previously dried for 2 hours under reduced pressure at 60 ℃ and dissolve exactly in 20 mL of a mixture of acetonitrile and water (17 : 3) to use as the standard solution. Take exactly 20 μL each of the test solution and standard solution and perform the test according to the Liquid Chromatography under the following conditions, and measure the A_T and A_S peak areas of nicergoline in each solution.

$$\text{Amount (mg) of nicergoline } (C_{24}H_{26}BrN_4O_3) = \text{Amount (mg) of nicergoline RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 288 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of 0.05 mol/L potassium dihydrogen phosphate TS (pH 7.0), methanol, and acetonitrile (350 : 350 : 300).

Flow rate: Adjust the flow rate so that the retention time of nicergoline is about 25 minutes.

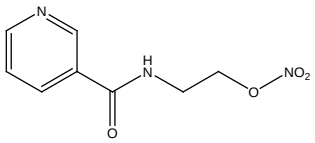
System suitability

System performance: Proceed with 20 μL of standard solution under the above conditions; the number of theoretical plates of nicergoline is NLT 8000 and the coefficient of symmetry is NMT 2.0.

System reproducibility: Repeat the test 6 times with 20 μL each of standard solution under the above conditions; the relative standard deviation of the nicergoline peak area is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Nicorandil
니코란딜



$C_8H_9N_3O_4$: 211.17

2-[(Pyridin-3-ylcarbonyl)amino]ethyl nitrate [*65141-46-0*]

Nicorandil contains NLT 98.5% and NMT 101.0% of nicorandil (C8H9N3O4), calculated on the anhydrous basis.

Description Nicorandil occurs as white crystals.
It is freely soluble in methanol, ethanol(99.5) and acetic acid(100), sparingly soluble in acetic anhydride and practically insoluble in water.

Melting point—About 92 °C (with decomposition).

Identification (1) Determine the absorption spectra of Nicorandil and nicorandil RS (1 in 50000) as directed

under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Nicorandil and nicorandil RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit the same intensities of absorption at the same wavenumbers.

Purity (1) ***Sulfate***—Dissolve 2.0 g of Nicorandil in 20 mL of dilute ethanol, add 1 mL of dilute hydrochloric acid and water to make 50 mL, and use this solution as the test solution. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid VS, 20 mL of dilute ethanol, 1 mL of dilute hydrochloric acid and water to make 50 mL (NMT 0.010%).

(2) ***Heavy metals***—Proceed with 2.0 g of Nicorandil as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 20 mg of Nicorandil in 10 mL of mobile phase and use this solution as the test solution. Perform the test with 10 μL of the test solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of the test solution by the automatic integration method; the peak area of *N*-(2-hydroxyethyl)isonicotinamide nitric acid ester, which has a relative retention time of about 0.86 with respect to nicorandil, is NMT 0.5% of the peak area of nicorandil, the each area of other peaks is NMT 0.1%, and the sum area of the peaks other than nicorandil and *N*-(2-hydroxyethyl)isonicotinamide nitric acid ester is NMT 0.25% of the total peak area.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of water, tetrahydrofuran, triethylamine and trifluoroacetic acid (982 : 10 : 5 : 3).

Flow Rate: Adjust the flow rate so that the retention time of nicorandil is about 18 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the test solution, add the mobile phase to make exactly 500 mL, and use this solution as the system suitability test solution. Pipet 1 mL of the system suitability test solution and add the mobile phase to make exactly 20 mL. Confirm that the peak area obtained from 10 μL of this solution is 2% to 8% of the peak area of nicorandil in the system suitability test solution.

System performance: Dissolve 10 mg of *N*-(2-hydroxyethyl)isonicotinamide nitric acid ester in the mobile phase to make 100 mL. Proceed with the solution, prepared by adding 10 mL of the test solution to 1 mL of this solution, according to the above conditions; *N*-(2-hydroxyethyl)isonicotinamide nitric acid ester and nicorandil are eluted in this order with the resolution between these peaks being NLT 3.0.

System repeatability: Repeat the test 6 times with 10 μL each of the system suitability solution according to the above condition; the relative standard deviation of the peak area of nicorandil is NMT 1.5%.

Time span of measurement: About 3 times the retention time of nicorandil after the solvent peak.

Water NMT 0.1% (2 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Nicorandil, dissolve in 30 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 21.12 mg of $C_8H_9N_3O_4$

Packaging and storage Preserve in tight containers at a temperature between 2 and 8 °C.

Nicorandil Tablets
니코란딜 정

Nicorandil Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of nicorandil ($C_8H_9N_3O_4$: 211.18).

Method of preparation Prepare as directed under Tablets, with Nicorandil.

Identification (1) Weigh an amount equivalent to 20 mg of nicorandil ($C_8H_9N_3O_4$), according to the labeled amount of Nicorandil Tablets, add 50 mL of water, shake to mix for 10 minutes, and then filter. Take 5 mL of the filtrate and add water to make 100 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 260 nm and 264 nm.

(2) Weigh an amount equivalent to 50 mg of nicorandil ($C_8H_9N_3O_4$), according to the labeled amount of Nicorandil Tablets, add 5 mL of dilute methanol (4 in 5), shake to mix for 10 minutes, and then filter. Use the filtrate as the test solution. Separately, weigh 50 mL of nicorandil RS, dissolve in 5 mL of dilute methanol (4 in 5), and use this solution as the standard solution. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescence indi-

cator). Next, develop the plate with acetone as the developing solvent to a distance of about 13 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 tablet of Nicorandil Tablets at 50 revolutions per minute according to Method 2, using 500 mL of water as the dissolution medium. Take the medium 15 minutes after starting the dissolution test, and filter. Discard the initial 10 mL of the filtrate and pipet V mL of the subsequent filtrate. Add water to make exactly V' mL so that the solution contains 4 μg of nicorandil ($C_8H_9N_3O_4$) per mL according to the labeled amount. Use this solution as the test solution. Separately, weigh accurately 20 mg of nicorandil RS, and dissolve in water to make 100 mL. Pipet 2 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine, A_T and A_S, of the peak area of nicorandil. The dissolution rate of Nicorandil Tablets in 15 minutes is NLT 70%.

Dissolution rate (%) with respect to the labeled amount of *nicorandil* ($C_8H_9N_3O_4$)

$$= W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C}$$

*W*s: Amount (mg) of nicorandil RS

C: The labeled amount (mg) of nicorandil ($C_8H_9N_3O_4$) in 1 tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless-steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of water and methanol (65 : 35).

Flow rate: 1.0 mL/min

Uniformity of dosage units Meets the requirements according to the following procedure. After adding 1 mL of water to 1 tablet of Nicorandil Tablets to disintegrate, add 15 mL of water, shake to mix for 10 minutes, and adjust the volume to V mL with water to contain about 0.1 mg of nicorandil ($C_8H_9N_3O_4$) in 1 mL. Then, filter the solution. Discard the initial 10 mL of the filtrate, take 10.0 mL of the subsequent filtrate, add water to make 50 mL, and use this solution as the test solution. Separately, weigh accurately 20 mg of nicorandil RS, and dissolve in water to make 100 mL. Take 5.0 mL of this solution, add water to make 50 mL, and use this solution as the standard solution. Determine the absorption spectra of the test solution and the standard solution, A_T and A_S, using water as the control solution, as directed under the Ultraviolet-visible Spectroscopy at a wavelength of 262 nm.

Amount (mg) of nicorandil ($C_8H_9N_3O_4$)

$$= \text{Amount (mg) of nicorandil RS} \times \frac{A_T}{A_S}$$

Assay Weigh accurately the mass of NLT 20 tablets of Nicorandil Tablets and powder. Weigh accurately an amount equivalent to about 20 mg of nicorandil ($C_8H_9N_3O_4$), and add the mobile phase to make 100 mL. After filtering this solution, take 10 mL of the filtrate, add the mobile phase to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of nicorandil RS and dissolve in the mobile phase to make 100 mL. Take 10 mL of this solution, add the mobile phase to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine, A_T and A_S, of the peak area of nicorandil.

Amount (mg) of nicorandil ($C_8H_9N_3O_4$)

$$= \text{Amount (mg) of nicorandil RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of water and methanol (65 : 35).

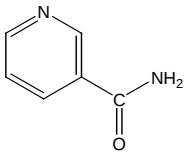
Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of nicorandil is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Nicotinamide
니코틴산아미드



$C_6H_6N_2O$: 122.13

Pyridine-3-carboxamide [*98-92-0*]

Nicotinamide, when dried, contains NLT 98.5% and NMT 102.0% of nicotinamide ($C_6H_6N_2O$).

Description Nicotinamide occurs as white crystals or a crystalline powder, which is odorless and has a bitter taste.
It is freely soluble in water or ethanol(95) and slightly soluble in ether.

Identification (1) Mix 5 mg of Nicotinamide with 10 mg of 1-chloro-2,4-dinitrobenzene, heat gently for 5 to 6 seconds to dissolve. After cooling, add 4 mL of potassium hydroxide-ethanol TS; the resulting solution exhibits a red color.

(2) Add 5 mL of sodium hydroxide TS to 20 mg of Nicotinamide and boil carefully; the gas produced changes the moistened red litmus paper to blue.

(3) Add water to 20 mg of Nicotinamide and nicotinamide RS to make 1000 mL, and determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

pH Dissolve 1.0 g of Nicotinamide in 20 mL of water; the pH of the resulting solution is between 6.0 and 7.5.

Melting point Between 128 and 131 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Nicotinamide in 20 mL of water; the resulting solution is clear and colorless.

(2) ***Chloride***—Proceed with about 0.5 g of Nicotinamide and perform the test. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.021%).

(3) ***Sulfate***—Proceed with about 1.0 g of Nicotinamide and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid (NMT 0.019%).

(4) ***Heavy metals***—Proceed with 1.0 g of Nicotinamide according to Method 1 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(5) ***Readily carbonizable substances***—Proceed with 0.20 g of Nicotinamide and perform the test. The color of this solution is not more intense than that of the matching fluid A.

Loss on drying NMT 0.5% (1 g, in vacuum, silica gel, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 25 mg of Nicotinamide and nicotinamide RS, previously dried, dissolve in 3 mL of water, respectively, and add the mobile phase to make exactly 100 mL. Pipet 8 mL of each of these solutions, and add the mobile phase to each solution to make exactly 50 mL. Pipet 5 mL of each of these solutions, add exactly 5 mL of internal standard solution to each solution, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of nicotinamide to internal standard, respectively.

$$\text{Amount (mg) of nicotinamide } (C_6H_6N_2O) = \text{Amount (mg) of nicotinamide RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of nicotinic acid (1 in 250000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 1.0 g of sodium 1-heptanesulfonate in water to make 1000 mL. Add 300 mL of methanol to 700 mL of this solution.

Flow Rate: Adjust the flow rate so that the retention time of nicotinamide is about 7 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the nicotinic acid and nicotinamide are eluted in this order with the resolution being NLT 5.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of nicotinamide to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

33.3% Nicotinamide Powder
니코틴산아미드 3배산

33.3% Nicotinamide Powder contains NLT 32.6% of nicotinamide ($C_6H_6N_2O$: 122.13).

Method of preparation Prepare by finely dispersing nicotinamide in edible fatty acid. 33.3% Nicotinamide Powder can be added with nicotinamide coated with silicon dioxide. 33.3% Nicotinamide Powder is a drug substance.

Description 33.3% Nicotinamide Powder occurs as a white to pale yellow powder.

Identification (1) Mix 5 mg of 33.3% Nicotinamide Powder with 10 mg of 2,4-dinitrochlorobenzene, heat gently for 5 to 6 seconds to dissolve. After cooling, add 4 mL of potassium hydroxide-ethanol TS; the resulting solution exhibits a red color.

(2) Add 5 mL of sodium hydroxide TS to 20 mg of 33.3% Nicotinamide Powder and boil over low heat; the gas produced changes moistened red litmus paper to blue.

(3) Dissolve about 20 mg of 33.3% Nicotinamide Powder in water to make 1000 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 261 nm and 263 nm and a minimum between 243 nm and 247 nm. When the absorbance of this solution at the absorbance maximum wavelength is represented as A_1 and the absorbance at the absorbance minimum wavelength is represented as A_2, A_2/A_1 is between 0.63 and 0.67.

Water NMT 1.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 1.3% (1 g).

Assay Weigh accurately about 20 mg of 33.3% Nicotinamide Powder, previously dried, and dissolve in water to make 100 mL. Take 5.0 mL of this solution and 8.0 mL of the internal standard solution, add water to make 100.0 mL, and use this solution as the test solution. Separately, weigh accurately 20 mg of nicotinamide RS, and dissolve in water to make 100.0 mL. Take 5.0 mL of this solution and 8.0 mL of the internal standard solution, add water to make 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography under the following conditions, and calculate the peak area ratios, Q_T and Q_S, of nicotinamide to internal standard, respectively.

$$\text{Amount (mg) of nicotinamide } (C_6H_6N_2O) = \text{Amount (mg) of nicotinamide RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh about 50 mg of anhydrous caffeine RS and dissolve in water to make 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

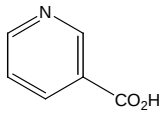
Mobile phase: Dissolve 1.0 g of sodium 1-hexanesulfonate in 750 mL of water and add 250 mL of methanol and 10 mL of acetic acid.

Flow Rate: Adjust the flow rate so that the retention time of nicotinamide is about 4 minutes.

Selection of column: Proceed with 20 μL of the standard solution under the above conditions. Use a column with the resolution of NLT 4.0 with nicotinamide and the internal standard being eluted in this order.

Packaging and storage Preserve in light-resistant, tight containers.

Nicotinic Acid
니코틴산



$C_6H_5NO_2$: 123.11

Pyridine-3-carboxylic acid [*59-67-6*]

Nicotinic Acid, when dried, contains NLT 99.5% and NMT 101.0% of nicotinic acid ($C_6H_5NO_2$).

Description Nicotinic Acid occurs as white crystals or a crystalline powder, which is odorless and has a slightly sour taste.

It is sparingly soluble in water, slightly soluble in ethanol(95) and very slightly soluble in ether.

It is soluble in sodium hydroxide TS or sodium carbonate TS.

Identification (1) Mix 5 mg of Nicotinic Acid with 10 mg of 1-chloro-2,4-dinitrobenzene and heat gently for 5 to 6 seconds to dissolve. After cooling, add 4 mL of potassium hydroxide-ethanol TS; the resulting solution exhibits a dark red color.

(2) Dissolve 20 mg of Nicotinic Acid and nicotinic acid RS in water to make 1000 mL. With these solutions, determine the absorption spectra as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Melting point Between 234 and 238 ℃.

pH Dissolve 0.20 g of Nicotinic Acid in 20 mL of water; the pH of this solution is between 3.0 and 4.0.

Purity (1) ***Clarity and color of solution***—Dissolve 0.20 g of Nicotinic Acid in 20 mL of water; the resulting solution is clear and colorless.

(2) ***Chloride***—Proceed with 0.5 g of Nicotinic Acid and perform the test. Prepare the control solution with

0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.021%).

(3) ***Sulfate***—Dissolve 1.0 g of Nicotinic Acid in 3 mL of dilute hydrochloric acid and water to make 50 mL. Use the resulting solution as the test solution to perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid and 3 mL of dilute hydrochloric acid to make 50 mL (NMT 0.019%).

(4) ***Nitro compounds***—Dissolve 8 mL of sodium hydroxide TS and water in 1.0 g of Nicotinic Acid to make 20 mL; the color of this resulting solution is not more intense than that of the matching fluid A.

(5) ***Heavy metals***—Proceed with 1.0 g of Nicotinic Acid according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Loss on drying NMT 0.5% (1 g, 105 ℃, 1 hour).

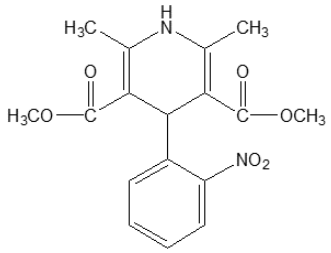
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Nicotinic Acid, previously dried, dissolve in 50 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 5 drops of phenolphthalein TS).

Each mL of 0.1 mol/L sodium hydroxide VS
= 12.311 mg of $C_6H_5NO_2$

Packaging and storage Preserve in well-closed containers.

Nifedipine
니페디핀



$C_{17}H_{18}N_2O_6$: 346.34

Dimethyl-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate [*21829-25-4*]

Nifedipine contains NLT 98.0% and NMT 102.0% of nifedipine ($C_{17}H_{18}N_2O_6$), calculated on the dried basis.

Description Nifedipine occurs as a yellow crystalline powder, and odorless and tasteless.
It is freely soluble in acetone or dichloromethane, sparingly soluble in methanol, ethanol(95) or acetic acid(100), slightly soluble in ether and practically insoluble in water.
It is changed by light.

Identification (1) Dissolve 50 mg of Nifedipine in 5 mL of ethanol(95), add 5 mL of hydrochloric acid and 2 g of zinc powder, allow to stand for 5 minutes, and filter. Perform the test with the filtrate as directed under the Qualitative Analysis for aromatic primary amine; the solution exhibits a purple color.

(2) Determine the absorption spectra of the solutions of Nifedipine and nifedipine RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Nifedipine and nifedipine RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 172 and 175 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Nifedipine in 5 mL of acetone; the solution is yellow and clear.

(2) ***Chloride***—To 2.5 g of Nifedipine, add 12 mL of dilute acetic acid and 13 mL of water, and heat to boiling. Filter it after cooling, discard the first 10 mL of the filtrate, take 5 mL of the subsequent filtrate, and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.021%).

(3) ***Sulfate***—Take 4 mL of the filtrate of (2) and add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution. Prepare the control solution with 0.45 mL of 0.005 mol/L sulfuric acid (NMT 0.054%).

(4) ***Heavy metal***—Proceed with 2.0 g of Nifedipine as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Arsenic***—Prepare the test solution with 1.0 g of Nifedipine according to Method 3 and perform the test it (NMT 2 ppm).

(6) ***Basic substances***—Perform the test in a light-resistant container away direct sunlight. To about 5.0 g of Nifedipine, dissolve 80 mL of a mixture of acetone and acetic acid(31) (5 : 3), and titrate with 0.02 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction. NMT 1.9 mL of 0.02 mol/L perchloric acid VS is consumed.

(7) ***Related substances***—Perform the test quickly using a light-resistant container. Weigh accurately 25 mg of Nifedipine, dissolve in 25 mL of methanol, add the mobile phase to make exactly 250 mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of nifedipine RS, and dissolve in methanol to make a solution containing 1 mg per mL. Take accurately an appropriate amount of this solution, add the mobile phase to make a solution containing 0.3 mg per mL, and use this solution as the standard solution for nifedipine. Also, weigh accurately an appropriate

amount of nifedipine nitrophenylpyridine analog RS, and dissolve in methanol to make a solution containing 1 mg per mL. Pipet an appropriate amount of this solution, add the mobile phase to make a solution containing 0.6 mg per mL, and use this solution as the standard solution (1). Weigh accurately an appropriate amount of nifedipine nitrosophenylpyridine analog RS, and dissolve in methanol to make a solution containing 1 mg per mL. Take an accurate amount of this solution, add the mobile phase to make a solution containing 0.6 μg per mL, and use this solution as the standard solution (2). Transfer accurately 5 mL each of the standard solution (1) and the standard solution (2) into a container, add exactly 5 mL of the mobile phase to the container, and use the solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Measure the peak areas of the nifedipine related substances, A_T and A_S in each solution to determine the amount of the nifedipine related substances. Nifedipine nitrosophenylpyridine analogues and nifedipine nitrosophenylpyridine analogues are NMT 0.2%.

Operating conditions

Detector: An ultraviolet absorbance photometer (wavelength: 265 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter). Fill the assistant column with octadecylsilanized silica gels.

Mobile phase: A mixture of water, methanol and acetonitrile (50 : 25 : 25).

Flow rate: 1 mL/min

System suitability

System performance: Proceed with 25 μL of a mixture of the standard solution for nifedipine, the standard solution (1) and the standard solution (2) under the above conditions; nitrophenylpyridine, nitrosophenylpyridine and nifedipine are eluted in this order, and the resolution of nitrophenylpyridine and nitrosophenylpyridine is NLT 1.5, and that of nitrosophenylpyridine and nifedipine is NLT 1.0.

System repeatability: Repeat the test 6 times with 25 μL each of the mixed solution according to the above conditions; the relative standard deviation of the peak area of each related substance is NMT 10%.

Loss on drying NMT 0.5% (0.5 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Perform the test in a light-resistant container away from direct sunlight. Weigh accurately about 0.12 g of Nifedipine and dissolve in methanol to make exactly 200 mL. Pipet 5 mL of this solution and add methanol to make exactly 100 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance of this solution, *A*, at the absorbance maximum wavelength at about 350 nm.

$$\text{Amount (mg) of nifedipine } (C_{17}H_{18}N_2O_6) = \frac{A}{142.3} \times 40000$$

Packaging and storage Preserve in light-resistant, tight containers.

Nifedipine Capsules
니페디핀 캡슐

Nifedipine Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$ 346.34).

Method of preparation Prepare as directed under Capsules, with Nifedipine.

Identification (1) Take the contents of 3 capsules of Nifedipine Capsules, put into a centrifuge tube, add 20 mL of 0.1 mol/L sodium hydroxide TS, and then add 25 mL of dichloromethane. Stopper the tube, and invert it several times to carefully release the pressure in the centrifuge tube. Stopper it again, shake gently for 1 hour, centrifuge for 10 minutes at 2000 to 2500 revolutions per minute, and use the clear liquid in the lower layer as the test solution. Separately, weigh an appropriate amount of nifedipine RS, dissolve in dichloromethane to make a solution containing 1.2 mg per mL, and use this solution as the standard solution. Mix equal volumes of the test solution and the standard solution, and use this solution as the mixed solution With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 500 μL each of the test solution, the standard solution and the mixed solution on a plate (0.5 mm in thickness) made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate and cyclohexane (1 : 1) as a developing solvent to a distance of about 15 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); each solution exhibits dark blue principal spots at a R_f value of about 0.3. Also, spray the plate with the coloring agent; the spots from each solution exhibit a light orange band against a yellow background.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Coloring agent—Dissolve 10 mL of 3 mol/L hydrochloric acid TS in 3 g of bismuth subnitrate and 30 g of potassium iodide, and add water to make 100 mL. Before use, take exactly 10 mL of this solution, add 10 mL of 3 mol/L hydrochloric acid TS and water to make 100 mL.

Related substances Perform the test quickly in a light-resistant container away from direct sunlight. Prepare the test solution as directed under the Assay. Separately, weigh accurately an appropriate amount of nifedipine RS,

and dissolve in methanol to make a solution containing 1 mg per mL. Pipet an appropriate amount of this solution, add the mobile phase to make a solution containing 0.3 mg per mL, and use this solution as the standard solution for nifedipine. Also, weigh accurately an appropriate amount of nifedipine nitrophenylpyridine analog RS, and dissolve in methanol to make a solution containing 1 mg per mL. Take an appropriate amount of this solution, add the mobile phase to make a solution containing 6 μg per mL, and use this solution as the standard solution (1). Weigh accurately an appropriate amount of nifedipine nitrosophenylpyridine analog RS, and dissolve in methanol to make a solution containing 1 mg per mL. Take an appropriate amount of this solution, add the mobile phase to make a solution containing 1.5 μg per mL, and use this solution as the standard solution (2). Pipet 5 mL each of the standard solution (1) and the standard solution (2), and make a solution by adding accurately 5 mL of the mobile phase. Use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and measure the peak areas A_T and A_S of nifedipine related substance of each solution to determine the amount of nifedipine related substance. Dimethyl 4-(2-nitrophenyl)-2,6-dimethylpyridine-3,5-dicarboxylic acid, equivalent to nifedipine nitrophenylpyridine, is NMT 2.0% and Dimethyl 4 (2-nitrosophenyl)-2,6-dimethylpyridine-3,5-dicarboxylic acid, equivalent to nifedipine nitrosophenylpyridine, is NMT 0.5%.

Operating conditions

For the detector, column, mobile phase and flow rate, comply with the operating conditions under the Assay.

System suitability

System performance: Proceed with 25 μL of the mixture of the standard solution for nifedipine, the standard solution (1), the standard solution (2) (1 : 1 : 1) under the above conditions; nitrophenylpyridine, nitrosophenylpyridine and nifedipine are eluted in this order. The resolution between the peaks of nitrophenylpyridine and nitrosophenylpyridine is NLT 1.5 and the resolution between the peaks of nitrosophenylpyridine and nifedipine is NLT 1.0.

System repeatability: Repeat the test 6 times with 25 μL each of the mixed solution under the above conditions; the relative standard deviation calculated on the peak area of each related substance is NMT 10%.

Dissolution Take 1 capsule of Nifedipine Capsules and perform the test at 50 revolutions per minute according to Method 2, using 900 mL of Solution 1 for the Disintegration as the test solution. Take the dissolved solution 20 minutes after starting the test, filter, and use the filtrate as the test solution by suitably diluting with the dissolution solution, if necessary. Separately, weigh accurately a portion of nifedipine RS, add the dissolution solution to make the same concentration with the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using the dissolution solution as the control solution, and determine the ultraviolet absorbance at the absorbance maximum wavelength at about 340 nm.

It meets the requirements when the dissolution rate of Nifedipine Capsules in 20 minutes is NLT 80%.

Uniformity of dosage units Meets the requirements.

Assay Perform this procedure quickly using a light-resistant container away direct sunlight. Take 5 capsules of Nifedipine Capsules, put the contents into a volumetric flask with a small amount of methanol, add the mobile phase to make a solution containing 0.1 mg of nifedipine per mL, and make the total amount *V* mL. Use this solution as the test solution. Separately, take accurately an appropriate amount of nifedipine RS, dissolve in methanol to make a solution containing 1 mg per mL. Take an appropriate amount of this solution, add the mobile phase to make a solution containing 0.1 mg per mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and measure the peak areas A_T and A_S.

$$\text{Amount (mg) of nifedipine } (C_{17}H_{18}N_2O_6) \text{ in 1 capsule} = \frac{V \times C}{5} \times \frac{A_T}{A_S}$$

C: Concentration (mg/mL) of standard solution

Operating conditions

Detector: An ultraviolet absorbance photometer (wavelength: 265 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with 5 μm octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter). Fill the assistant column with octadecylsilanized silica gels.

Mobile phase: A mixture of water, methanol and acetonitrile (50 : 25 : 25).

Flow rate: 1 mL/min

System suitability

System performance: Proceed with 25 μL of the standard solution according to the above conditions; the symmetry factor is NMT 1.5.

System repeatability: Repeat the test 6 times with 25 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area for nifedipine is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers at between 15 and 25 °C.

Nifedipine Tablets
니페디핀 정

Nifedipine Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$: 346.33).

Method of preparation Prepare as directed under Tablets, with Nifedipine.

Identification Weigh an amount equivalent to 20 mg of nifedipine according to the labeled amount, add 5 mL of acetone, shake well to dissolve, centrifuge, and use the clear supernatant as the test solution. Separately, weigh 20 mg of nifedipine RS, dissolve in 5 mL of acetone, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography (fluorescent indicator added). Next, develop the plate with a mixture of ethyl acetate and cyclohexane (50 : 50) as a developing solvent to a distance of about 15 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm), the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

Dissolution Perform the test quickly using a light-resistant container. Take 1 tablet of Nifedipine Tablets and perform the test at 100 revolutions per minute according to Method 2, using 900 mL of the test solution. Take the dissolved solution 60 minutes after starting the test and filter it. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add the test solution to contain about 10 μg of nifedipine per mL according to the labeled amount. Make it exactly *V′* mL and use this solution as the test solution. Separately, weigh accurately about 100 mg of nifedipine RS and dissolve in methanol to make exactly 100 mL. Take exactly 1 mL of this solution, add the test solution to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution according to the Liquid Chromatography under the following conditions, and measure the peak areas A_T and A_S of nifedipine ($C_{17}H_{18}N_2O_6$) in each solution. It meets the requirements when the dissolution rate of Nifedipine Tablets in 60 minutes is NLT 50%.

Dissolution rate (%) relative to the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$)

$$= W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 9$$

*W*s: Amount (mg) of nifedipine RS

C: Labeled amount (mg) of nifedipine ($C_{17}H_{18}N_2O_6$) in 1 tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 338 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of acetonitrile, methanol and water (7 : 7 : 5).

Flow rate: 1 mL/min

System suitability

System repeatability: Repeat the test 6 times under the above conditions with 25 μL each of standard solution; the relative standard deviation of the peak area of nifedipine is NMT 2.0%.

Test solution—Dissolve 180 g of polysorbate 80 in Solution 2 of the Dissolution to make 6 L.

Uniformity of dosage unit Meets the requirements.

Assay Perform this procedure quickly using a light-resistant vessels. Weigh accurately the mass of NLT 20 Nifedipine Tablets, and power. Weigh accurately an amount equivalent to about 50 mg of nifedipine ($C_{17}H_{18}N_2O_6$) and dissolve in methanol to make exactly 50 mL. Filter it, discard the first 10 mL of the filtrate, take exactly 10 mL of the subsequent filtrate, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of nifedipine RS and dissolve in methanol to make exactly 50 mL. Pipet 10 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas A_T and A_S of the test solution and the standard solution of nifedipine, respectively.

Amount (mg) of nifedipine ($C_{17}H_{18}N_2O_6$)

$$= \text{amount (mg) of nifedipine RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 265 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of water, acetonitrile and methanol (2 : 1 : 1).

Flow rate: 1 mL/min

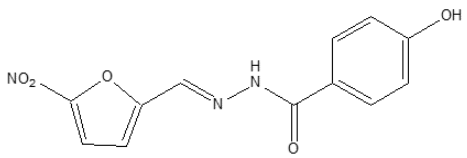
System suitability

System repeatability: Repeat the test 6 times with 25 μL each of standard solution under the above conditions; the relative standard deviation of the peak area of

nifedipine is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Nifuroxazide
니푸록사지드



$C_{12}H_9N_3O_5$: 275.22

(*E*)-4-Hydroxy-*N'*-((5-nitrofuran-2-yl)methylene) benzohydrazide [*965-52-6*]

Nifuroxazide, when dried, contains NLT 98.5% and NMT 101.5% of nifuroxazide ($C_{12}H_9N_3O_5$).

Description Nifuroxazide is a bright yellow crystalline powder.
It is slightly soluble in ethanol(95) and dichloromethane, and practically insoluble in water.

Identification Determine the infrared spectra of Nifuroxazide and nifuroxazide RS, both previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Absorbance $E_{1cm}^{1\%}$ (367 nm): Between 940 and 1000.
Weigh accurately 10.0 mg of Nifuroxazide in the dark, dissolve in 10 mL of ethylene glycol monomethyl ether, and add methanol to make exactly 100 mL. Pipet 5.0 mL of this solution and add methanol to make 100 mL.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Nifuroxazide as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances I***—Dissolve 1 g of Nifuroxazide in dimethyl sulfoxide to make 10 mL, and use this solution as the test solution (1). While stirring, add 50.0 mL of water to 5.5 mL of the test solution (1), allow to stand for 15 minutes, filter, and use this solution as test solution (2). To 0.5 mL of the test solution (1), add 5.0 mL of the solution, obtained by dissolve 50 mg of nifuroxazide related substance I (4-hydroxybenzohydroxazide) in dimethyl sulfoxide to make 1000 mL, and put 50.0 mL of water while stirring. Then, allow it to stand for 15 minutes, filter, and use this solution as the control solution. Add 0.5 mL of phosphomolybdic acid-tungstic acid TS and 10.0 mL of 2 mol/L sodium carbonate TS to 10 mL each of the test solution (2) and the control solution, and allow to stand for 1 hour. With these solutions, determine the absorption at 750 nm as directed under the Ultraviolet-visible Spectroscopy; the absorbance obtained from the test solution (2) is not greater than the absorbance from the control solution (NMT 0.05%).

(3) ***Other related substances***—Weigh accurately about 0.1 g of Nifuroxazide, dissolve in dimethyl sulfoxide, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Weigh exactly 10 mg of nifuroxazide analog II (methyl *p*-hydroxybenzoate), dissolve in 2 mL of *N*,*N*-dimethylformamide, and add the mobile phase to make 20 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the control solution (1). Weigh exactly 5 mg of Nifuroxazide and 10 mg of the related substance II, dissolve in 2 mL of *N*,*N*-dimethylformamide, and add the mobile phase to make 20 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the control solution (2). After preparing the test solution, the control solution (1) and the control solution (2), immediately protected from light, perform the test with 20 μL each of the solution as directed under the Liquid Chromatography according to the following conditions. The number of peak having NMT 0.6 times the area of the major peak obtained from the standard solution (1) is NMT 1 from the test solution (0.3%), and the peak is greater than 0.2 times (0.1%) of the major peak area obtained from the control solution (1). Also, the total area of the peaks of the related substances from the test solution is not greater than the area of the major peak from the control solution (1) (0.5%). Exclude any peak having the area NMT 0.1 times the area of the major peak obtained from the control solution (1) (0.05%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of water and acetonitrile (65 : 35).

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 20 μL of the control solution (2) under the above conditions; the resolution between peaks of nifuroxazide and related substance II is NLT 4. With regard to about 6.5 minute of the reference retention time for nifuroxazide, the related substances I, II, III and IV are eluted at about 0.4, 1.2, 2.8 and 5.2 minutes, respectively.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Nifuroxazide, previously dried, dissolve by heating, if necessary, in 30 mL of *N*,*N*-dimethylformamide, add 20 mL of water, mix, and titrate with 0.1 mol/L sodium hydroxide VS

(potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 27.52 mg of $C_{12}H_9N_3O_5$

Packaging and storage Preserve in light-resistant, tight containers

Nifuroxazide Capsules
니푸록사지드 캡슐

Nifuroxazide Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of nifuroxazide ($C_{12}H_9N_3O_5$: 275.22).

Method of preparation Prepared as directed under Capsules, with Nifuroxazide.

Identification Take the contents of the capsule, weigh an amount equivalent to 50 mg of nifuroxazide, and add 1 mL of dimethylformamide to mix. Add 4 mL of acetone, shake to mix, and use the filtrate as the test solution. Separately, take 50 mg of nifuroxazide RS, dissolve in 1 mL of dimethylformamide, add 4 mL of acetone, and use this solution as the standard solution. With these solutions, spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography (fluorescent indicator added) as directed under the Thin Layer Chromatography. Then, develop the plate with a mixture of acetone and acetic anhydride (100 : 2) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f value and color of the spots obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the contents of NLT 20 capsules of Nifuroxazide Capsules. Weigh accurately an amount equivalent to about 0.1 g of nifuroxazide ($C_{12}H_9N_3O_5$), and dissolve in 2-methoxyethanol to make 100 mL. After filtering, discard the first 20 mL of the filtrate, take the subsequent 10.0 mL of the filtrate, and add methanol to make 100 mL. Take 5.0 mL of this solution, add methanol to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of nifuroxazide RS, dilute it to the same concentration as the test solution, and use this solution as the standard solution. With the test solution and the standard solution, determine the absorbance A_T and A_S at 367 nm as directed under the Ultraviolet-visible Spectroscopy, using methanol as the control solution.

$$\text{Amount (mg) of nifuroxazide } (C_{12}H_9N_3O_5) = \text{Amount (mg) of nifuroxazide RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in well-closed containers.

Nifuroxazide Suspension
니푸록사지드 현탁액

Nifuroxazide Suspension contains NLT 95.0% and NMT 105.0% of the labeled amount of nifuroxazide ($C_{12}H_9N_3O_5$: 275.22).

Method of preparation Prepare as directed under Suspension, with Nifuroxazide.

Identification Shake Nifuroxazide Suspension well to mix, take an amount equivalent to 50 mg of nifuroxazide, and evaporate to dryness. Add 1 mL of dimethylformamide to the residue, mix, add 4 mL of acetone, shake to mix, centrifuge, and use the clear supernatant as the test solution. Separately, take 50 mg of nifuroxazide RS, dissolve in 1 mL of dimethylformamide, and add 4 mL of acetone, and use this solution as the standard solution. With these solutions, spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate (fluorescent indicator added) made of silica gel for thin-layer chromatography as directed under the Thin Layer Chromatography, develop the plate with a mixture of acetone and acetic anhydride (100 : 2) as a developing solvent to about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values and colors of the spots obtained from the test and standard solutions are the same.

pH Between 4.5 and 6.5.

Assay Shake the Nifuroxazide Suspension well to mix, take exactly an amount equivalent to about 0.1 g of nifuroxazide ($C_{12}H_9N_3O_5$), dissolve in 2-methoxyethanol, and make 100.0 mL. After filtering this, discard the first 20 mL of the filtrate, take the subsequent 10.0 mL of the filtrate, add methanol to make 100.0 mL. Take 5.0 mL of this solution, add methanol to make 100.0 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of nifuroxazide RS, dilute it to make the same concentration as the test solution, and use this solution as the standard solution. With the test solution and standard solution, perform the test as directed under the Ultraviolet-visible Spectroscopy, using methanol as a control solution, and determine the absorbances, A_T and A_S at a wavelength of 367 nm.

$$\text{Amount (mg) of nifuroxazide } (C_{12}H_9N_3O_5) = \text{Amount (mg) of nifuroxazide RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in light-resistant, tight

containers.

Nimesulide Tablets
니메술리드 정

Nimesulide Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of nimesulide ($C_{13}H_{12}N_2O_5S$: 308.30).

Method of preparation Nimesulide Tablets are prepared as directed under Tablets, with Nimesulide.

Identification Weigh an amount equivalent to 0.1 g of nimesulide ($C_{13}H_{12}N_2O_5S$) according to the labeled amount of Nimesulide Tablets, add 10 mL of methanol, shake well to mix, centrifuge, and use the clear liquid at the top layer as the test solution. Weigh about 0.1 g of nimesulide RS, add 10 mL of methanol, and use it as the standard solution. Perform the test with the test solution and the standard solution as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of acetone, ethyl acetate, and 28% aqueous ammonia (90 : 90 : 3.5) as a developing solvent to about 10 cm, air-dry the plate, and expose it to ultraviolet rays (main wavelength: 254 nm). The R_f value and color of the spots obtained from the test solution and standard solution are the same.

Disintegration Meets the requirements.

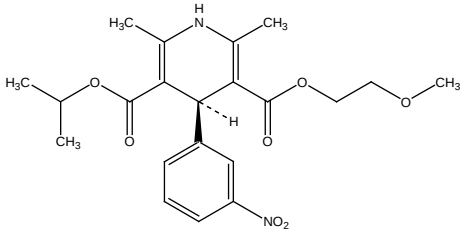
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Nimesulide Tablets and powder. Weigh accurately an amount equivalent to about 50 mg of nimesulide ($C_{13}H_{12}N_2O_5S$), add 70 mL of 0.1 mol/L ethanolic hydrochloric acid, dissolve by heating at 70 ℃ for 30 minutes, cool, and add 0.1 mol/L ethanolic hydrochloric acid to make 100 mL. Filter this solution, take 5.0 mL of the filtrate, add 0.1 mol/L ethanolic hydrochloric acid to make 200 mL, and use it as the test solution. Separately, weigh accurately about 50 mg of nimesulide RS and dissolve in 0.1 mol/L ethanolic hydrochloric acid to make 100 mL. Take 5.0 mL of this solution, add 0.1 mol/L ethanolic hydrochloric acid to make 200 mL, and use it as the standard solution. Determine the absorbances A_T and A_S of the test solution and the standard solution, respectively, at 297 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of nimesulide } (C_{13}H_{12}N_2O_5S) = \text{Amount (mg) of nimesulide RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in well-closed containers.

Nimodipine
니모디핀



and enantiomer

$C_{21}H_{26}N_2O_7$: 418.44

(*RS*)-3-(2-Methoxyethyl) 5-propan-2-yl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate [*66085-59-4*]

Nimodipine contains NLT 98.5% and NMT 101.5% of nimodipine ($C_{21}H_{26}N_2O_7$), calculated on the dried basis.

Description Nimodipine occurs as a bright yellow or yellow crystalline powder.
It is freely soluble in ethyl acetate, sparingly soluble in ethanol(95) and practically insoluble in water.
It is affected by light.
It shows crystalline polymorphism.

Identification Determine the infrared spectra of Nimodipine and nimodipine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -10° and +10° (1 g, acetone, 20 mL, 100 mm).

Purity ***Related substances***—Weigh accurately about 40 mg of Nimodipine and dissolve in 2.5 mL of tetrahydrofuran, add the mobile phase to make exactly 25 mL, and use it as the test solution. Separately, weigh accurately about 40 mg of nimodipine RS, dissolve in 2.5 mL of tetrahydrofuran, add the mobile phase to make exactly 25 mL, and add the mobile phase to 1 mL of this solution to make exactly 100 mL. Use this solution as the standard stock solution (1). Weigh accurately about 20 mg of nimodipine related substance I [2-methoxyethyl-1-methylethyl-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate] RS and dissolve it in 2.5 mL of tetrahydrofuran. Add the mobile phase to 5 mL of this solution to make exactly 100 mL, and use this solution as the standard stock solution (2). Add the mobile phase to 2 mL of standard stock solution (1) to make exactly 10 mL, and use it as the standard solution (1). Take 2.5 mL of the standard stock solution (1) and 1 mL of the standard stock solution (2), put them in a 25 mL volumetric flask, add the mobile phase to make exactly 25 mL, and use it as the standard solution (2). Perform the test with 20 μL

each of the test solution, the standard solution (1) and the standard solution (2) as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of each related substance in the test solution, A_T, the peak area of the related substance I in the standard solution (2), A_{S1}, and the peak area of nimodipine in the standard solution (1), A_{S2}; related substance I is NMT 0.1%, other related substances is NMT 0.2%, and the total amount of related substances is NMT 0.5%.

$$\text{Content (\%) of related substance I} = (A_{T1} / A_{S1}) \times (C_{S1} / C_{T1}) \times 100$$

A_{T1}: Peak area of related substance I in the test solution

A_{S1}: Peak area of related substance I in the standard solution (2)

C_{S1}: Concentration of related substance I in the standard solution (2) (μg/mL)

C_{T1}: Concentration of nimodipine in the test solution (μg/mL)

$$\text{Content (\%) of other related substances} = (A_{T2} / A_{S2}) \times (C_{S2} / C_{T2}) \times 100$$

$$(AT2 / AS2) \times (CS2 / CT2) \times 100$$

A_{T2}: Peak area of related substances other than related substance I in the test solution

A_{S2}: Peak area of nimodipine in the standard solution (1)

C_{S2}: Concentration of nimodipine in the standard solution (1) (μg/mL)

C_{T2}: Concentration of nimodipine in the test solution (μg/mL)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 235 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 - 10 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of water, methanol and tetrahydrofuran (3 : 1 : 1).

Flow rate: 2 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution (4) under the above conditions; the relative retention times of the related substance I peak and the nimodipine peak are about 0.9 and 1.0, respectively, and the resolution between these two peaks are NLT 1.5.

System reproducibility: Repeat the test 5 times under the above conditions with 20 μL each of standard solution (4); the relative standard deviation of the peak area of nimodipine is NMT 2.0%.

Time span of measurement: About 4 times the retention time of nimodipine.

Loss on drying NMT 0.5% (1.0 g, 105 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.180 g of Nimodipine, add it to a mixture of 25 mL of *t*-butyl alcohol and 25 mL of perchloric acid TS, and heat gently to dissolve. After cooling, add 0.l mL of ferroin TS and titrate with 0.1 mol/L cerium sulfate VS. Perform a blank test in the same manner and make any necessary correction.

$$\text{Each mL of 0.1 mol/L cerium sulfate VS} = 20.92 \text{ mg of } C_{21}H_{26}N_2O_7$$

Packaging and storage Preserve in light-resistant, tight containers at 15 to 30 ℃.

Nimodipine Injection
니모디핀 주사액

Nimodipine Injection contains NLT 90.0% and NMT 110.0% of nimodipine ($C_{21}H_{26}N_2O_7$: 418.45) of the labeled amount.

Method of preparation Prepared as directed under Injection, with Nimodipine.

Identification The retention time of the major peak obtained from the test solution and the standard solution from the Assay and the ultraviolet absorption spectrum between 200 and 400 nm are the same.

pH Between 6.0 and 8.0.

Alcohol number Alcohol number is NLT 2.3 when tested according to Method 2, Gas chromatography under the Alcohol Determination.

Purity ***Related Substance***—Use Nimodipine Injection as the test solution. If necessary, take an amount exactly equivalent to about 2 mg of nimodipine ($C_{21}H_{26}N_2O_7$) according to the labeled amount with Nimodipine Injection, add ethanol(99.5) to make exactly 10 mL, and use it as the test solution. Pipet 1 mL of the test solution, add the mobile phase to make exactly 100 mL, take exactly 2 mL again, and add the mobile phase to make exactly 10 mL. Use it as the standard solution (1). Separately, take accurately about 2 mg of nimodipine related substance[2-methoxyethyl-1-methylethyl-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate] RS, add ethanol(99.5) to make exactly 20 mL, take exactly 1 mL again, and add ethanol(99.5) to make exactly 100 mL. Use it as the standard solution (2). With 20 μL each of the test solution, the standard solution (1) and the standard solution (2), perform the test as directed under the Liquid Chromatography under the following conditions. Calculate the peak area of nimodipine related substance I ob-

tained from the test solution, A_{T1}, and the peak area of nimodipine related substance I obtained from the standard solution (2), A_{S1}. In addition, determine the peak area of each related substance excluding nimodipine related substance I obtained from the test solution, A_{T2}, and the peak area of nimodipine from the standard solution (1), A_{S2}. The amount of nimodipine related substance I is NMT 0.5%, the amount of other related substances is NMT 0.2%, and the total amount of related substances is NMT 0.5%.

$$\text{Content (\%) of related substance I} = (A_{T1} / A_{S1}) \times (C_{S1} / C_{T1}) \times 100$$

A_{T1}: Peak area of nimodipine related substance I in the test solution

A_{S1}: Peak area of nimodipine related substance I in the standard solution (2)

C_{S1}: Concentration (μg/mL) of nimodipine related substance I in the standard solution (2)

C_{T1}: Concentration (μg/mL) of nimodipine related substance I in the test solution

$$\text{Content (\%) of other related substances} = (A_{T2} / A_{S2}) \times (C_{S2} / C_{T2}) \times 100$$

A_{T2}: Peak area of related substances other than related substance I in the test solution

A_{S2}: Peak area of nimodipine in the standard solution (1)

C_{S2}: Concentration (μg/mL) of nimodipine in the standard solution (1)

C_{T2}: Concentration (μg/mL) of nimodipine in the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 235 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of water, tetrahydrofuran and acetonitrile (16 : 6 : 3).

Flow rate: 1.5 mL/min

System suitability

System performance: Proceed with 20 μL of the system suitability solution according to the above operating conditions, the resolution of nimodipine and nimodipine related substance I is more than 1.5, and the symmetry coefficient of the nimodipine peak is NMT 2.0.

System reproducibility: Repeat the test 6 times under the above conditions with 20 μL each of the standard solution (1), the relative standard deviation of the peak area of nimodipine is NMT 2.0%.

System suitability solution—Take exactly 2 mg each of nimodipine RS and nimodipine related substance I RS, add ethanol(99.5) to make exactly 20 mL, take exactly 1 mL again, and add ethanol(99.5) to make 100 mL. Use it as the system suitability solution.

Bacterial endotoxins Less than 5.0 EU/mL.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Particulate matter for injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Take exactly an amount, equivalent to about 10 mg of nimodipine ($C_{21}H_{26}N_2O_7$), according to the labeled amount of Nimodipine Injection, add water to make exactly 50 mL, and use it as the test solution. Separately, weigh accurately about 10 mg of nimodipine RS, dissolve in ethanol(95), add ethanol(95) to make 50 mL, and use it as the standard solution. Perform the test as directed under the Liquid Chromatography with 10 μL each of the test and standard solutions under the following conditions, and determine, A_T and A_S, of the peak area of nimodipine.

$$\text{Amount (mg) of nimodipine } (C_{21}H_{26}N_2O_7) = \text{Amount (mg) of nimodipine RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorbance photometer (wavelength: 235 nm). However, a photo-diode array detector (200 nm to 400 nm) is used when the Identification is performed.

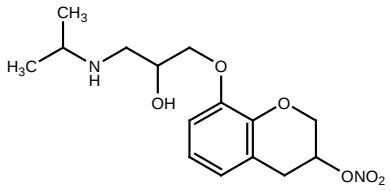
Column: A stainless steel column about 4.0 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of water, tetrahydrofuran and acetonitrile (64 : 24 : 12).

Flow rate: 1.2 mL/min

Packaging and storage Preserve in hermetic containers.

Nipradilol
니프라딜롤



and enantiomer

$C_{15}H_{22}N_2O_6$: 326.34

3,4-Dihydro-8-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-2*H*-1-benzopyran-3-ol 3-nitrate, [*81486-22-8*]

Nipradilol, when dried, contains NLT 99.0% and NMT 101.0% of nifradilol ($C_{15}H_{22}N_2O_6$).

Description Nipradilol occurs as a white to light yellowish white crystalline powder and is odorless.
It is freely soluble in acetic acid(100), soluble in chloroform, sparingly soluble in methanol or acetone, slightly soluble in anhydrous ethanol, ethyl acetate or water and practically insoluble in hexane.
It is soluble in dilute hydrochloric acid.
It is colored by light.
A solution of Nipradilol in 0.2 mol/L hydrochloric acid (1 in 20) shows no optical rotation.

Identification (1) Add a few drops of diphenylamine TS to 5 mg of Nipradilol; it turns dark brown.

(2) Dissolve 2 mL of diluted hydrochloric acid (1 in 100) in 20 mg of Nipradilol, and add 1 mL of Reinecke salt TS; a pale red precipitate is formed.

(3) Determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy with a solution of Nipradilol in methanol (1 in 10000); it exhibits a maximum between 273 and 277 nm.

(4) Determine the infrared absorption spectrum of Nipradilol as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; it exhibits absorption at the wavenumbers of about 3277 cm^{-1}, 3117 cm^{-1}, 1620 cm^{-1}, 1587 cm^{-1}, 1382 cm^{-1}, 1367 cm^{-1}, 1280 cm^{-1} and 765 cm^{-1}.

Absorbance $E_{1cm}^{1\%}$ (275 nm): Between 59 and 60 (10 mg after drying, 100 mL of methanol).

Purity (1) ***Clarity and color of solution***—Dissolve 10 mL of 0.5 mol/L hydrochloric acid in 1.0 g of Nipradilol; the resulting solution is clear and its color is not more intense than that of the matching fluid for B.

(2) ***Heavy metals***—Proceed with 1.0 g of Nipradilol according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Nipradilol according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related Substance***—Weigh accurately about 25 mg of Nipradilol, add the mobile phase, dissolve it to make exactly 20 mL, and use this solution as the test solution. Take exactly 1.0 mL of the test solution, add the mobile phase to make exactly 200 mL, and use this solution as the standard solution. With 20 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography; the sum of each peak other than the major peak obtained from the test solution is NMT 3 times the area of the major peak from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase, flow rate and selection of column, comply with the operating conditions of the Assay.

Detection sensitivity: Add 1 mL of the mobile phase to the test solution to make 50 mL. Take 20 μL of this solution and adjust the peak height of nifradilol to be 70% of the full scale.

Time span of measurement: About 5 times the retention time of nifradilol from the solvent peak.

Loss on drying NMT 0.5% (1 g, in vacuum, phosphorus pentoxide 60 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Isomer ratio Dissolve 1 mL of anhydrous pyridine solution of p-nitrobenzoyl chloride (3 in 100) in 5 mg of Nipradilol, and evaporate the solvent under reduced pressure. Dissolve the residue in 5 mL of chloroform, wash twice with 5 mL of sodium bicarbonate TS, then with 5 mL of 1 mol/L hydrochloric acid and then with 5 mL of water. Add 5 mL of chloroform and 2 g of anhydrous sodium sulfate, shake to mix, centrifuge, and use the above clear supernatant as the test solution. With 2 μL of the test solution, perform the test as directed under the Liquid Chromatography according to the following conditions.
Determine the areas of two adjacent peaks, S_a and S_b, according to the automatic integration method, having retention times of about 7 minutes, where S_a is the peak area of shorter retention time (racemic A) and S_b is the peak area of longer retention time (racemic B); $S_a/(S_a+S_b) \times 100$ is between 45 and 55.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 264 nm).

Column: A stainless steel column about 4 mm and about 20 cm in length, packed with silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: A mixture of hexane and ethyl acetate (7 : 5).

Flow rate: Adjust the flow rate so that the retention time of racemic B is about 6 minutes.

Assay Weigh accurately about 0.06 g each of Nipradilol and nipradilol RS, previously dried, and dissolve in the mobile phase respectively to make exactly 50 mL. Pipet 5 mL of this solution, add exactly 5 mL of internal standard solution to each solution, put the mobile phase to make 20 mL, and use these solutions as the test solution and the standard solution, respectively. With 10 μL each of the test solution and standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the ratios of peak areas of nifradilol, Q_T and Q_S to the peak area of the internal standard of each solution.

Amount (mg) of nifradilol ($C_{15}H_{22}N_2O_6$)

$$= \text{amount (mg) of nifradilol RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Propranolol hydrochloride solution (1 in 2000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 274 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of water, acetonitrile, acetic acid(100) and Tetramethylammonium hydroxide (110 : 50 : 1 : 1)

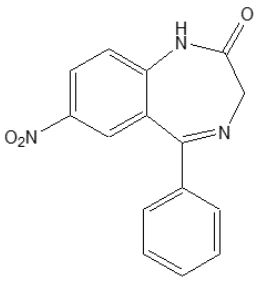
Flow rate: Adjust the flow rate so that the retention time of nifradilol is about 8 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; nifradilol and internal standard are eluted in this order with resolution between their peaks being over 2.0.

Packaging and storage Preserve in light-resistant, tight containers.

Nitrazepam
니트라제팜



$C_{15}H_{11}N_3O_3$: 281.27

7-Nitro-5-phenyl-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one [*146-22-5*]

Nitrazepam, when dried, contains NLT 99.0% and NMT 101.0% of nitrazepam ($C_{15}H_{11}N_3O_3$).

Description Nitrazepam occurs as white to pale yellow crystals or a crystalline powder, which is odorless.

It is freely soluble in acetic acid(100), soluble in acetone or chloroform, slightly soluble in methanol, ethanol or anhydrous ethanol, very slightly soluble in ether and practically insoluble in water.

Melting point—About 227 °C (with decomposition).

Identification (1) Add 0.1 mL of sodium hydroxide TS to 3 mL of a solution of Nitrazepam in methanol (1 in 500); the resulting solution exhibits a yellow color.

(2) Add 15 mL of dilute hydrochloric acid to 20 mg of Nitrazepam, boil for 5 minutes, and filter after cooling. The filtrate responds to the Qualitative Analysis for primary aromatic amines.

(3) Put 0.5 mL of sodium hydroxide TS to the filtrate obtained in (2) to neutralize, add 2 mL of ninhydrin TS, and heat on a steam bath; the resulting solution exhibits a violet color.

(4) Determine the absorption spectra of solutions of Nitrazepam and nitrazepam RS in anhydrous ethanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Nitrazepam in 20 mL of acetone; the resulting solution is clear and pale yellow.

(2) ***Heavy metals***—Proceed with 1.0 g of Nitrazepam according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Nitrazepam according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.25 g of Nitrazepam in 10 mL of a mixture of methanol and chloroform (1 : 1), and use this solution as the test solution. Pipet 1.0 mL of this solution and add a mixture of methanol and chloroform (1 : 1) to make exactly 20 mL. Pipet 2.0 mL of this solution, add a mixture of methanol and chloroform (1 : 1) to make exactly 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel (with a fluorescent indicator) for thin-layer chromatography. Next, develop the plate with a mixture of nitromethane and ethyl acetate (17 : 3) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

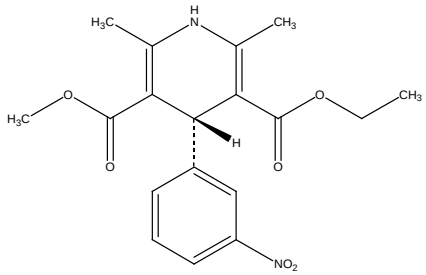
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Nitrazepam, previously dried, dissolve in 40 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 28.127mg of $C_{15}H_{11}N_3O_3$

Packaging and storage Preserve in light-resistant, tight containers.

Nitrendipine
니트렌디핀



and enantiomer

$C_{18}H_{20}N_2O_6$: 360.36

Ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro pyridine-3,5-dicarboxylate [*39562-70-4*]

Nitrendipine, when dried, contains NLT 98.5% and NMT 101.0% of nitrendipine ($C_{18}H_{20}N_2O_6$).

Description Nitrendipine occurs as a yellow crystalline powder.
It is soluble in acetonitrile, sparingly soluble in methanol or ethanol(99.5) and practically insoluble in water.
It is gradually colored to brownish yellow by light.
A solution of Nitrendipine in acetonitrile (1 in 50) exhibits no optical rotation.

Identification (1) Determine the absorption spectra of solutions of Nitrendipine and nitrendipine RS in methanol (1 in 80,000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Nitrendipine and nitrendipine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point—Between 157 and 161 ℃.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Nitrendipine as directed under Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Proceed quickly using light-resistant containers. Dissolve 40.0 mg of Nitrendipine in 5 mL of acetonitrile, add the mobile phase to make exactly 25 mL, and use this solution as the test solution. Add the mobile phase to 1.0 mL of this solution to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the area of the peaks other than the major peak in the test solution, A_i, and the peak area of nitrendipine in the standard solution, A_S, by the automatic integration method; the related substances having the relative retention time with regard to nitrendipine of about 0.8 is NMT 1.0%, the related substances having the relative retention time with regard to nitrendipine of about 1.3 is NMT 0.25%, and the amount of each of the other related substances is NMT 0.2%. In addition, the total amount of related substances other than nitrendipine is NMT 2.0%.

$$\text{Content (\%) of related substances} = \frac{A_i}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of water, tetrahydrofuran and acetonitrile (14 : 6 : 5).

Flow rate: Adjust the flow rate so that the retention time of nitrendipine is about 12 minutes.

System suitability

Test for required detectability: Pipet 2 mL of the standard solution and add the mobile phase to make exactly 10 mL. The peak area of nitrendipine from 10 μL of this solution is between 14% and 26% of that from the standard solution.

System performance: Dissolve 10 mg of Nitrendipine and 3 mg of propyl p-hydroxybenzoate in 5 mL of acetonitrile, and add the mobile phase to make 100 mL. Proceed with 5 μL of this solution according to the above conditions; propyl p-hydroxybenzoate and nitrendipine are eluted in this order with the resolution being NLT 6.

System repeatability: Repeat the test 6 times according to the above conditions with 10 μL each of the standard solution; the relative standard deviation of the peak area of nitrendipine is NMT 2.0%.

Time span of measurement: About 2.5 times the retention time of nitrendipine after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

Residue on ignition 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Nitrendipine, previously dried, dissolve in 60 mL of a solution of sulfuric acid in ethanol(99.5) (3 in 100), add 50 mL of water, and titrate with 0.1 mol/L ammonium ceric sulfate VS (indicator: 3 drops of 1,10-phenanthroline monohydrate TS). The endpoint of the titration is when the reddish brown color disappears. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L ammonium ceric sulfate VS
= 18.02 mg of $C_{18}H_{20}N_2O_6$

Packaging and storage Preserve in light-resistant, tight containers.

Nitroglycerin Tablets
니트로글리세린 정

Nitroglycerin Tablets contain NLT 80.0% and NMT 120.0% of the labeled amount of nitroglycerin ($C_3H_5N_3O_9$: 227.09).

Method of preparation Prepare as directed under Tablets, with Nitroglycerin.

Identification (1) Weigh an amount of Nitroglycerin Tablets, previously powdered, equivalent to 6 mg of nitroglycerin ($C_3H_5N_3O_9$) according to the labeled amount, add 12 mL of ether, shake well to mix, and filter. Use the filtrate as the test solution. Take 5 mL of the test solution, evaporate ether, dissolve the residue in 1 - 2 drops of sulfuric acid, and add 1 drop of diphenylamine TS; the resulting solution exhibits a dark blue color.

(2) Take 5 mL of the test solution obtained in (1), evaporate ether, add 5 drops of sodium hydroxide TS to the residue, and heat over a low flame to concentrate to about 0.1 mL. After cooling, put 20 mg of potassium hydrogen sulfate to the residue, and heat; the odor of acrolein is perceptible.

Purity ***Free nitrate ion***—Weigh accurately an amount of Nitroglycerin Tablets, previously powdered, equivalent to 20 mg of nitroglycerin ($C_3H_5N_3O_9$), according to the labeled amount, transfer to a separatory funnel, add 40 mL of isopropyl ether and 40 mL of water, and then shake to mix for 10 minutes to collect the aqueous layer. Add 40 mL of isopropyl ether to this solution, shake to mix for 10 minutes, then collect the aqueous layer, and filter. Use this solution as the test solution. Separately, transfer 10 mL of nitric acid standard solution into a separatory funnel, add 30 mL of water and 40 mL of the isopropyl ether layer of the first extraction used in the preparation of the test solution, and shake to mix for 10 minutes. Prepare the standard solution in the same manner as the preparation of the test solution below. Transfer 20 mL each of the test solution and the standard solution into a separate Nessler tube, add 30 mL of water and 60 mg of Griess-Romijin's nitric acid reagent, shake well to mix, and allow to stand for 30 minutes; the color of the test solution is not more intense than that of the standard solution when observed from the side of the tubes.

Disintegration Meets the requirements. However, the time of the test is limited within 2 minutes and fluted discs are not used.

Uniformity of dosage units It meets the requirements when tested according to the following procedure. Transfer 1 tablet of Nitroglycerin Tablets into a stoppered centrifuge tube, add exactly *V* mL of acetic acid(100) to make a solution containing about 30 μg of nitroglycerin ($C_3H_5N_3O_9$) per mL, and shake vigorously to mix for 1 hour. After disintegrating the tablet, centrifuge and use the clear supernatant as the test solution. When the tablet does not disintegrate during this procedure, transfer 1 tablet of Nitroglycerin Tablets into a stoppered centrifuge tube, coat the tablet with 0.05 mL of acetic acid(100), and grind with a glass rod. While washing the glass rod, add acetic acid(100) to make exactly *V* mL of a solution containing about 30 μg of nitroglycerin (C3H5N3O9) per mL. Then, shake to mix for 1 hour, centrifuge, and use the clear supernatant as the test solution. Separately, dry potassium nitrate at 105 ℃ for 4 hours, weigh accurately 90 mg of the dried potassium nitrate, dissolve in 5 mL of water, and add acetic acid(100) to make exactly 100 mL. Pipet 5.0 mL of this solution, add acetic acid(100) to make exactly 100 mL, and use this solution as the standard solution. Pipet 2 mL each of the test solution and the standard solution, add 2 mL of salicylic acid TS to each solution, shake to mix, and allow to stand for 15 minutes. While cooling with ice after adding 10 mL of water, put about 12 mL of sodium hydroxide (2 in 5) to make alkaline, and add water to make exactly 50 mL. With these solutions, perform the test as directed under the Ultraviolet-visible Spectroscopy, using a solution prepared with 2 mL of acetic acid(100) in the same manner as a control. Determine the absorbances, A_T and A_S, of each solution, obtained from the test solution and the standard solution, at 410 nm.

$$\text{Amount (mg) of nitroglycerin } (C_3H_5N_3O_9) \text{ (mg)} = \text{Amount (mg) of potassium nitrate RS} \times 0.7487 \times \frac{A_T}{A_S} \times \frac{V}{2000}$$

It meets the requirements when the acceptable deviation criterion (%) is NMT 25% between the average content of 10 tablets of Nitroglycerin Tablets and the content of each tablet. When the deviation is NLT 25% and NMT 30% only for 1 tablet, perform the test again with 20 tablets of Nitroglycerin Tablets in the same manner. It meets the requirements when the acceptable deviation criterion (%) is NLT 25% and NMT 30% for NMT 1 tablet and NMT 30% for none between the average content of 30 tablets of Nitroglycerin Tablets, tested twice, and the content of each tablet.

Assay Weigh accurately NLT 20 tables of Nitroglycerin Tablets and softly press to disintegrate. Weigh accurately an amount of Nitroglycerin Tablets, equivalent to about 3.5 mg of nitroglycerin ($C_3H_5N_3O_9$), add exactly 50 mL of acetic acid(100), shake to mix for 1 hour, filter, and use this filtrate as the test solution. Separately, dry potassium nitrate at 105 ℃ for 4 hours, weigh accurately about 90 mg of the dried potassium nitrate, dissolve in 5 mL of water, and add acetic acid(100) to make exactly 100 mL. Pipet 10 mL of this solution, add acetic acid(100) to make exactly 100 mL, and use this solution as the standard solution. Pipet 2 mL each of the test solution and the standard solution, add 2 mL of salicylic acid TS to each

solution, shake to mix, allow to stand for 15 minutes, and add 10 mL of water. While cooling with ice, add about 12 mL of sodium hydroxide (2 in 5) to make alkaline, and add water to make exactly 50 mL. With these solutions, perform the test as directed under the Ultraviolet-visible Spectroscopy, using a solution prepared with 2 mL of acetic acid(100) in the same manner as a control. Determine the absorbances, A_T and A_S, of each solution, obtained from the test solution and the standard solution, at 410 nm.

$$\text{Amount (mg) of nitroglycerin } (C_3H_5N_3O_9) = \text{Amount (mg) of potassium nitrate} \times 0.7487 \times \frac{A_T}{A_S} \times \frac{1}{20}$$

Packaging and storage Preserve in light-resistant, tight containers at below 20 ℃.

Nitrous Oxide
아산화질소

N_2O : 44.01

Nitrous oxide [*10024-97-2*]

Nitrous Oxide contains NLT 97.0 vol% and NMT 101.0 vol% of nitrous oxide (N_2O).

Description Nitrous Oxide occurs as a colorless gas at room temperature and atmospheric pressure. It is odorless.

1 mL of Nitrous Oxide is soluble in 1.5 mL of water or 0.4 mL of ethanol(95) at 20 ℃, 101.3 kPa, and soluble in ether or fatty oils.

1000 mL of Nitrous Oxide weighs approximately 1.96 g at 0 ℃, 101.3 kPa.

Identification (1) Put a glowing splinter of wood to Nitrous Oxide; it bursts into flame immediately.

(2) Take 1 mL each of Nitrous Oxide and nitrous oxide directly from pressure-resistant metal hermetic container with a pressure-reducing valve to gas measuring tubes for gas chromatography or syringes, respectively, using a polyvinyl chloride-based introduction tube. Perform the test with these gases as directed under the Gas Chromatography according to the operating conditions under the Assay; the retention time of the major peak obtained from Nitrous Oxide corresponds with that of nitrous oxide.

Purity Calculate the collected amount of Nitrous Oxide by maintaining the temperature of the container at 18 to 22 ℃ for more than 6 hours before the test, and correcting the volume at 20 ℃, 101.3 kPa.

(1) ***Acidity or alkalinity***—Add 0.3 mL of methyl red TS and 0.3 mL of bromothymol blue TS to 400 mL of freshly boiled and cooled water, and boil for 5 minutes. Transfer 50 mL of this solution to each of three Nessler tubes A, B and C. Add 0.10 mL of 0.01 mol/L hydrochloric acid to tube A and 0.20 mL of 0.01 mol/L hydrochloric acid VS to tube B, and cover each tube with a stopper to allow to cool. Next, pass 1000 mL of Nitrous Oxide through the solution in tube A for 15 minutes, while placing the end of the gas introduction tube with a diameter of approximately 1 mm at a position of 2 mm from the bottom of the Nessler tube; the color of the solution in tube A is not more intense than the reddish orange color of the solution in tube B or than the yellowish green color of the solution in tube C.

(2) ***Carbon dioxide***—Pass 1000 mL of Nitrous Oxide through 50 mL of barium hydroxide TS in a Nessler tube in the same manner as directed in (1); the resulting solution exhibits no more turbidity than the following control solution.

Control solution—Add 50 mL of barium hydroxide TS to a Nessler tube, and add 1 mL of a solution prepared by dissolving 0.1 g of sodium bicarbonate in 100 mL of freshly boiled and cooled water.

(3) ***Oxidizing substances***—Take 15 mL each of potassium iodide starch TS into each of two Nessler tubes A and B, add acetic acid(100) dropwise to each of the tubes, mix, and use these solutions as solution A and solution B, respectively. Pass 2000 mL of Nitrous Oxide through solution A for 30 minutes in the same manner as directed in (1); the color of solution A is the same as that of the stoppered, untreated solution B.

(4) ***Potassium permanganate reducing substances***—Take 50 mL of water into each of two Nessler tubes A and B, add 0.10 mL of 0.02 mol/L potassium permanganate to each of the tubes, and use these solutions as solutions A and B, respectively. Pass 1000 mL of Nitrous Oxide through solution A in the same manner as directed in (1); the color of solution A is the same as that of solution B.

(5) ***Chloride***—Take 50 mL of water into each of two Nessler tubes A and B, add 0.5 mL of silver nitrate TS to each of the tubes, and use these solutions as solutions A and B, respectively. Pass 1000 mL of Nitrous Oxide through solution A in the same manner as directed in (1); the turbidity of solution A is the same as that of solution B.

(6) ***Carbon monoxide***—Take 5.0 mL of Nitrous Oxide directly from a pressure-resistant metal hermetic container with a pressure-reducing valve to gas measuring tubes for gas chromatography or syringes, using a polyvinyl chloride-based introduction tube. Perform the test with this according to as directed under the Gas Chromatography according to the following conditions; it exhibits no peak at the elution position of carbon monoxide.

Operating conditions

Detector: A thermal conductivity detector

Column: A column about 3 mm in internal diameter and about 3 m in length, packed with 300 to 500 μm zeolite for gas chromatography (pore diameter 0.5 nm).

Column temperature: A constant temperature of

about 50 °C.

Carrier gas: Hydrogen or helium

Flow rate: Adjust the flow rate so that the retention time of carbon monoxide is about 20 minutes.

System suitability

Detection sensitivity: Adjust the sensitivity so that the peak height of carbon monoxide obtained from 5.0 mL of the mixed gas used in the system performance is about 10 cm.

System performance: Take 0.1 mL each of carbon monoxide and air into a gas mixer, add carrier gas to make 100 mL, and mix well. Proceed with 5.0 mL of this mixed gas according to the above conditions; oxygen, nitrogen, and carbon monoxide are eluted in this order with each peak completely resolved.

(7) ***Nitrogen monoxide***—Proceed in the same manner as directed in (8) Nitrogen dioxide, pass 500 ± 50 mL of Nitrous Oxide in the form of vapor through a nitric oxide-nitrogen dioxide detector tube at a constant rate, and determine the amount of nitrogen monoxide; the amount is less than 1 ppm.

(8) ***Nitrogen dioxide***—Prepare a container with a tube of sufficient length so that, when the valve of the container is opened, the content of the liquid phase is vaporized during passage and the injection port connected to the detector tube has no frost. Pass 550 ± 50 mL of Nitrous Oxide in the form of vapor through a nitric oxide-nitrogen dioxide detector tube at a constant rate via the tube (previously flush the system with Nitrous Oxide to displace air), and determine the amount of nitrogen dioxide; the amount is less than 1 ppm. However, measure the gas with a gas volume meter placing downward from the detector tube in order to prevent contamination.

Assay Take Nitrous Oxide as directed under the Purity. Take 1.0 mL of Nitrous Oxide directly from a pressure-resistant metal hermetic container with a pressure-reducing valve to gas measuring tubes for gas chromatography or syringes, respectively, using a polyvinyl chloride-based introduction tube. Perform the test with this as directed under the Gas Chromatography according to the following conditions, and calculate the peak area of air, A_T. Separately, take 3.0 mL of nitrogen into a gas mixer, add carrier gas to make the total volume exactly 100 mL, mix well, and use this gas as the standard mixed gas. Proceed with 1.0 mL of this mixed gas in the same manner as Nitrous Oxide, and calculate the peak area of nitrogen, A_S.

$$\text{Amount (vol\%) of nitrous oxide } (N_2O) = 100 - 3 \times \frac{A_T}{A_S}$$

Operating conditions

Detector: Thermal conductivity detector

Column: A column about 3 mm in internal diameter and about 3 m in length, packed with silica gel for gas chromatography (300 μm to 500 μm in particle diameter).

Column temperature: A constant temperature of about 50 °C.

Carrier gas: Hydrogen or helium

Flow rate: Adjust the flow rate so that the retention time of nitrogen is about 2 minutes.

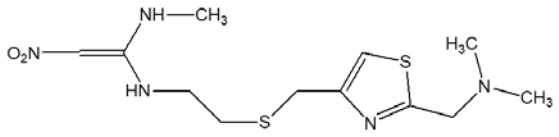
System suitability

System performance: Take 3.0 mL of nitrogen into a gas mixer, add Nitrous Oxide to make 100 mL, and mix well. Proceed with 1.0 mL of this mixed gas according to the above conditions; nitrogen and Nitrous Oxide are eluted in this order with each peak completely resolved.

System repeatability: Repeat the test 6 times with the standard mixed gas according to the above conditions; the relative standard deviation of the peak area of nitrogen is NMT 2.0%.

Packaging and storage Preserve in pressure-resistant metal hermetic containers at below 40 ℃.

Nizatidine
니자티딘



$C_{12}H_{21}N_6O_2S_2$: 331.46

(E)-1-*N'*-[2-[[2-[(Dimethylamino)methyl]-1,3-thiazol-4-yl]methylsulfanyl]ethyl]-1-*N*-methyl-2-nitroethene-1,1-diamine [*76963-41-2*]

Nizatidine contains NLT 98.0% and NMT 101.0% of nizatidine ($C_{12}H_{21}N_6O_2S_2$), calculated on the dried basis.

Description Nizatidine occurs as a white or pale brown crystalline powder.

It is freely soluble in acetic acid(100), soluble in methanol, sparingly soluble in water, slightly soluble in ethanol(99.5), 2-propanol or acetic anhydride and practically insoluble in ether.

Identification (1) Determine the infrared spectra of Nizatidine and nizatidine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Melting point Between 130 and 135 ℃. Perform the test with Nizatidine, previously dried.

Purity (1) ***Heavy metals***—Proceed with 0.1 g of Nizatidine as directed under Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Weigh accurately about 50 mg of Nizatidine, dissolve in a mixture of ammonium acetate buffer and methanol (76 : 24) to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of nizatidine RS and dissolve in a mixture of ammonium acetate buffer and methanol (76 : 24) to make exactly 100 mL. To 5.0 mL of this solution, add a mixture of ammonium acetate buffer and methanol (76 : 24) to make exactly 50 mL, and use this solution as the standard solution (1). Take a certain amount of the standard solution (1), dilute with a mixture of ammonium acetate buffer and methanol (76 : 24) to make 25 μg/mL and 15 μg/mL of solutions, respectively, and use these solutions as the standard solution (2) and the standard solution (3). Perform the test with 50 μL each of the test solution, the standard solutions (1), (2) and (3) by the peak percentage peak area method under the Liquid Chromatography according to the following conditions; the total area of each peak other than the major peak obtained from the test solution is NMT 3 times the area of the major peak obtained from the standard solution (2) (1.5%) and the area of each peak is NMT the area of the major peak obtained from the standard solution (3) (0.3%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).

Control the step or gradient elution by mixing the mobile phases A and B as directed under the following table.

Mobile phase A: Ammonium acetate buffer

Mobile phase B: Methanol

Adjust the composition of the mobile phase so that the retention time of nizatidine is about 12 minutes.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 3	76	24
3 - 20	76 → 50	24 → 50
20 - 45	50	50
45 - 50	50 → 76	50 → 24
50 - 70	76	24

Flow rate: 1 mL/min

System suitability

System performance: Proceed with 50 μL of the standard solution (1) according to the above conditions; the symmetry factor of nizatidine peak is NMT 2.0.

Time span of measurement: About 3 times the retention time of nizatidine peak.

Ammonium acetate buffer—Weigh 5.9 g of ammonium acetate, dissolve in 760 mL of water to make 0.1 mol/L solution, add 1 mL of diethylamine, and adjust the pH to 7.5 with acetic acid.

Loss on drying NMT 1.0% (2 g, 100 °C, 1 hour).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 15 mg of Nizatidine, dissolve in mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 15 mg of nizatidine RS, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas of nizatidine, A_T and A_S respectively.

$$\text{Amount (mg) of nizatidine } (C_{12}H_{21}N_6O_2S_2) = \text{Amount (mg) of nizatidine RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of ammonium acetate buffer and methanol (76 : 24).

Flow rate: 1 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the number of theoretical plates is NLT 1,500 with the symmetry factor being NMT 2.0.

System repeatability: Repeat the test 5 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of nizatidine is NMT 1.5%.

Packaging and storage Preserve in light-resistant, tight containers.

Nizatidine Tablets
니자티딘 정

Nizatidine contains NLT 90.0% and NMT 110.0% of the labeled amount of nizatidine ($C_{12}H_{21}N_5O_2S_2$: 331.47).

Method of preparation Prepare as directed under Tablets, with Nizatidine.

Identification (1) Weigh an amount equivalent to 0.15 g of nizatidine ($C_{12}H_{21}N_5O_2S_2$) according to the labeled amount of Nizatidine Tablets, add 20 mL of methanol, shake well to mix, and filter it. Separately, weigh 0.15 g of nizatidine RS, add 20 mL of methanol, shake well to

mix, and filter it. Determine the infrared spectra of the residues, obtained by evaporating the filtrate to dryness, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Proceed with Nizatidine Tablets as directed under the Assay; the test solution and the standard solution exhibit peaks at the same retention time.

Dissolution Perform the test with 1 tablet of Nizatidine Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take 20 mL of the medium 30 minutes after starting the test and filter. Take 10.0 mL of the filtrate, add water to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 75 mg of nizatidine RS, and dissolve in water to make 100 mL. To 2.0 mL of this solution, add the dissolution medium to make 100 mL, and use this solution as the standard solution. Determine the absorbances of the test solution and the standard solution, A_T and A_S at 314 nm as directed under the Ultraviolet-visible Spectroscopy. The dissolution rate in 30 minutes of Nizatidine Tablets is NLT 75%.

Dissolution rate (%) with respect to the labeled amount of nizatidine ($C_{12}H_{21}N_5O_2S_2$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 90$$

W_S: Amount (mg) of nizatidine RS

C: Labeled amount (mg) of nizatidine ($C_{12}H_{21}N_5O_2S_2$) in 1 tablet

Purity ***Related substances*—**Weigh accurately the mass of NLT 20 tablets of Nizatidine Tablets and powder. Weigh accurately about 0.2 g of nizatidine ($C_{12}H_{21}N_5O_2S_2$), add 50 mL of the mobile phase, shake to mix, and add the mobile phase to make 100 mL. Use this solution as the test solution. Separately, weigh accurately nizatidine RS, make the concentration of 40 μg per mL, and use this solution as the standard solution. Perform the test with 10 μL each of test solution and standard solution as directed under the Assay and determine the peak area of each related substance in the test solution and the peak area of nizatidine in the standard solution, A_T and A_S. Each related substance is NMT 0.5% and the total related substances are NMT 1.5%.

$$\text{Content (\%) of each related substance} = 2 \times \frac{A_T}{A_S}$$

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately NLT 20 tablets of Nizatidine Tablets and powder. Weigh accurately about 0.1 g of nizatidine ($C_{12}H_{21}N_5O_2S_2$), add 50 mL of the mobile phase, shake well to mix, and make 100 mL with the mobile phase. Filter this solution, take 5.0 mL of the filtrate, add the mobile phase to make 50.0 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of nizatidine RS, proceed in the same manner with the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography and determine the peak area of nizatidine, A_T and A_S.

Amount (mg) of nizatidine ($C_{12}H_{21}N_5O_2S_2$)

$$= \text{Amount (mg) of nizatidine RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

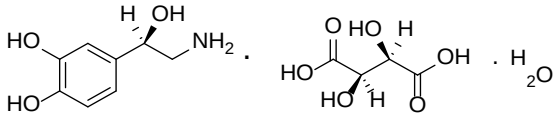
Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of methanol and acetate buffer solution, pH 7.5 (24 : 76).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Norepinephrine Tartrate Hydrate
노르에피네프린타르타르산염수화물



and enantiomer

Noradrenaline Tartrate

Norepirenamine Tartrate

$C_8H_{11}NO_3 \cdot C_4H_6O_6 \cdot H_2O$: 337.28

(*RS*)-4-(2-Amino-1-hydroxyethyl)benzene-1,2-diol; (*RR*)- & (*SS*)-2,3-dihydroxybutanedioic acid; hydrate [*69815-49-2*] [*51-40-1,* anhydride]

Norepinephrine Tartrate Hydrate contains NLT 97.0% and NMT 102.0% of *dl*-norepinephrine tartrate ($C_8H_{11}NO_3 \cdot C_4H_6O_6$), calculated on the anhydrous basis.

Description Norepinephrine Tartrate Hydrate occurs as a white to pale brown or slightly reddish brown crystalline powder.

It is freely soluble in acetic acid(100), very slightly soluble in water and practically insoluble in ethanol(95) or ether.

It dissolves in dilute hydrochloric or acetic acid.

It is gradually changed to brown by air or light.

Identification (1) Determine the infrared spectra of Norepinephrine Tartrate Hydrate and norepinephrine tartrate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve 50 mg of Norepinephrine Tartrate Hy-

drate in 10 mL of water and add one drop of ferric chloride TS to this solution; the resulting solution exhibits a strong green.

(3) Take 1 mL of the solution from (2), add water to make 500 mL, and take 1 mL again to make 1000 mL. To 10 mL of this solution, add 1.0 mL of 0.10 mol/L iodine solution, allow to stand for 5 minutes, and add 2.0 mL of 0.10 mol/L sodium thiosulfate solution; the resulting solution is colorless or light pink.

Optical rotation $[\alpha]_D^{20}$: Between -10° and -12° (0.50 g calculated on the anhydrous basis, 100 mL of water, 100 mm).

Purity ***Arterenone***—Dissolve 0.2 g of Norepinephrine Tartrate Hydrate in water to make exactly 100 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at 310 nm is NMT 0.2.

Water Between 4.5% and 5.8% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (0.2 g).

Assay Weigh accurately about 0.25 g of Norepinephrine Tartrate Hydrate, previously dried, add 100 mL of acetic acid for non-aqueous titration, dissolve by warming, if necessary, and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of methylosaniline chloride TS). The endpoint of the titration is when the bluish purple color of this solution turns to blue and then finally to bluish green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 31.93 mg of $C_8H_{11}NO_3 \cdot C_4H_6O_6$

Packaging and storage Preserve in light-resistant, tight containers at room temperature.

Norepinephrine Tartrate Injection
노르에피네프린타르타르산염 주사액

Noradrenaline Tartrate Injection
Norepirenamine Tartrate Injection

Norepinephrine Tartrate Injection is an aqueous solution for injection, which contains NLT 90.0% and NMT 115.0% of the labeled amount of *dl*-norepinephrine ($C_8H_{11}NO_3$: 169.18).

Method of preparation Prepare as directed under Injections, with Norepinephrine Tartrate Hydrate.

Description Norepinephrine Tartrate Injection occurs as a clear and colorless liquid.

pH—Between 3.0 and 4.5.

Identification (1) Perform the test according to the Identification (2) of Norepinephrine Tartrate Hydrate.

(2) Weigh accurately the amount equivalent to 2 mg of norepinephrine according to the labeled amount of Norepinephrine Tartrate Injection, put the water to make 10 mL, add 2.0 mL of 0.10 mol/L iodine solution, and allow to stand for 5 minutes. Then, add 3.0 mL of 0.10 mol/L sodium thiosulfate solution; the resulting solution is colorless or pale pink.

Purity (1) ***Clarity and color of solution***—Pipet an appropriate amount of Norepinephrine Tartrate Injection, put into the test tube, and observe against a white background; no pink color or precipitation appears. If the yellow color appears, use this solution as the test solution. Put 2.0 mL of 0.1 mol/L iodine solution into the water to make 500 mL and use this solution as the standard solution. With the test solution and the standard solution, determine the absorbance at 460 nm as directed under the Ultraviolet-visible Spectroscopy; the absorbance of the test solution is not greater than that of the standard solution.

Sterility Meets the requirements.

Bacterial endotoxins Less than 83.4 EU per mg of norepinephrine.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Weigh accurately an amount of Norepinephrine Tartrate Injection, equivalent to about 5 mg of *dl*-norepinephrine ($C_8H_{11}NO_3$), add dilute acetic acid (1 in 25) to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of norepinephrine tartrate injection RS, dissolve by adding dilute acetic acid (1 in 25) to make 0.4 mg/mL concentration, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas A_T and A_S of norepinephrine, respectively.

$$\text{Amount (mg) of } dl\text{-norepinephrine } (C_8H_{11}NO_3) \text{ in 1 mL of Norepinephrine Tartrate Injection} = \frac{\text{Concentration of standard solution (mg / mL)}}{\text{Amount of Norepinephrine Tartrate Injection taken (mL)}} \times \frac{A_T}{A_S} \times 25 \times \frac{169.18}{337.28}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 1.1 g of sodium 1-heptanesulfonate in 800 mL of water, add 200 mL of methanol, adjust pH to 3.0 ± 0.1 with 1 mol/L phosphoric acid, and filter using a membrane filter.

Flow rate: 2.0 mL/min

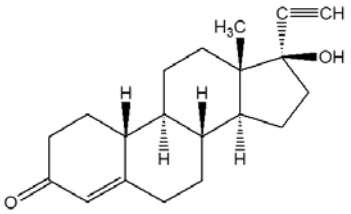
System suitability

System performance: Weigh accurately an appropriate amount each of isoproterenol and norepinephrine tartrate RS respectively, and dissolve in dilute acetic acid (1 in 25) to make 20 mL of solution at a concentration of 0.4 mg/mL. Proceed with 20 μL of the resulting solution under the above conditions; the resolution of norepinephrine and isoproterenol peaks is NLT 4.0.

System repeatability: Repeat the test 5 times with 20 μL standard solution according to the above conditions; the relative standard deviation of norepinephrine peak area is NMT 2.0%

Packaging and storage Preserve in light-resistant, hermetic containers.

Norethisterone
노르에티스테론



Norethindrone

$C_{20}H_{26}O_2$: 298.42

(8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-Ethynyl-17-hydroxy-13-methyl-1,2,6,7,8,9,10,11,12,14,15,16-dodecahydrocyclopenta[a]phenanthren-3-one [*68-22-4*]

Norethisterone, when dried, contains NLT 97.0% and NMT 103.0% of norethisterone ($C_{20}H_{26}O_2$).

Description Norethisterone occurs as a white to pale yellow crystalline powder. It is odorless.
It is sparingly soluble in ethanol(95), acetone or tetrahydrofuran, slightly soluble in ether and very slightly soluble in water.
It is affected by light.

Identification (1) Add 2 mL sulfuric acid to 2 mg of Norethisterone; the resulting solution exhibits a reddish brown color with a yellowish green fluorescence. Add 10 mL of water to this solution cautiously; the resulting solution exhibits a yellow color and a pale brown precipitate is produced.

(2) To 25 mg of Norethisterone, add 3.5 mL of a solution made by dissolving 50 mg of hydroxylamine hydrochloride and 50 mg of anhydrous sodium acetate in 25 mL of methanol. Heat on a steam bath for 5 hours under a reflux condenser. After cooling, take the precipitate obtained by adding 15 mL of water and filtering. Wash this precipitate with 1 - 2 mL of water, recrystallize with methanol, and dry in a desiccator (in vacuum, silica gel) for 5 hours; the crystals melt between 112 and 118 ℃.

Optical rotation $[\alpha]_D^{20}$: Between -32 and -37° (After drying, 0.25 g, acetone, 25 mL, 200 mm).

Melting point Between 203 and 209 ℃.

Purity ***Related substances***—With 0.1 g each of Norethisterone and norethisterone RS, prepare the test and standard solutions according to Purity (2), Related substances (A) of Norethisterone Acetate. With these solutions, perform the test as directed under the Thin Layer Chromatography. Next, develop the plate with a mixture of chloroform and methanol (95 : 5) as the developing solvent to a distance of 3/4 of entire length, and air-dry the plate. Spray evenly with a mixture of methanol and sulfuric acid, and heat the plate at 100 ℃ for 5 minutes; The R_f value of the principal spot from the test solution is identical with that of the standard solution (1), and the spots other than the principal spot from the test solution are not more intense (0.5%) than the spots from the standard solution. The total intensity of the spots other than the principal spot from the test solution is not more intense (1.5%) than the spots from the standard solution (1).

Loss on drying NMT 0.5% (0.5 g, in vacuum, silica gel, 4 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately 0.2 g of Norethisterone, previously dried, dissolve in 40 mL of tetrahydrofuran, add 10 mL of silver nitrate solution (1 in 20), and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 29.843 mg of $C_{20}H_{26}O_2$

Packaging and storage Preserve in light-resistant, tight containers.

Norethisterone Tablets
노르에티스테론 정

Norethindrone Tablets

Norethisterone Tablets contains NLT 90.0% and NMT 110.0% of the labeled amount of norethisterone

($C_{20}H_{26}O_2$: 298.42).

Method of preparation Prepare as directed under Tablets, with Norethisterone.

Identification Weigh an amount of Norethisterone Tablets, previously powdered, equivalent to about 50 mg of norethisterone according to the labeled amount, add 15 mL of hexane, and shake occasionally for 15 minutes. Centrifuge this mixture and discard the hexane layer. Extract the residues with each 10 mL of hexane twice, centrifuge, and discard the hexane layer. Add 25 mL of chloroform to the residue, shake for 1 - 2 minutes, and filter. Evaporate the filtrate until it is concentrated to 3 mL, add an appropriate amount of hexane to separate crystals, and evaporate to dryness. Determine the infrared spectra of this residue and norethisterone RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Dissolution Perform the test with 1 tablet of Norethisterone Tablet at 75 revolutions per minute according to Method 2 under the Dissolution, using 500 mL of 0.1 mol/L hydrochloric acid TS containing 0.09% sodium lauryl sulfate degassed with the dissolution medium. Take NLT 20 mL of the dissolved solution 30 minutes after starting the Dissolution and filter using a 0.45 μm membrane filter. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 35 mg of norethisterone RS, put in a 500-mL volumetric flask, add 100 mL of methanol, and sonicate to completely dissolve. After cooling at room temperature, add methanol to make exactly 500 mL. Pipet 2.0 mL of this solution, add the test solution to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 100 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of each solution. The acceptable dissolution criterion is NLT 80% (Q) of Norethisterone Tablets dissolved in 30 minutes.

Dissolution rate (%) of the labeled amount of norethisterone ($C_{20}H_{26}O_2$)
= Amount (mg) of norethisterone RS $\times \frac{A_T}{A_S} \times \frac{1}{C}$

C: Labeled amount (mg) of norethisterone ($C_{20}H_{26}O_2$) in 1 tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of water and acetonitrile (3 : 2).

Flow rate: 1.5 mL/min

System suitability

System repeatability: Repeat the test 5 times with each 100 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of norethisterone is NMT 3.0%.

Uniformity of dosage units Meets the requirements.

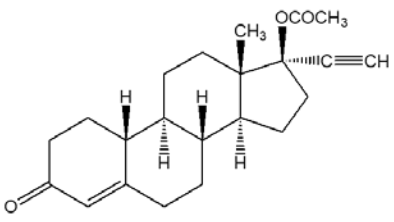
Assay Weigh accurately the mass of NLT 20 tables of Norethisterone Tablets and powder. Weigh accurately an amount of Norethisterone Tablets, equivalent to about 0.7 mg of norethisterone ($C_{20}H_{26}O_2$), put in a volumetric flask, add purified methanol to the gauge line, and shake to mix. Allow it to stand for 10 minutes with occasional shaking. Filter the mixture, transfer 10.0 mL of the filtrate to a suitable flask, add 2.0 mL of isoniazid TS, and allow it to stand for 30 minutes with the stopper closed. Use this solution as the test solution. Transfer 10.0 mL of the remaining filtrate to a suitable flask, add 2.0 mL of methanol, and use this solution as a control solution of the test solution. Take 10.0 mL of methanol to a suitable flask, add 2.0 mL of isoniazid TS, shake to mix with the stopper closed, and allow it to stand for 30 minutes. Use this solution as a control solution of the reagent solution. Separately, weigh accurately a certain amount of norethisterone RS and dissolve in methanol to make a solution containing 14 μg per mL. Pipet 10.0 mL of this solution, add 2.0 mL of isoniazid TS, and allow it to stand for 30 minutes with a stopper closed. Use this solution as the standard solution. With these solutions, determine the absorbances, A_T, A_B and A_S, of the test solution, the control solution of the test solution and the standard solution at 380 nm as directed under the Ultraviolet-visible Spectroscopy, using methanol as the control for the control solution of the test solution and using the control solution of the reagent solution as the control for the test solution and the standard solution.

Amount (mg) of norethisterone ($C_{20}H_{26}O_2$)
$= 0.05 \times C \times \frac{A_T - A_B}{A_S}$

C: Concentration of standard solution (μg/mL)

Packaging and storage Preserve in well-closed containers.

Norethisterone Acetate
노르에티스테론아세테이트



Norethindrone Acetate $C_{22}H_{28}O_3$: 340.46
[(8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-Ethynyl-13-methyl-3-oxo-1,2,6,7,8,9,10,11,12,14,15,16-dodecahydrocyclopenta[a]phenanthren-17-yl] acetate [*51-98-9*]

Norethisterone Acetate contains NLT 97.0% and NMT 103.0% of norethisterone acetate ($C_{22}H_{28}O_3$), calculated on the dried basis.

Description Norethisterone Acetate occurs as a white to milky white crystalline powder. It is odorless.
It is soluble in ether or ethanol(95) and practically insoluble in water.

Identification Determine the infrared spectra of Norethisterone Acetate and norethisterone acetate RS, both previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -30° and -35° (0.50 g as a calculated dried basis, ethanol(95), 25 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Norethisterone Acetate in ethanol(95); the solution is clear.

(2) ***Related substances***—(i) Dissolve 0.1 g of Norethisterone Acetate in chloroform to make exactly 10 mL and use it as the test solution. Separately, dissolve 0.1 g of norethisterone acetate RS in chloroform to make exactly 10 mL and dilute this solution by adding chloroform to make the standard solutions (1), (2), (3), and (4) at concentrations of 150, 50, 30 and 10 μg/mL, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Next, develop the plate with a mixture of toluene and ethyl acetate (1 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray evenly a mixture of methanol and sulfuric acid on the plate and heat the plate at 100 ℃ for 5 minutes; spots other than the principal spot from the test solution are not more intense than the spot from the standard solution (2), and the total intensity of the spots other than the principal spot from the test solution is not more intense than that from the standard solution (1).

(ii) Dissolve 62.5 mg of Norethisterone Acetate in the mobile phase to make exactly 25 mL, and use this solution as the test solution. To 1.0 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of these solutions; each peak area other than the major peak of the test solution is not greater than 1/2 of the major peak area of the standard solution (0.5%), and the total peak area other than the major peak of the test solution is not greater than the major peak area of the standard solution (1.0%). Exclude the peak area NMT 0.025 times of the area of the major peak of the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 to 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and water (6: 4).

Flow rate: 1.0 mL/min

System suitability

System performance: Dissolve 8 mg each of desoxycorticosterone acetate RS and norethisterone acetate RS in the mobile phase to make exactly 100 mL. Proceed with 20 μL of this solution according to the above conditions; desoxycorticosterone acetate and norethisterone acetate are eluted in this order with the resolution between these peaks being NLT 3.5.

Time span of measurement: About 2 times the retention time of norethisterone acetate.

(3) ***Ethinyl-group***—Weigh accurately about 0.2 g of Norethisterone Acetate, add 40 mL of tetrahydrofuran and 10 mL of silver nitrate solution (1 in 10), and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.
The content of ethinyl group is between 7.13% and 7.17%.

Each mL of 0.1 mol/L sodium hydroxide VS
= 2.503 mg of -C≡CH

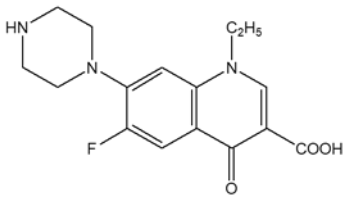
Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

Assay Weigh accurately about 0.1 g each of Norethisterone Acetate and norethisterone acetate RS and dissolve in ethanol(95) to make exactly 200 mL. Pipet 5.0 mL each of these solutions in ethanol(95) to make exactly 250 mL and use these solutions as the test solution and the standard solution, respectively. Measure the absorbances of the test solution (A_T) and the standard solution (A_S) at the wavelength of 240 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of norethisterone acetate ($C_{22}H_{28}O_3$)
= Amount (mg) of norethisterone acetate RS× $\frac{A_T}{A_S}$

Packaging and storage Preserve in light-resistant, well-closed containers.

Norfloxacin
노르플록사신



$C_{16}H_{18}FN_3O_3$: 319.33
Ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid [*70458-96-7*]

Norfloxacin, when dried, contains NLT 99.0% and NMT 101.0% of norfloxacin ($C_{16}H_{18}FN_3O_3$).

Description Norfloxacin occurs as a white to light yellow and crystalline powder.
It is freely soluble in acetic acid(100), slightly soluble in ethanol(99.5) or acetone, very slightly soluble in methanol and practically insoluble in water.
It dissolves in dilute hydrochloric acid or sodium hydroxide TS.
It is hygroscopic.
It is gradually colored by light.

Identification (1) Dissolve 10 mg of Norfloxacin and norfloxacin RS in the sodium hydroxide solution (1 in 250) to make 10 mL, respectively. Add sodium hydroxide solution (1 in 250) to 5 mL each of these solutions to make 100 mL and determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Dissolve Norfloxacin and norfloxacin RS in acetone, respectively, evaporate the acetone in vacuum, and dry the residues. Determine the infrared spectra of the residues as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Sulfates***—Dissolve 1.0 g of Norfloxacin in 7 mL of 0.5 mol/L sodium hydroxide TS and 23 mL of water, add 1 drop of phenolphthalein TS, add gradually diluted hydrochloric acid (1 in 3) until the red color disappears, add 0.5 mL of dilute hydrochloric acid, and cool on ice for 30 minutes. Filter through a glass filter, wash the residues with 10 mL of water, combine the filtrate and the washings, and add 1 mL of dilute hydrochloric acid and water to make exactly 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution as follows. To 0.5 mL of 0.005 mol/L sulfuric acid, add hydrochloric acid diluted with 7 mL of 0.5 mol/L sodium hydroxide TS and 1 drop of phenolphthalein TS until the red color disappears, and then add 1.5 mL of dilute hydrochloric acid and 1 - 2 drops of bromophenol blue TS and water to make exactly 50 mL (NMT 0.024%).

(2) ***Heavy metals***—Proceed with 2.0 g of Norfloxacin according to Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 15 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Norfloxacin according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Perform the test using light-resistant containers. Dissolve 0.10 g of Norfloxacin in 50 mL of a mixture of methanol and acetone (1 : 1) and use this solution as the test solution. Pipet 1 mL of this solution and add a mixture of methanol and acetone (1 : 1) to make exactly 100 mL. Pipet 2 mL of this solution, add a mixture of methanol and acetone (1 : 1) to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (5 μm to 7 μm in particle diameter with fluorescent indicator). Develop the plate with a mixture of chloroform, toluene, diethylamine and water (20 : 20 : 10 : 7 : 4) to a distance of about 9 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm and 366 nm); the number of spots other than the principal spot from the test solution is NMT 2 and these spots are not more intense than the spots from the standard solution.

Loss on drying NMT 1.0% (1 g, 105℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Norfloxacin, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 31.933 mg of $C_{16}H_{18}FN_3O_3$

Packaging and storage Preserve in light-resistant, tight containers.

Norfloxacin Capsules
노르플록사신 캡슐

Norfloxacin Capsules contains NLT 90.0% and NMT 110.0% of the labeled amount of norfloxacin ($C_{16}H_{18}FN_3O_3$: 319.34).

Method of preparation Prepare as directed under Capsules, with Norfloxacin.

Identification Proceed as directed under the Assay described below; the test solution shows the major peak at the same retention time as the standard solution.

Dissolution Perform the test with 1 capsule of Norfloxacin Capsules at 50 revolutions per minutes according to Method 2, using 900 mL of 0.05 mol/L sodi-

um acetate buffer (pH 4.0) as the dissolution medium. Filter the medium 45 minutes from the start of the test and use this solution as the test solution. Separately, weigh accurately about 22 mg of norfloxacin RS, dissolve in 0.05 mol/L sodium acetate buffer (pH 4.0) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution according to the following conditions as directed under the Liquid Chromatography and determine the peak areas A_T and A_S of norfloxacin, respectively. The dissolution rate in 45 minutes of Norfloxacin Capsules is NLT 80%.

Dissolution rate (%) of the labeled amount of norfloxacin ($C_{16}H_{18}FN_3O_3$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 900$$

*W*s: Amount (mg) of norfloxacin RS

C: Labeled amount (mg) of norfloxacin ($C_{16}H_{18}FN_3O_3$) in 1 capsule

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 278 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of phosphoric acid (1 in 1000) and acetonitrile (850:150).

Flow rate: 2.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above conditions; the relative standard deviation of norfloxacin peak areas is NMT 2.0%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately about the mass of NLT 20 capsules of Norfloxacin Capsules equivalent to 0.1 g as norfloxacin ($C_{16}H_{18}FN_3O_3$), put it with about 80 mL of the mobile phase in a 200-mL flask, sonicate for 10 minutes, adjust the scale with phosphoric acid solution (1 in 1000), and mix it. Pipette 10.0 mL of this solution, put into a 25-mL flask, dilute with the mobile phase, filter, and use the filtrate as the test solution. Separately, weigh accurately about 0.1 g of norfloxacin RS, add the mobile phase to make exactly 500 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution according to the following conditions as directed under the Liquid Chromatography and determine, A_T and A_S, of the peak area of norfloxacin.

Amount (mg) of norfloxacin ($C_{16}H_{18}FN_3O_3$)

$$= \text{Amount (mg) of norfloxacin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 275 nm).

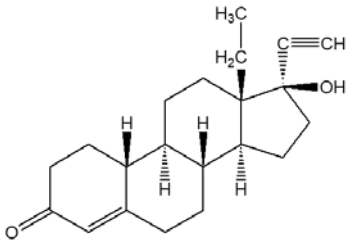
Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel.

Mobile phase: A mixture of perchloric acid solution (1 in 1000) and acetonitrile (850 : 150).

Flow rate: 2.0 mL/min

Packaging and storage Preserve in light-resistant, well-closed containers.

Norgestrel
노르게스트렐



$C_{21}H_{28}O_2$: 312.45

(8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-13-Ethyl-17-ethynyl-17-hydroxy-1,2,6,7,8,9,10,11,12,14,15,16-dodecahydrocyclopenta[a]phenanthren-3-one [*6533-00-2*]

Norgestrel, when dried, contains NLT 98.0% and NMT 101.0% of norgestrel ($C_{21}H_{28}O_2$).

Description Norgestrel occurs as white crystals or a crystalline powder.

It is soluble in chloroform or tetrahydrofuran, sparingly soluble in ethanol(95), slightly soluble in ether, and practically insoluble in water.

Identification (1) Dissolve 1 mg of Norgestrel in 2 mL of ethanol(95) and add 1 mL of sulfuric acid; the resulting solution exhibits a purple color. Examine this solution under ultraviolet light (main wavelength: 365 nm); the solution shows an orange fluorescence.

(2) Determine the infrared spectra of Norgestrel and norgestrel RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 206 and 212 ℃.

Purity (1) ***Heavy metals***—Weigh 1.0 g of Norgestrel, heat gently to carbonize. After cooling, add 10 mL solution of magnesium nitrate in ethanol(95) (1 in 10) and ignite in ethanol(95) to burn. After cooling, proceed with 1 mL of sulfuric acid as directed under Method 4 below and perform the test. Prepare the control solution with 2.0

mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 30 mg of Norgestrel in 5 mL of chloroform and use this solution as the test solution. Pipet 1 mL of this solution, add chloroform to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of dichloromethane and ethyl acetate (2 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

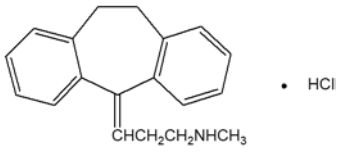
Residue on ignition NMT 0.2% (0.5 g).

Assay Weigh accurately about 0.2 g of Norgestrel, previously dried, dissolve in 40 mL of tetrahydrofuran, add 10 mL of silver nitrate solution (1 in 20), and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 31.245 mg of $C_{21}H_{28}O_2$

Packaging and storage Preserve in well-closed containers.

Nortriptyline Hydrochloride
노르트립틸린염산염



$C_{19}H_{21}N \cdot HCl$: 299.84

3-(10,11-Dihydro-5*H*-dibenzo[a,d]cycloheptен-5-ylidene)-*N*-methylpropan-1-amine hydrochloride [*894-71-3*]

Nortriptyline Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of nortriptyline hydrochloride ($C_{19}H_{21}N \cdot HCl$).

Description Nortriptyline Hydrochloride occurs as a white to yellow crystalline powder. It is odorless or a slight characteristic odor.

It is freely soluble in acetic acid(100) or chloroform, soluble in ethanol(95), sparingly soluble in water and practically insoluble in ether.

pH—Dissolve 1.0 g of Nortriptyline Hydrochloride in 100 mL of water; the pH of this solution is about 5.5.

Melting point—Between 215 and 220 ℃.

Identification (1) Add 1 mL of bromine TS to 5 mL of Nortriptyline Hydrochloride solution (1 in 100); the color of the test solution disappears.

(2) Add 1 - 2 drops of a solution of quinhydrone in methanol (1 in 40) to 5 mL of Nortriptyline Hydrochloride solution (1 in 100); the resulting solution gradually exhibits a red color.

(3) Determine the absorption spectra of Nortriptyline Hydrochloride and nortriptyline hydrochloride RS solution (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared spectra of Nortriptyline Hydrochloride and nortriptyline hydrochloride RS, previously dried, as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(5) A solution of Nortriptyline Hydrochloride (1 in 100) responds to the Qualitative Analysis for chloride.

Purity (1) ***Clarity and Color of Solution***—Dissolve 0.10 g of Nortriptyline Hydrochloride in 10 mL of water; the solution is colorless to light yellow and clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Nortriptyline Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Prepare the test solution with 1.0 g of Nortriptyline Hydrochloride according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Weigh 0.50 g of Nortriptyline Hydrochloride, dissolve in 20 mL of chloroform, and use this solution as the test solution. Pipet 2 mL of this solution and add chloroform to make exactly 100 mL. Pipet 5 mL of this solution, add chloroform to make exactly 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 4 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of cyclohexane, methanol and diethylamine (8 : 1 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

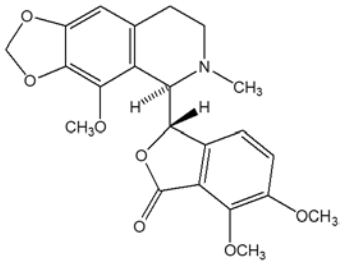
Assay Weigh accurately about 0.5 g of Nortriptyline Hydrochloride, previously dried, dissolve in 5 mL of acetic acid(100), add 50 mL acetic anhydride, and titrate

with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry) Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 29.984 mg of $C_{19}H_{21}N \cdot HCl$

Packaging and storage Preserve in tight-resistant, well-closed containers.

Noscapine
노스카핀



Narcotine $C_{22}H_{23}NO_7$: 413.42
(3*S*)-6,7-Dimethoxy-3-((5*R*)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)isobenzofuran-1(3*H*)-one [*128-62-1*]

Noscapine, when dried, contains NLT 98.5% and NMT 101.0% of noscapine ($C_{22}H_{23}NO_7$).

Description Noscapine occurs as white crystals or a crystalline powder. It is odorless and tasteless.
It is very soluble in acetic acid(100), slightly soluble in ethanol(95) or ether, and practically insoluble in water.

Identification (1) Determine the absorption spectra of Noscapine and noscapine RS in methanol solution (1 in 20000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Noscapine and noscapine RS, previously dried, according to the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Specific optical rotation $[\alpha]_D^{20}$: Between +42° and +48° (After drying, 0.5 g, 0.1 mol/L hydrochloric acid TS, 25 mL, 100 mm).

Melting point Between 174 and 177 ℃.

Purity (1) ***Chloride***—Dissolve 0.7 g of Noscapine in 20 mL of acetone, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution. Add 20 mL of acetone, 6 mL of dilute nitric acid and water to 0.4 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.02%). Use this solution as the control solution.

(2) ***Heavy metals***—Weigh 2.0 g of Noscapine and perform the test according to Method 2. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Morphine***—Dissolve 10 mg of Noscapine in 1 mL of water and 5 mL of 1-nitroso-2-naphthol TS by shaking to mix, add 2 mL of potassium nitrate solution (1 in 10), and warm at 40℃ for 2 minutes. Then, add 1 mL of sodium nitrate solution (1 in 5000) and warm the mixture at 40 ℃for 5 minutes. After cooling, add 10 mL of chloroform, mix by shaking, centrifuge, and collect the aqueous layer; the color of the resulting solution is not more intense than light red.

(4) ***Related substances***—Dissolve 0.7 g of Noscapine in 50 mL of acetone and use this solution as the test solution. Pipet 5 mL of this solution and add acetone to make exactly 50 mL. Pipet 5 mL of this solution, add acetone to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of acetone, toluene, ethanol(99.5) and ammonia water(28) (60 : 60 : 9 : 2) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray dilute bismuth subnitrate-potassium iodide TS for spray evenly onto the plate; spots other than the principal spot from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 0.5% (2 g, 105℃, 4 hours).

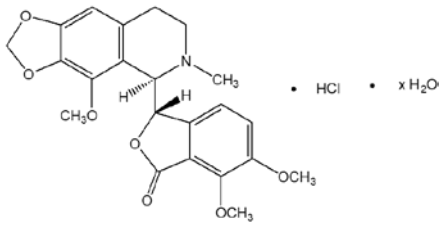
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.8 g of Noscapine, previously dried, dissolve in 30 mL of acetic acid, and titrate with 0.1 mol/L perchloric acid VS (indicator: 3 drops of methylosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 41.34 mg of $C_{22}H_{23}NO_7$

Packaging and storage Preserve in light-resistant, well-closed container.

Noscapine Hydrochloride Hydrate
노스카핀염산염수화물



Noscapine Hydrochloride
Narcotine Hydrochloride $C_{22}H_{23}NO_7 \cdot HCl \cdot xH_2O$
(3*S*)-6,7-Dimethoxy-3-((5*R*)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)isobenzofuran-1(3*H*)-one hydrate hydrochloride [*912-60-7*]

Noscapine Hydrochloride Hydrate, when dried, contains NLT 98.0% and NMT 101.0% of noscapine hydrochloride ($C_{22}H_{23}NO_7 \cdot HCl$: 449.88).

Description Noscapine Hydrochloride Hydrate occurs as colorless or white crystals or a crystalline powder. It is odorless and has a bitter taste.
It is freely soluble in water, acetic acid(100) or acetic anhydride, soluble in ethanol(95) and practically insoluble in ether.

Identification (1) To 1 mg of Noscapine Hydrochloride Hydrate, add 1 drop of formaldehyde-sulfuric acid TS; the resulting solution exhibits a purple color, and then changes to yellowish brown.

(2) To 1 mg of Noscapine Hydrochloride Hydrate, add 1 drop of ammonium vanadate in sulfuric acid (1 in 200); the resulting solution exhibits an orange color.

(3) Dissolve 20 mg of Noscapine Hydrochloride Hydrate in 1 mL of water and add 3 drops of sodium acetate TS; the resulting solution exhibits a white, flocculent precipitate.

(4) Dissolve 1 mg of Noscapine Hydrochloride Hydrate in 1 mL of diluted sulfuric acid (1 in 35), mix with 5 drops of chromotropic acid (1 in 50), and add 2 mL of sulfuric acid by drop; the resulting solution exhibits a purple color.

(5) Dissolve 0.1 g of Noscapine Hydrochloride Hydrate in 10 mL of water, make the solution alkaline with ammonia TS, and shake to mix with 10 mL of chloroform. Separate the chloroform layer, wash with 5 mL water, and filter. Evaporate most of the filtrate on a steam bath, add 1 mL purified methanol, and evaporate to dryness. Dry the residues at 105 ℃ for 4 hours; the residue melts between 174 and 177 ℃.

(6) Make a solution of Noscapine Hydrochloride Hydrate (1 in 50) alkaline with ammonia TS and filter the precipitate. Acidify the filtrate with dilute nitric acid; the solution responds to the Qualitative Analysis (2) for chloride.

Purity ***Morphine***—Dissolve 10 mg of Noscapine Hydrochloride Hydrate in 1 mL of water, add 5 mL of 1-nitroso-2-naphthol TS and 2 mL of potassium nitrate (1 in 10), and warm at 40 ℃ for 2 minutes. Then add 1 mL of sodium nitrate solution (1 in 5000) and warm at 40 ℃for 5 minutes. After cooling, add 10 mL of chloroform, shake to mix, centrifuge, and collect the aqueous layer; the color of resulting solution is not more intense than light red.

Loss on drying NMT 9.0% (0.5 g, 120 ℃, 4 hours).

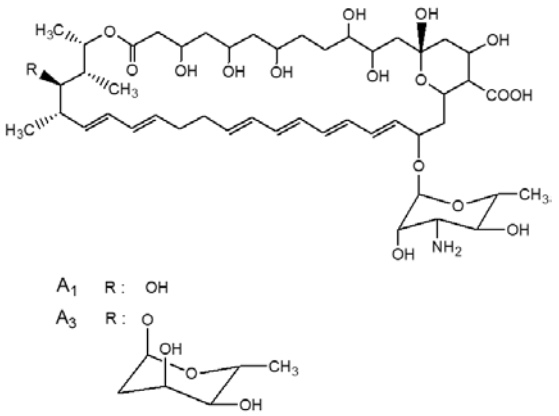
Residue on ignition NMT 0.5% (1 g).

Assay Weigh accurately about 0.5 g of Noscapine Hydrochloride Hydrate, previously dried, dissolve in 50 mL of a mixture of acetic acid(100) and acetic anhydride (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 44.99 mg of $C_{22}H_{23}NO_7 \cdot HCl$

Packaging and storage Preserve in light-resistant, well-closed containers.

Nystatin
니스타틴



Nystatin A_1 $C_{47}H_{75}NO_{17}$: 926.10
(4*E*,6*E*,8*E*,10*E*,14*E*,16*E*,18*S*,19*R*,20*R*,21*S*,35*S*)-3-[(2*S*,3*S*,4*S*,5*S*,6*R*)-4-Amino-3,5-dihydroxy-6-methyloxan-2-yl]oxy-19,25,27,29,32,33,35,37-octahydroxy-18,20,21-trimethyl-23-oxo-22,39-dioxabicyclo[33.3.1]nonatriaconta-4,6,8,10,14,16-hexaene-38-carboxylic acid [*1400-61-9*]

Nystatin is a mixture of polyene macrolide compounds with antifungal activity obtained by culturing *Streptomyces noursei*.

Nystatin contains more than 4600 units (potency) of nystatin A1 ($C_{47}H_{75}NO_{17}$) per mg, calculated on the dried basis. 1 unit corresponds to 0.27 μg of nystatin.

Description Nystatin occurs as a white to light brown powder.
It is soluble in formamide, sparingly soluble in methanol, slightly soluble in ethanol(95) and very slightly soluble in water.
It is soluble in sodium hydroxide TS.

Identification (1) Weigh 1 mg of Nystatin, dissolve in 5 mL of water and 1 mL of sodium hydroxide TS, heat for 2 minutes, and cool. Add 3 mL of a methanol solution of 4-aminoacetophenone (1 in 200) and 1 mL of hydrochloric acid to this solution; the solution exhibits a purple color.

(2) Weigh 10 mg each of Nystatin and nystatin RS, add a mixture of 0.25 mL of sodium hydroxide TS and 50 mL of diluted methanol (4 in 5), melt it by heating at below 50 °C, and add diluted methanol (4 in 5) to make 500 mL. Determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

pH The pH of a solution obtained by suspending 0.3 g of Nystatin in 10 mL of water is between 6.5 and 8.0.

Purity ***Heavy metals***—Weigh about 1.0 g of Nystatin and perform the test according to Method 4. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Abnormal toxicity It meets the requirements when used in the manufacturing of preparations other than those applied to the skin. Suspend an amount equivalent to 600 IU of Nystatin in 5% arabic gum solution, dissolve, and inject intraperitoneally into 5 healthy mice weighing 17 to 24 g. For animals, ones that showed no abnormality for at least 5 days before the test are used for testing. No animals die when observed for 24 hours after administration. If 1 animal dies, repeat the test with 5 animals, and make sure that no animal dies when observed for 24 hours.

Loss on drying NMT 5.0% (0.3 g, in vacuum, 60 °C, 3 hours).

Content ratio of Nystatin Weigh accurately about 20 mg each of Nystatin and the nystatin RS, dissolve in dimethyl sulfoxide to make exactly 50 mL, and use them as the test solution and the standard solution, respectively. Store the test solution and the standard solution in a refrigerator, protected from light and use within 24 hours. Perform a test with 20 μL each of the test solution and the standard solution according to the Liquid Chromatography under the following conditions to obtain individual peak areas. Calculate their amounts according to the percentage peak area method; the content of nystatin A_1 is NLT 85.0% and that of other components is NMT 4.0%. However, peaks with a holding time of less than 2 minutes are excluded.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 304 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 150 mm in length, packed with octadecyl silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: A mixture of 0.05 mol/L ammonium acetate solution and acetonitrile (71 : 29).

Mobile phase B: A mixture of acetonitrile and 0.05 mol/L ammonium acetate solution (60 : 40).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 25	100	0
25 - 35	100 → 0	0 → 100
35 - 40	0	100
40 - 45	0 → 100	100 → 0
45 - 50	100	0

Flow rate: 1 mL/min

System suitability

System performance: Weigh accurately about 20 mg of nystatin RS, dissolve in 25 mL of methanol, and add water to make 50 mL. Add 2 mL of dilute hydrochloric acid to 10 mL of this solution, and allow it to stand at room temperature for 1 hour. Proceed with 20 μL of this solution under the above conditions; the resolution between the two major peaks is NLT 3.5, and the retention time of nystatin A_1 is about 14 minutes.

Assay ***Cylinder plate method*** (1) Medium: Agar medium for gradation and base layer Use the medium of the Microbial Assays for Antibiotics A) (2) (A) ④ (a).

(2) Test organism: Use *Saccharomyces cerevisiae* ATCC 9763 as the test organism.

(3) Weigh accurately an amount equivalent to about 60,000 units of Nystatin, dissolve in *N*,*N*-dimethylformamide to make a solution containing 3,000 units per mL, and use the solution as the test stock solution. Take accurately an appropriate amount of this solution, dilute with 1% phosphate buffer (pH 6.0) to contain 300 and 150 units per mL, and use these solutions as a high-concentration test solution and a low-concentration test solution, respectively. Use light-resistant containers. Separately, weigh accurately an amount equivalent to about 60,000 units of nystatin RS (previously dried under reduced pressure at NMT 0.67 kPa at 40 °C for 2 hours) and dissolve in *N*,*N*-dimethylformamide to prepare a standard stock solution containing 3,000 units per mL. Store this standard solution below 5 °C and use it within 3 days. Take exactly an appropriate amount of this standard stock solution and dilute with 1% phosphate buffer

(pH 6.0) to contain 300 and 150 units per mL, and use them as high-concentration standard solutions and low-concentration standard solutions, respectively. Use light-resistant containers. Perform the test with these solutions according to the Microbial Assays for Antibiotics A) (8).

Packaging and storage Preserve in light-resistant, tight containers (in a cold place).

Nystatin Tablets
니스타틴 정

Nystatin Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of nystatin ($C_{47}H_{75}NO_{17}$: 926.10).

Method of preparation Prepare as directed under Tablets, with Nystatin.

Identification Powder Nystatin Tablets, weigh an amount equivalent to 10 mg of nystatin, add 5 mL of water, and shake to mix. Add 2 drops of phosphomolybdic acid-tungstic acid TS and allow to stand for 1 hour; the resulting solution exhibits a green color.

Loss on drying NMT 5.0% (0.1 g, 0.7 kPa, 60 ℃, 3 hours).

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Perform the test according to the Assay under Nystatin. However, weigh accurately NLT 20 tablets of Nystatin Tablets and powder them. Weigh accurately an amount equivalent to about 600,000 units (potency) according to the labeled potency of Nystatin Tablets, put in a blender, add 150 mL of *N,N*-dimethylformamide, and mix for 2 minutes. Then, add *N,N*-dimethylformamide to make exactly 200 mL, and filter or centrifuge, if necessary. Take exactly an appropriate amount of this solution, dilute it with 1% phosphate buffer (pH 6.0) to make it the same concentration as in (3), and use this solution as the test solution.

Packaging and storage Preserve in light-resistant, tight containers.

Nystatin, Neomycin Sulfate and Polymyxin B Sulfate Suppositories
니스타틴·네오마이신황산염·폴리믹신B황산염 좌제

Nystatin, Neomycin Sulfate and Polymyxin B Sulfate Suppositories contain NLT 90.0% and NMT 120.0% of the labeled amount of nystatin ($C_{47}H_{75}NO_{17}$: 926.10), neomycin ($C_{23}H_{46}N_6O_{13}$: 614.65) and polymyxin B.

Method of preparation Prepare as directed under Suppositories, with Nystatin, Neomycin Sulfate and Polymyxin B Sulfate.

Identification Weigh 5 g of Nystatin, Neomycin Sulfate and Ploymyxin B Sulfate Suppositories, put it into a centrifuge tube, add 20 mL of chloroform, shake vigorously to mix, and centrifuge. Discard the clear liquid at the top layer, add 20 mL of chloroform again, and perform the same procedure. Dissolve the remaining precipitate in 10 mL of a mixture of dimethylformamide and 1 mol/L hydrochloric acid TS (1 : 1), and use this solution as the test solution. Separately, weigh about 200,000 units (potency) of nystatin RS, dissolve in 10 mL of a mixture of dimethylformamide and 1 mol/L hydrochloric acid TS (1 : 1), and use this solution as the standard solution (i). Separately, weigh about 70 mg (potency) of neomycin sulfate RS, dissolve in 10 mL of water, and use this solution as the standard solution (ii). Separately, weigh about 70,000 units (potency) of polymyxin B sulfate RS, dissolve in 10 mL of water, and use this solution as the standard solution (3). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test and standard solutions (i), (ii) and (iii) on the thin-layer chromatographic plate made using silica gel for thin-layer chromatography, and develop with a mixture of n-butanol, acetic acid(100), water and pyridine (40 : 17 : 16 : 8) as a developing solvent. Then, air-dry the plate and evenly spray with 0.5% ninhydrin in ethanol(95); the R_f values of the spots obtained from the test and standard solutions are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Take NLT 20 suppositories of Nystatin, Neomycin Sulfate and Polymyxin B Sulfate Suppositories, weigh accurately the mass, cut into small pieces, if necessary, and mix evenly to use samples of (1), (2) and (3).

(1) ***Nystatin Standard curve method***—(i) Medium: Agar medium for seed and base layer Use the medium of the Potency assay a)(ii)(a)④ⓐ.

(ii) Test organism: Use *Saccharomyces cerevisiae* ATCC 9763 as the test organism.

(iii) Weigh accurately about 100,000 units (potency) according to the indicated potency of nystatin of Nystatin, Neomycin Sulfate and Polymyxin B Sulfate Suppositories, add dimethylformamide to make 100 mL. Pipet an appropriate amount of this solution, dilute with 1% phosphate buffer (pH 6.0) to contain 200 units (potency) per mL, and use it as the test solution. Separately, weigh accurately about 10 mg of the nystatin RS and dissolve in dimethylformamide to prepare the standard stock solution containing 3000 units (potency) per mL. Store this standard stock solution at below 5 ℃ and use within 3 days. Pipet an appropriate amount of the standard stock solu-

tion, dilute with 1% phosphate buffer (pH 6.0) to contain 120, 160, 200, 240 and 280 units (potency) per mL, and use them as the standard solutions. Use the solution containing 200 units (potency) per mL as the standard intermediate diluent. Perform the test as directed under the Microbial Assays for Antibiotics b) (iv) with the test solution, the standard solution and the standard intermediate diluent.

(2) ***Neomycin sulfate***—*Cylinder plate method* (i) Medium: (a) Agar medium for seed layer and base layer

Peptone	6.0 g
Sodium chloride	2.5 g
Yeast extract	3.0 g
Glucose	1.0 g
Meat extract	1.5 g
Agar	15.0 - 20.0 g

Weigh the above, add purified water to make 1000 mL, and adjust the pH to 7.8 - 8.0 after sterilizing with 1 mol/L sodium hydroxide TS.

(ii) Test organism and test suspension: Use *Staphylococcus aureus* ATCC 6538 P as the test organism. However, make a test suspension so that the transmittance of the test suspension is 80% when measured using an absorbance photometer at a wavelength of 650 nm.

(iii) Weigh accurately about 0.1 g (potency) according to the labeled potency of neomycin of Nystatin, Neomycin Sulfate and Polymyxin B Sulfate Suppositories, add 0.1 mol/L phosphate buffer (pH 8.0), shake vigorously to mix, and filter or centrifuge to make a solution containing 1 mg (potency) in 1 mL. Then, take exactly an appropriate amount of this solution, dilute with 0.1 mol/L phosphate buffer (pH 8.0) to contain 80.0 and 20.0 μg (potency) in 1 mL, and use these solutions as the high concentration test solution and the low concentration test solution, respectively. Separately, take an appropriate amount of neomycin sulfate RS, dry it, weigh accurately about 20 mg (potency), and dissolve in 0.1 mol/L phosphate buffer (pH 8.0) to prepare a standard stock solution containing 1 mg (potency) in 1 mL. Store the standard stock solution at below 5 ℃ and use it within 30 days. Pipet an appropriate amount of this standard stock solution and dilute with 0.1 mol/L phosphate buffer (pH 8.0) to contain 80.0 μg and 20.0 μg (potency) in 1 mL, and use them as the high concentration standard solution and the low concentration standard solution, respectively. With these solutions, perform the test according to a)(8) under the Microbial Assays for Antibiotics.

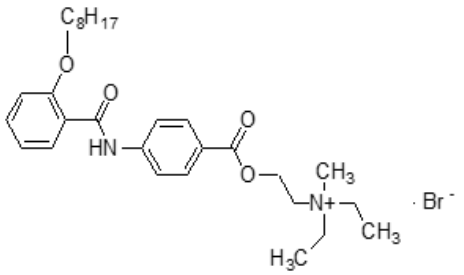
(3) ***Polymyxin B sulfate***—*Cylinder plate method* (i) Medium: Agar medium for seed and base layer Use the medium of the Microbial Assays for Antibiotics a) (ii) (a)⑤ⓐ.

(ii) Test organism: Use *Escherichia coli* NIHJ or NCCP 14134 as the test organism.

(iii) Weigh accurately about 200,000 units (potency) according to the labeled potency of Polymyxin B of Nystatin, Neomycin Sulfate and Polymyxin B Sulfate Suppositories, add 20 mL of 1% phosphate buffer (pH 6.0), shake vigorously to mix, and filter or centrifuge. Pipet an appropriate amount of this solution, dilute with 1% phosphate buffer (pH 6.0), dilute it to contain 4,000 and 1000 units (potency) in 1 mL, and use them as the high concentration test solution and the low concentration test solution. Separately, weigh accurately about 200,000 units (potency) of polymyxin B sulfate RS and dissolve in 1% phosphate buffer (pH 6.0) to prepare a standard stock solution containing 10,000 units (potency) per mL. Store the standard stock solution at below 5 ℃ and use it within 14 days. Pipet an appropriate amount of this standard stock solution, dilute with 1% phosphate buffer (pH 6.0) to make solutions containing 4,000 units and 1000 units per mL, and use these solutions as the high concentration standard solution and the low concentration standard solution, respectively. With these solutions, perform the test according to a)(8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in tight containers.

Octylonium Bromide
옥틸로늄브롬화물



$C_{29}H_{43}O_4N_2Br$: 563.57

N,*N*-Diethyl-*N*-methyl-2-[[4-[[2-(octyloxy)benzoyl]amino]benzoyl]oxy]-ethanaminium bromide, [*26095-59-0*]

Octylonium Bromide, when dried, contains NLT 97.0% and NMT 101.0% of octylonium bromide ($C_{29}H_{43}N_4O_2$).

Description Octylonium Bromide occurs as white acicular crystals.
It is odorless and extremely bitter.
It is freely soluble in water, ethanol(95), chloroform or acetic acid(31) and practically insoluble in ether.

Identification (1) An aqueous solution of Octylonium Bromide responds to the Qualitative Analysis for bromide.

(2) Determine the absorption spectrum of a solution of Octylonium Bromide in ethanol(95) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum near 292 nm.

(3) Determine the infrared spectra of Octylonium Bormide and octylonium bromide RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

(4) To 3 mL of an aqueous solution of Octylonium

Bromide, add potassium ferrocyanide TS; a pale yellow precipitate develops.

Melting point Between 167 and 169 ℃.

Absorbance ratio The absorbance ratio for a 0.001% solution of Octylonium Bromide in ethanol(95) at the absorbance maximum wavelength near 292 nm and the absorbance minimum wavelength near 247 nm is between 4.7 and 5.2.

Purity (1) ***Clarity and color of solution***—A 5% aqueous solution of Octylonium Bromide is clear and colorless.

(2) ***Heavy metals***—Weigh 1.0g of Octylonium Bromide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Sulfate***—Weigh 0.5 g of Octylonium Bromide and perform the test. Prepare the control solution with 1 mL of 0.005 mol/L sulfuric acid (NMT 0.1%).

Loss on drying NMT 0.1% (1 g, 105 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.45 g of Octylonium Bromide, previously dried, transfer to a beaker, add 2 mL of anhydrous formic acid, dissolve in 50 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 56.36 mg of $C_{29}H_{43}O_4N_2Br$

Packaging and storage Preserve in well-closed containers.

Octylonium Bromide Tablets
옥틸로늄브롬화물 정

Octylonium Bromide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of octylonium bromide ($C_{29}H_{43}O_4N_2Br$: 563.57).

Method of preparation Prepare as directed under Tablets, with Octylonium Bromide.

Identification Weigh an amount of Octylonium Bromide Tablets, equivalent to about 20 mg of octylonium bromide according to the labeled amount, dissolve in 5 mL of water, then centrifuge, and use the clear supernatant as the test solution. Dissolve about 20 mg of octylonium bromide RS in water to make 5 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of methanol, acetone and acetic acid(100) (45 : 5 : 2) as the developing solvent, and air-dry the plate. Spray evenly Dragendorff's TS on the plate; the R_f values and the colors of the spots obtained from the test and the standard solutions are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Octylonium Bromide Tablets, and powder. Weigh accurately an amount of this powder, equivalent to about 20 mg of octylonium bromide ($C_{29}H_{43}O_4N_2Br$), and add the mobile phase to make exactly 100 mL. After filtering this solution, pipet 10 mL of the filtrate, add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of octylonium bromide RS, and add the mobile phase to make exactly 100 mL. Pipet 10 mL of this solution, add the mobile phase to it make exactly 50 mL, and use this solution as the standard solution. Pipet 20 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of octylonium in each solution.

Amount (mg) of octylonium bromide ($C_{29}H_{43}O_4N_2Br$)
= Amount (mg) of octylonium bromide RS × (A_T / A_S)

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 292 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of acetonitrile and 0.01 mol/L potassium dihydrogen phosphate TS (3 : 1).

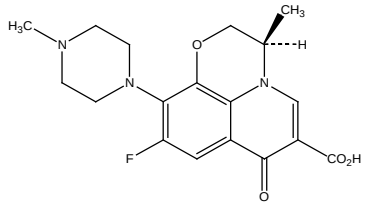
Flow rate: 0.8 mL/min

System suitability

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of octylonium is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Ofloxacin
오플록사신



and enantiomer

$C_{18}H_{20}FN_3O$: 361.37

7-Fluoro-2-methyl-6-(4-methylpiperazin-1-yl)-10-oxo-4-oxa-1-azatricyclo[7.3.1.0^{5,13}]trideca-5(13),6,8,11-tetraene-11-carboxylic acid [*82419-36-1*]

Ofloxacin, when dried, contains NLT 99.0% and NMT 101.0% of ofloxacin ($C_{18}H_{20}FN_3O$).

Description Ofloxacin occurs as white to pale yellowish white crystals or a crystalline powder.
It is freely soluble in acetic acid(100), slightly soluble in water, and very slightly soluble in acetonitrile or ethanol(99.5).
A solution of Ofloxacin in sodium hydroxide TS (1 in 20) shows no optical rotation.
It is changed in color by light.

Melting point—About 265 °C (with decomposition).

Identification (1) Determine the absorption spectra of the solutions of Ofloxacin and ofloxacin RS in 0.1 mol/L hydrochloric acid TS (1 in 150000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Ofloxacin and ofloxacin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +74.5° and +78.0° (1 g, Water, 100 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Ofloxacin according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Proceed with 2.0 g of Ofloxacin according to Method 2 and perform the test (NMT 1 ppm).

(3) ***Related substances***—Proceed the test keeping, protected from light. Dissolve 10 mg of Ofloxacin in 50 mL of a mixture of water and acetonitrile (6 : 1) and use this solution as the test solution. Pipet 1 mL of this solution and add a mixture of water and acetonitrile (6 : 1) to make exactly 20 mL. Pipet 1 mL of this solution and add a mixture of acetonitrile and water (6 : 1) to make 10 mL, and use this solution as the standard solution. Take exactly each 10 μL of the test solution and the standard solution and perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; each peak area other than the major peak from the test solution is not greater than 0.4 times the peak area of ofloxacin from the standard solution. The total area of the peaks is not greater than the peak area from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 294 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 45 °C.

Mobile phase: Dissolve 4.0 g of sodium perchlorate and 4.0 g of ammonium acetate in 1300 mL of water, adjust the pH to 2.2 with phosphoric acid, and add 240 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of ofloxacin is about 20 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution and add a mixture of water and acetonitrile (6 : 1) to make exactly 20 mL. Proceed with 10 μL of this solution according to the above conditions, and confirm that the peak area of ofloxacin is equivalent to 4% - 6% of the peak area of ofloxacin from the standard solution.

System performance: Pipet 0.5 mL of the test solution, add 1 mL of a solution of ofloxacin demethylation in a mixture of water and acetonitrile (6 : 1) (1 in 20000), and add 100 mL of a mixture of water and acetonitrile (6 : 1) to make 100 mL. Proceed with 10 μL of the resulting solution according to the above operating conditions; ofloxacin demethylation and ofloxacin are eluted in this order with the resolution being NLT 2.5.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of ofloxacin is NMT 2.0%.

Time span of measurement: About 1.8 times the retention time of ofloxacin after the solvent peak.

Loss on drying NMT 0.2% (1 g, 105℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Ofloxacin, previously dried, dissolve in 100 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Separately, perform a blank test and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 36.14 mg of $C_{18}H_{20}FN_3O$

Packaging and storage Preserve in light-resistant, tight containers.

Ofloxacin Ophthalmic Ointment
오플록사신 안연고

Ofloxacin Ophthalmic Ointment contains NLT 90.0% and NMT 110.0% of the labeled amount of ofloxacin ($C_{18}H_{20}FN_3O_4$: 361.37).

Method of preparation Prepare as directed under Ophthalmic Ointments, with Ofloxacin.

Identification The retention time of the major peak obtained from the test solution and the standard solution from the Assay and the ultraviolet absorption spectrum between 200 and 400 nm are the same.

Foreign metallic matter Meets the requirements.

Sterility Meets the requirements.

Assay Weigh accurately an amount of Ofloxacin Ophthalmic Ointment equivalent to about 7.5 mg of ofloxacin ($C_{18}H_{20}FN_3O_4$) according to the labeled amount, add 15 mL of chloroform, and dissolve by warming on a steam bath at 60 °C. After cooling, add 0.1 mol/L hydrochloric acid TS to make exactly 50 mL, and stir for 30 minutes to centrifuge. Pipet 5 mL of the supernatant, place it in a 50-mL volumetric flask, add water to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 15 mg of ofloxacin RS, dissolve in 0.1 mol/L hydrochloric acid TS to make 50 mL, pipet 5 mL of this solution, place it in a 100-mL volumetric flask, and add water to make exactly 100 mL. Use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of ofloxacin, A_T and A_S, in each solution.

Amount (mg) of ofloxacin ($C_{18}H_{20}FN_3O_4$)
= Amount (mg) of ofloxacin RS ($C_{18}H_{20}FN_3O_4$)
× A_T / A_S × 1 / 2

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 294 nm). However, proceed with a photo-diode array detector (200 to 400 nm) for the Identification.

Column: A stainless-steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of 0.1 mol/L citric acid-sodium hydroxide buffer solution (pH 5.0) and methanol (5 : 2).

Flow rate: 1.2 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of ofloxacin is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Ofloxacin Optic Solution
오플록사신 점이액

Ofloxacin Optic Solution contains NLT 90.0% and NMT 110.0% of the labeled amount of ofloxacin ($C_{18}H_{20}FN_3O_4$: 361.37).

Method of preparation Prepare as directed under Optic solution, with Ofloxacin.

Identification The retention time and the UV spectrum between 200 nm and 400 nm of the major peak of the Sample solution correspond to those of the Standard solution, as obtained in the Assay.

pH Between 5.5 and 7.5.

Sterility Meets the requirements.

Assay Take exactly an amount of Ofloxacin Optic Solution, equivalent to 3 mg of ofloxacin ($C_{21}H_{20}N_3O_4$), according to the labeled amount, add water to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately about 0.15 g of ofloxacin RS, dissolve in 0.1 mol/L hydrochloric acid to make 100 mL. Pipet 10 mL of the resulting solution, and add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of ofloxacin from each solution.

Amount (mg) of ofloxacin ($C_{18}H_{20}FN_3O_4$)
= Amount (mg) of ofloxacin RS × (A_T/ A_S) × 0.02

Operating conditions

Detector: An ultraviolet absorbance spectrophotometer (wavelength: 294 nm). However, a photo-diode array detector (200 nm - 400 nm) is used when the Identification is performed.

Column: A stainless steel column 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of 0.1 mol/L citric acid-sodium hydroxide buffer solution (pH 5.0) and methanol (5 : 2).

Flow rate: Adjust the flow rate so that the retention

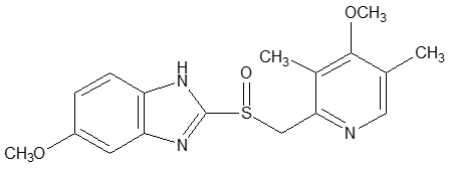
time of ofloxacin is about 5 minutes.

System suitability

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak areas of ofloxacin is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Omeprazole
오메프라졸



$C_{17}H_{19}N_3O_3S$: 345.42

5-Methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl) methylsulfinyl)-1*H*-benzo[d]imidazole [*73590-58-6*]

Omeprazole contains NLT 98.0% and NMT 102.0% of omeprazole ($C_{17}H_{19}N_3O_3S$) calculated on the dried basis.

Description Omeprazole occurs as a white to pale purple powder.

It is soluble in dichloromethane, methanol or ethanol(95), and very slightly soluble in water.

Melting point—About 150 °C (with decomposition).

Identification Determine the infrared spectra of Omeprazole and omeprazolen RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the spectra, dissolve Omeprazole and omeprazolen RS in methanol, evaporate to dryness, and perform the test with the residue in the same manner.

Purity (1) ***Clarity and color of solution***—Dissolve 0.2 g of Omeprazole in 10 mL of dichloromethane; the resulting solution is clear. Perform the test with the resulting solution as directed under Ultraviolet-visible Spectrophotometry using dichloromethane as the control solution; the absorbance at the wavelength of 440 nm is NMT 0.10.

(2) ***Heavy metals***—Proceed with 2.0 g of Omeprazole according to Method 2 under the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—(i) Weigh 1.0 g of Omeprazole, dissolve in a mixture of dichloromethane and methanol (1 : 1) to make 20 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of dichloromethane and methanol (1 : 1) to make exactly 200 mL, and use this solution as the test solution for identification. Separately, weigh accurately about 15 mg of omeprazole RS, add a mixture of dichloromethane and methanol (1 : 1) to make 100 mL, and use this solution as standard solution (1). Pipet 10 mL of this solution, add a mixture of dichloromethane and methanol (1 : 1) to make 30 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution, the standard solution (1) and (2) on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of dichloromethane saturated with ammonia water, dichloromethane and 2-propanol (2 : 2 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); any spot other than the principal spot obtained from the test solution is not more intense than the spots from the standard solution 1 (NMT 0.3%) and the total amount of all spots other than the principal spot from the test solution is NMT 1.0% compared to the principal spots from the standard solution (1) and the standard solution (2).

(ii) Weigh accurately about 16 mg of Omeprazole, dissolve in the mobile phase to make 100 mL, and use this solution as the test solution (prepare this test solution before use). Perform the test with 40 μL each of the test solution and the mobile phase as directed under the Liquid Chromatography according to the following operating conditions; the each peak area other than the major peak for the total peak areas obtained from the test solution, as the peak which does not appear in the mobile phase, is NMT 0.3% and the sum of each peak area is NMT 1.0%.

Operating conditions

For the detector, column, mobile phase and flow rate, comply with the operating conditions under the Assay.

Time span of measurement: NLT twice of the retention time of omeprazole

Loss on drying NMT 0.2% (1.0 g, in vacuum, phosphorus pentoxide, 50 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.1 g each of Omeprazole and omeprazole RS and dissolve in a mixture of sodium borate and acetonitrile (3 : 1) to make exactly 50 mL. Pipet 5 mL each of these solutions, add a mixture of 0.01 mol/L sodium borate and acetonitrile (3 : 1) to make exactly 50 mL, and use the resulting solutions as the test solution and the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of omeprazole in each solution.

$$\text{Amount (mg) of omeprazole } (C_{17}H_{19}N_3O_3S) = \text{Amount (mg) of omeprazole RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of phosphate buffer solution and acetonitrile (3 : 1).

Flow rate: 0.8 mL/min

System suitability

System repeatability: Repeat the test 6 times with a solution prepared by dissolving 10 mL of the standard solution in 0.01 mol/L sodium borate and acetonitrile (3 : 1) to make 20 mL; the relative standard deviation of the peak area of omeprazole is NMT 1.0%.

Phosphate buffer solution—Dissolve 0.725 g of sodium dihydrogen phosphate dihydrate and 4.472 g of anhydrous sodium dihydrogen phosphate in 300 mL of water to make 1000 mL. Take 250 mL of this solution and add water to make 1000 mL.

Packaging and storage Preserve in light-resistant, tight containers in a cold place.

Omeprazole Tablets
오메프라졸 정

Omeprazole Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of omeprazole ($C_{17}H_{19}N_3O_3S$: 345.42).

Method of preparation Prepare as directed under Tablets, with Omeprazole.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Dissolution Take 1 tablet of Omeprazole Tablets and perform the test at 100 revolutions per minute according to Method 2 under the Dissolution, using 500 mL of solution 1 from the Disintegration as the dissolution medium. After 2 hours, filter solution 1 from the Disintegration through a filter paper, discard the filtrate, and wash the residue on the filtrate paper with water. Dissolve this residue in 60 mL of 0.01 mol/L sodium borate solution using ultrasonic extraction for 5 minutes, add 20 mL of ethanol and 0.01 mol/L sodium borate solution to make 100 mL, and filter. Take 5.0 mL of the filtrate, add 20 mL of ethanol and 0.01 mol/L sodium borate solution to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of omeprazole RS, dissolve in 10 mL of ethanol, and add 0.01 mol/L sodium borate solution to make 100 mL. Take 5.0 mL of this solution, add 10 mL of ethanol and 0.01 mol/L sodium borate solution to make 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Assay. After 2 hours, the remaining amount of omeprazole in solution 1 from the Disintegration is NLT 85% of the labeled amount.

Dissolution Take 1 tablet of Omeprazole Tablets and perform the test at 100 revolutions per minute according to Method 2, using 500 mL of solution 1 from the Disintegration as the dissolution medium. 2 hours after starting the dissolution test, add 400 mL of 0.235 mol/L dibasic sodium phosphate, perform the dissolution test for 30 minutes, take 20 mL of the dissolved solution, and filter. Take 5.0 of the filtrate, add 1.0 mL of 0.25 mol/L sodium hydroxide solution, and use this solution as the test solution. Separately, weigh accurately about 20 mg of omeprazole RS, dissolve in 10 mL of ethanol, and add buffer solution, pH 6.8, to make 100 mL. Take 5.0 mL of this solution, and add buffer solution, pH 6.8, to make 50 mL. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the conditions of the Assay, and determine the peak areas, A_T and A_S, of omeprazole in each solution. The acceptable dissolution criterion is NLT 80% of Omeprazole Tablets dissolved in 30 minutes.

Dissolution rate (%) of the labeled amount of omeprazole ($C_{17}H_{19}N_3O_3S$)

$$= \text{Amount (mg) of omeprazole RS} \times \frac{A_T}{A_S} \times \frac{900}{5} \times \frac{1}{C} \times 100$$

C: Labeled amount (mg) of omeprazole ($C_{17}H_{19}N_3O_3S$) in 1 tablet

pH 6.8 buffer solution—Mix with 100 mL of solution 1 from the Disintegration and 80 mL of 0.235 mol/L dibasic sodium phosphate.

Related substances Weigh accurately the mass of NLT 20 tablets of Omeprazole Tablets, and powder. Weigh accurately an amount of this powder, equivalent to about 20 mg of omeprazole ($C_{17}H_{19}N_3O_3S$), add 60 mL of the mobile phase, shake to mix while protected from light, and add the mobile phase to make 100 mL. Filter this solution, and use the filtrate as the test solution. Take 1.0 mL of the test solution, add the mobile phase to make 200 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas of each solution by the automatic integration method, and calculate the amount of related substances; all peaks other than the major peak from the test solution are not greater than the peak area of the major peak from the standard solution (NMT 0.5%), and the total area of peaks other than the major peak from the test solution is not greater than 4 times the peak area of the major peak from the standard solution (NMT 2%).

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 280 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with porous silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of dichloromethane and ammonia methanol solution (975 : 25).

Flow rate: 1.0 mL/min

Time span of measurement: About 2 times the retention time of omeprazole after the solvent peak.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Omeprazole Tablets, and powder. Weigh accurately an amount of this powder, equivalent to about 20 mg of omeprazole ($C_{17}H_{19}N_3O_3S$), dissolve in 60 mL of 0.01 mol/L sodium borate solution using ultrasonic extraction for 5 minutes, add 20 mL of ethanol and 0.01 mol/L sodium borate solution to make 100 mL, mix, and filter. Take 5.0 mL of the filtrate, add 10 mL of ethanol and 0.01 mol/L sodium borate solution to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of omeprazole RS, add 20 mL of ethanol and 0.01 mol/L sodium borate solution to make 100 mL, take 5.0 mL of this solution, add 10 mL of ethanol and 0.01 mol/L sodium borate solution to make 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of omeprazole in each solution.

$$\text{Amount (mg) of omeprazole } (C_{17}H_{19}N_3O_3S) = \text{Amount (mg) of omeprazole RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 280 nm).

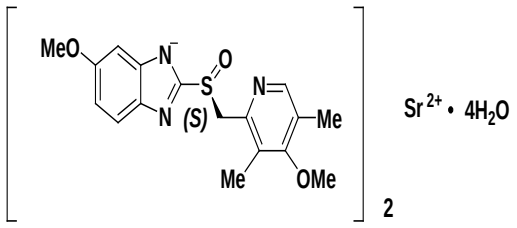
Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 20 μm in particle diameter).

Mobile phase: A mixture of pH 7.6 phosphate buffer solution and acetonitrile (66 : 34).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Esomeprazole Strontium Tetrahydrate
에스오메프라졸스트론튬수화물



$(C_{34}H_{36}N_6O_6S)2Sr{\cdot}4H_2O$: 848.50

Bis(5-Methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethylpyridine-2-yl)methyl]sulfinyl]-1*H*-benzimidazol-1-yl) strontium salt tetrahydrate [*934714-36-0*]

Esomeprazole Strontium Tetrahydrate contains NLT 98.0% and NMT 102.0% of esomeprazole strontium [$(C_{17}H_{18}N_3O_3S)2{\cdot}Sr$: 776.44] calculated on the dries basis.

Description Esomeprazole Strontium Tetrahydrate occurs as a white to almost white crystalline powder.
It is soluble in water.

Identification (1) Determine the infrared spectra of Esomeprazole Strontium Tetrahydrate and esomeprazole strontium tetrahydrate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The major peaks of the test solution and standard solution obtained under the Assay are the same in the retention time.

(3) Dissolve about 50 mg of 20% acetonitrile solution in Esomeprazole Strontium Tetrahydrate, and perform the test according to the Flame Coloration (1); it exhibits a red color (strontium).

Purity (1) ***Clarity and color of solution***—Dissolve 0.2 g of Esomeprazole Strontium Tetrahydrate in acetone to make 10 mL. Determine the absorbance of this solution at 440 nm and 650 nm as directed under the Ultraviolet-visible Spectroscopy; it is NMT 0.2.

(2) ***Isomer***—Weigh 50 mg of Esomeprazole Strontium Tetrahydrate, dissolve it in diluent to make 100 mL, and use this solution as the test solution. Perform the test with 5 μL of the test solution according to the following condition as directed under the percentage peak area method under the Liquid Chromatography; the amount of *R*-isomer is NMT 0.1%.

$$\text{Content (\%) of } R\text{-isomer} = A_i / A_S \times 100$$

A_i: Peak area of *R*-isomer in the test solution

A_S: Total areas of esomeprazole and *R*-isomer in the test solution

Diluent—A mixture of phosphate buffer solution (pH 7.6) and acetonitrile (3 : 1).

Phosphate buffer solution, pH 7.6—Dissolve 1.12 g of anhydrous sodium hydrogen phosphate and 0.18 g of anhydrous sodium dihydrogen phosphate in 1000 mL of water. Adjust the pH to 7.6 with phosphoric acid.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 15 cm in length, packed with α1-acid glycoprotein-coated silica gel for liquid chromatography of 5 μm.

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: Weigh 1.42 g of dibasic sodium phosphate, dissolve in 900 mL of water, adjust the pH to 6.5 with 85% phosphoric acid, and add water to make 1000 mL.

Mobile phase B: Acetonitrile

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 20	90	10
20 - 25	90 → 70	10 → 30
25 - 30	70	30
30 - 35	70 → 90	30 → 10
35 - 40	90	10

Flow rate: 0.8 mL/min

Time span of measurement: About 4 times the retention time of esomeprazole.

System suitability

System performance: Weigh accurately about 5 mg of omeprazole RS, dissolve in 25 mL of diluent and add diluent to make 50 mL. Pipet 5 mL of this solution and add diluent to make 100 mL as the system suitability solution. Proceed with 5 μL of the system suitability solution under the above operating conditions; *R*-isomer and esomeprazole are eluted in this order with the resolution being NLT 5.

System repeatability: Repeat the test 6 times with 5 μL of the system suitability solution under the above conditions; the relative standard deviation of the peak area of *R*-isomer and esomeprazole is NMT 10.0%, respectively.

(3) ***Related substances***—Weigh accurately 50 mg of Esomeprazole Strontium Tetrahydrate, dissolve in the mobile phase A to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of omeprazole, about 10 mg of related substance A RS, and about 5 mg of related substance B RS, and add the mobile phase A to make exactly 200 mL. Pipet 1 mL of this solution, add the mobile phase A to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of both solutions by the automatic integration method; the amount of related substance A with the relative retention time about 0.7 is NMT 0.1%, the amount of related substance B with the relative retention time about 3.9 is NMT 0.05%, and the amount of other individual related substances is NMT 0.10%, and the total amount of related substances is NMT 0.3%.

$$\text{Content (\%) of each related substance} = C_S / C_T \times A_i / A_S \times 100$$

C_S: Concentration (mg/mL) of each related substance in the standard solution

C_T: Concentration (mg/mL) of each related substance in the test solution

A_i: Peak area of each related substance obtained from the test solution

A_S: Peak area of each related substance obtained from the standard solution

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

System performance: Dissolve 10 mg of related substance A RS in the mobile phase A to make 200 mL. Use this solution as the related substances A standard stock solution. Separately, add 1 mL of related substance A standard stock solution to 50 mg of omeprazole RS and dissolve it in the mobile phase A to make 100 mL. Use this solution as the system suitability solution. Proceed with 5 μL of the system suitability solution according to the above conditions; the resolution between omeprazole and related substance A is NLT 2.0.

System repeatability: Repeat the test 6 times with 5 μL of the system suitability solution under the above operating conditions; the relative standard deviation of the peak area of omeprazole and related substance A is NMT 10.0%, respectively.

Loss on drying Between 7.5% and 9.5% (1.0 g, 125 °C, constant mass).

Strontium Weigh accurately about 400 mg of Esomeprazole Strontium Tetrahydrate, dissolve in 30 mL of methanol, and add 40 mL of ammonia-ammonium chloride buffer solution. To this solution, add 0.5 mL of phosphate buffer solution (pH 7.0) and 1 mL of diluent, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction (10.8 to 11.8% calculated on the dried basis).

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS = 4.381mg of Sr

Ammonia-ammonium chloride buffer solution—Dissolve 54 g of ammonium chloride with water, add 350 mL of ammonia water(28), and dilute with water to make 1000 mL.

Diluent—Mix the same amount of ethylenediaminetetraacetic acid disodium salt solution (37.2 mg/mL) and copper sulfate solution (24.9 mg/mL).

Assay Weigh accurately about 50 mg of Esomeprazole Strontium Tetrahydrate, add the mobile phase A to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of omeprazole RS, dissolve in the mobile phase A, and make exactly 100 mL. Use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of esomeprazole from each solution, AT and AS, respectively.

$$\text{Content (\%) of esomeprazole strontium } [(C_{17}H_{18}N_3O_3S)_2 \cdot Sr] = A_T / A_S \times 776.44 / (345.42 \times 2) \times 100$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: Stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octylsilanized porous silica gel for liquid chromatography of 5 μm.

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows:

Mobile phase A: A mixture of phosphate buffer solution (pH 7.6) and acetonitrile (3 : 1).

Mobile phase B: A mixture of phosphate buffer solution (pH 7.6) and acetonitrile (3 : 2).

For dispensing of phosphate buffer solution, pH 7.6, follow Purity (2).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 15	100	0
15 - 25	100 → 0	0 → 100
25 - 50	0	100
50 - 60	0 → 100	100 → 0
60 - 65	100	0

Flow rate: 1.0 mL/min

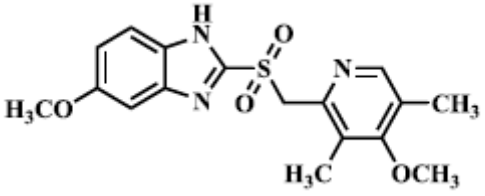
System suitability

System performance: Weigh accurately about 10 mg of related substance A RS and add the mobile phase A to make exactly 200 mL. Use this solution as the related substance A standard stock solution. Separately, weigh accurately about 50 mg of omeprazole RS, take exactly 1 mL of related substance A standard stock solution, and add the mobile phase A to make 100 mL. Use this solution as the system suitability solution. Proceed with 5 μL of the system suitability solution according to the above operating conditions; the resolution of esomeprazole and related substance A is NLT 2.0, respectively, and the symmetry coefficient of the esomeprazole peak is NMT 1.5.

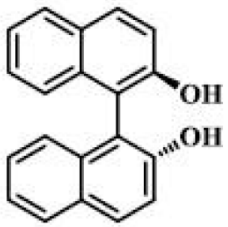
System repeatability: Repeat the test 5 times with each 5 μL of the system suitability solution; the relative standard deviation of the peak area of esomeprazole is NMT 0.73%.

Packaging and storage Preserve in light-resistant, tight containers.

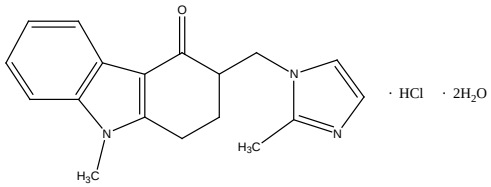
Note ***Related substance A***—Omeprazole sulfone., 5-Methoxy-2-[[(4-methoxy-3.5-dimethylpyridine-2-yl)methyl]sulfonyl]-1*H*-benzimidazole



Related substance B— (*S*)-Binol., (*S*)-(-) 1,1'-Bi(2-naphthol)



Ondansetron Hydrochloride Hydrate
온단세트론염산염수화물



Ondansetron Hydrochloride

$C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$: 365.85

9-Methyl-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-2,3,4,9-tetrahydro-1*H*-carbazol-4-one dihydrate hydrochloride

Ondansetron Hydrochloride Hydrate contains NLT 98.0% and NMT 102.0% of ondansetron hydrochloride ($C_{18}H_{19}N_3O \cdot HCl$: 329.824), calculated on the anhydrous basis.

Description Ondansetron Hydrochloride Hydrate occurs as a white powder.
It is soluble in methanol, sparingly soluble in ethanol(95), slightly soluble in 2-propanone or dichloromethane, and very slightly soluble in acetone, chloroform or ethyl acetate.

Identification (1) Determine the infrared spectra of Ondansetron Hydrochloride Hydrate and ondansetron hydrochloride hydrate RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

(2) Dissolve 20 mg of Ondansetron Hydrochloride Hydrate in 2 mL of water, add 2 mol/L nitric acid and filter; the filtrate responds to the Qualitative Analysis (2) for chloride.

Purity (1) ***Related substance I***—Weigh accurately about 50 mg of Ondansetron Hydrochloride Hydrate, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately weigh exactly 4.0 mg of ondansetron related substance I (1,2,3,9-tetrahydro-9-methyl-3-methylene-4*H*-carbazol-4-on) RS and dissolve in the mobile phase to make 100 mL. To 1.0 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area, A_T and A_S, of related substance I from each solution.

$$\text{Content (\%) of related substance I} = 10 \times \frac{C}{W} \times \frac{A_T}{A_S}$$

C: Concentration (μg/mL) of related substance I in the standard solution

W: Weight (mg) of sample taken

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 328 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 20 cm in length, packed with nitrilated silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of phosphate buffer solution and acetonitrile (80 : 20).

Flow rate: 1.5 mL/min

System suitability

System performance: Dissolve 6 mg of ondansetron related substance I RS and 10 mg of ondansetron related substance II (1,2,3,9-tetrahydro-9-methyl-4*H*-carbazol-4-on) RS in the mobile phase to make 100 mL. Pipet 1.0 mL of this solution and add the mobile phase to make 100 mL. Proceed with 20 μL of this solution according to the above conditions; the relative retention times of the related substance I peak and the related substance II peak are about 1 and 0.8, respectively, and the resolution between these two peaks is NLT 1.5. Proceed with 20 μL of the standard solution according to the above operating conditions; the number of theoretical plates is NLT 400.

System repeatability: Repeat the test 5 times with 20 μL of the standard solution according to the above conditions; the relative standard deviation of the peak areas of ondansetron is NMT 2.0%.

Phosphate buffer solution—Add 1 mol/L sodium hydroxide TS to 0.02 mol/L potassium dihydrogen phosphate buffer solution to adjust pH to 5.4.

(2) ***Other related substances***—(i) Weigh accurately 125 mg of Ondansetron Hydrochloride Hydrate, dissolve in methanol to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately 25 mg of ondansetron hydrochloride hydrate RS and dissolve in methanol to make exactly 100 mL. Dilute this solution quantitatively with methanol to prepare the solutions according to the following table, and use these solutions as the standard solutions.

Standard solution	Dilution factor	Concentration (μg/mL)	Percent (%) compared to sample
1	1 in 5	50	0.4
2	1 in 10	25	0.2
3	1 in 20	12.5	0.1

Separately, dissolve 1.0 mg of ondansetron related substance III {3[(dimethylamino)methyl]-1,2,3,9-tetrahydro-9-methyl-4*H*-carbazole-4-on} RS in methanol to make exactly 10 mL, and use this solution as the resolution test solution. Further, dissolve 1.0 mg of ondansetron related substance IV {6,6'-methylene bis[(1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1*H*-

imidazole-1-yl)-methyl]-4*H*-carbazole-4-on} RS in methanol to make exactly 10 mL, and use this solution as the identification solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solutions and 10 μL of the identification solution onto the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Further, to test system suitability, spot 20 μL of the test solution on the same plate, then drop 10 μL of each of the resolution test solution and identification solution, overlapping the droplets. Develop the plate with a mixture of chloroform, ethyl acetate, methanol and ammonia water(28) (90 : 50 : 40 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine under ultraviolet rays (principal wavelength 254 nm) and compare the spots other than the principal spot from the test solution to the principal spot from the standard solution; the three sports for the system suitability test are completely separated, the spots other than the principal spot from the test solution having the same R_f value as the principal spot from the identification solution are not larger or more intense than the principal spot from standard solution 1 (0.4%), the spots other than the principal spot from the test solution are not larger or more intense than the principal spot from standard solution 2 (0.2%), and the total intensity of the spots other than the principal spot from the test solution is NMT 1.0%.

(ii) The test solution, the standard solution, the mobile phase and operating conditions: proceed as directed under the Assay. Perform the test with 10 μL of the test solution according to the percentage peak area method under the Liquid Chromatography according to the following conditions, and measure the peak areas of the related substances; the amount of each related substance is NMT 0.2% and the amount of total related substances is NMT 0.5%.

$$\text{Content (\%) of each related substance} = 100 \times \frac{A_i}{A_S}$$

A_i: Peak area of each related substance
A_S: Total area of related substance peaks

Water Between 9.0 and 10.5% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 45 mg of Ondansetron Hydrochloride Hydrate, dissolve in the mobile phase to make exactly 50 mL. To 5.0 mL of this solution, add the mobile phase to make exactly 50 mL and use this solution as the test solution. Separately weigh accurately about 9.0 mg of ondansetron hydrochloride hydrate RS (measure water content previously), dissolve in the mobile phase to make exactly 100 mL, use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of ondansetrone from each solution.

$$\text{Amount (mg) of ondansetron hydrochloride} = 500 \times C \times \frac{A_T}{A_S}$$

C: Concentration (mg/mL) of ondansetron hydrochloride in the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 216 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 20 cm in length, packed with nitrilated silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of phosphate buffer solution and acetonitrile (50 : 50).

Flow rate: 1.5 mL/min

System suitability

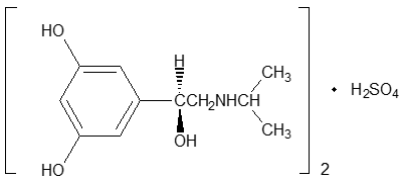
System performance: Dissolve 9 mg of ondansetron hydrochloride RS and 5 mg of ondansetron related substance III RS in the mobile phase to make exactly 100 mL. Proceed with 10 μL of this solution according to the above conditions; the relative retention times of the ondansetron peak and related substances III peak are 1.0 and 1.1, respectively, and the resolution between the two peaks is NLT 1.5. Proceed with 10 μL of the standard solution according to the above operating conditions; the symmetry factor for the ondansetron peak is NMT 2.0.

System repeatability: Repeat the test 5 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak areas of ondansetron is NMT 1.5%.

Phosphate buffer solution—Add 1 mol/L sodium hydroxide TS to 0.02 mol/L potassium dihydrogen phosphate buffer solution to adjust pH to 5.4.

Packaging and storage Preserve in light-resistant, tight containers.

Orciprenaline Sulfate
오르시프레날린황산염



and enantiomer

$(C_{11}H_{17}NO_3)_2 \cdot H_2SO_4$: 520.59

bis{5-[1-Hydroxy-2-(propan-2-ylamino)ethyl] benzene-1,3-diol} sulfate [*5874-97-5*]

Orciprenaline Sulfate contains NLT 98.5% and NMT 101.0% of orciprenaline sulfate $[(C_{11}H_{17}NO_3)_2 \cdot H_2SO_4]$, calculated on the dried basis.

Description Orciprenaline Sulfate occurs as white crystals or a crystalline powder.
It is freely soluble in water, slightly soluble in acetic acid(100), and practically insoluble in ether.
An aqueous solution of Orciprenaline Sulfate (1 in 20) shows no optical rotation.

Melting point—About 220 °C (with decomposition).

Identification (1) Determine the absorption spectra of the solutions of Orciprenaline Sulfate and orciprenaline sulfate RS in 0.01 mol/L hydrochloric acid TS (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Orciprenaline Sulfate and orciprenaline sulfate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Orciprenaline Sulfate (1 in 100) responds to the Qualitative Analysis for sulfate.

pH Dissolve 1.0 g of Orciprenaline Sulfate in 10 mL of water; the pH of this solution is between 4.0 and 5.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Orciprenaline Sulfate in 10 mL of water; the solution is clear and its color is not more intense than that of the following control solution.

Control solution—To 3 mL of matching fluids T for color, add 1 mL of diluted hydrochloric acid (1 in 40).

(2) ***Orciprenaline sulfate***—Weigh 0.200 g of Orciprenaline Sulfate, dissolve in 0.01 mol/L hydrochloric acid TS to make exactly 20 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at a wavelength of 328 nm is NMT 0.075.

(3) ***Heavy metals***—Proceed with 2.0 g of Orciprenaline Sulfate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Iron***—Dissolve 2.0 g of Orciprenaline Sulfate in 45 mL of water, add 2 mL of hydrochloric acid, and use this solution as the test solution. Add water to 1.0 mL of iron standard solution to make 45 mL, add 2 mL of hydrochloric acid, and use this solution as the standard solution. Add 50 mg of ammonium peroxydisulfate and 3 mL of 30% ammonium thiocyanate to the test solution and the standard solution, and mix; the color of the test solution is not more intense than that of the standard solution. (NMT 5 ppm).

(5) ***Related substances***—Dissolve 0.2 g of Orciprenaline Sulfate in a mixture of water and methanol (1 : 5) to make 10 mL, and use this solution as the test solution. Pipet 1 mL of the test solution, add a mixture of water and methanol (1 : 5) to make 100 mL, and use this solution as the standard solution (1). Pipet 5 mL of the standard solution (1), add a mixture of water and methanol (1 : 5) to make 10 mL, and use this solution as the standard solution (2). Pipet 5 mL of the standard solution (1), add a mixture of water and methanol (1 : 5) to make 20 mL, and use this solution as the standard solution (3). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution, the standard solution (1), the standard solution (2) and the standard solution (3) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, 2-propanol, water and ammonia water(28) (50 : 30 : 16 : 4) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Expose the plate to iodine vapor; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution (1) (NMT 1.0%) and the number of the spots more intense than the spots from the standard solution (2) is NMT 1 (NMT 0.5%). However, if the spots obtained from the standard solution (3) is not clearly visible, the test is not valid.

Loss on drying NMT 1.5% (1 g, in vacuum, 105 °C, 4 hours).

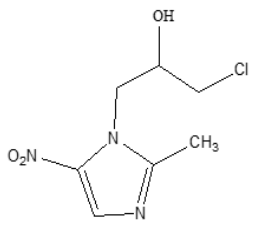
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.7 g of Orciprenaline Sulfate, add 100 mL of acetic acid(100), warm on a steam bath, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 52.06 mg of $(C_{11}H_{17}NO_3)_2 \cdot H_2SO_4$

Packaging and storage Preserve in light-resistant, tight containers.

Ornidazole
오르니다졸



$C_7H_{10}ClN_3O_3$: 219.63
α-(Chloromethyl)-2-methyl-5-nitro-1*H*-imidazole-1-ethanol, [*16773-42-5*]

Ornidazole, when dried, contains NLT 98.5% and

NMT 101.0% of ornidazole ($C_7H_{10}ClN_3O_3$).

Description Ornidazole occurs as a white to pale yellow crystalline powder.

Identification (1) Weigh about 20 mg of Ornidazole and ornidazole RS, dissolve them in 10 mL of methanol, and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Next, develop the plate with a mixture of ethyl acetate and methanol (9 : 1), and air-dry the plate. Expose the plate to ultraviolet irradiation or chlorine vapor, spray o-Tolidine TS evenly on the plate; the R_f value and color (yellow spots with blue band) of spots obtained from the test solution and the standard solution are the same.

Chlorine vapor—Prepare with 2% potassium permanganate and hydrochloric acid.

(2) Weigh accurately about 0.18 g of Ornidazole and add ethanol(95) to make 200 mL. Take 10 mL of this solution, add ethanol(95) to make 100 mL, and take again 10 mL of this solution, add ethanol(95) to make 100 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy, using ethanol(95) as the control solution; it exhibits a maximum between 308 nm and 312 nm.

(3) Determine the infrared spectra of Ornidazole and ornidazole RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

pH Between 4.5 and 7.5 (1% aqueous solution).

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g of Ornidazole in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Ornidazole according to Method 2 under the Heavy Metals, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Loss on drying NMT 0.5% (1 g, in vacuum, 60 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Ornidazole, previously dried, dissolve in 50 mL of acetic acid(100) for non-aqueous titration, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS

= 21.96 mg of $C_7H_{10}ClN_3O_3$

Packaging and storage Preserve in well-closed containers.

Ornidazole Injection
오르니다졸 주사액

Ornidazole Injection is an oily injection and contains NLT 95.0% and NMT 105.0% of the labeled amount of ornidazole ($C_7H_{10}ClN_3O_3$: 219.63).

Method of preparation Prepare as directed under Injections, with Ornidazole.

Description Ornidazole Injection occurs as a clear, greenish pale yellow liquid.

Identification Weigh an amount of Ornidazole Injection equivalent to 0.1 g of ornidazole according to the labeled amount, add 50 mL of methanol, shake to mix, centrifuge, and use the clear supernatant as the test solution. Separately, dissolve 20 mg of ornidazole RS in 10 mL of methanol and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate and methanol (9 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots from the test solution and the standard solution are the same in R_f value.

pH The pH of an aqueous solution of Ornidazole Injection (1 in 2) is between 4.3 and 6.3.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets requirements.

Extractable volume of injections Meets the requirements.

Pyrogen It meets the requirements when tested by injecting 0.5 mL per kg body weight of a rabbit.

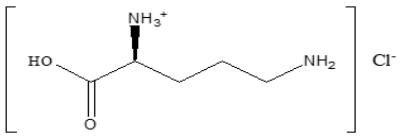
Assay Pipet an amount of Ornidazole Injection equivalent to 50 mg of ornidazole ($C_7H_{10}ClN_3O_3$), and add ethanol(95) to make exactly 100 mL. Pipet 2 mL of this solution and add ethanol(95) to make exactly 100 mL. Pipet 5 mL of this resulting solution, add ethanol(95) to make

exactly 100 mL, and use this solution as the standard solution. Separately, weigh accurately about 50 mg of ornidazole RS, proceed in the same manner as the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 312 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of ornidazole ($C_7H_{10}ClN_3O_3$)
= Amount (mg) of ornidazole RS × (A_T / A_S)

Packaging and storage Preserve in hermetic containers.

L-Ornithine Hydrochloride
L-오르니틴염산염



$C_5H_{12}N_2O_2 \cdot HCl$: 168.62
L-Ornithine hydrochloride, [*3184-13-2*]

L-Ornithine Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of L-ornithine hydrochloride ($C_5H_{12}N_2O_2 \cdot HCl$).

Description L-Ornithine Hydrochloride occurs as white crystals or a crystalline powder, and is odorless.

Identification (1) Dissolve 10 mg of L-Ornithine Hydrochloride in 100 mL of water. To 1 mL of this solution, add 1 mL of acetic acid(31) and 1 mL of ninhydrin TS, heat on a steam bath for 30 minutes; the resulting solution exhibits a bluish purple color.

(2) Dissolve 20 mg of L-Ornithine Hydrochloride in 10 mL of water. To 1 mL of this solution, add 1 mL of 1% sodium pentacyanonitrosylferrate(III) TS and 10% acetaldehyde solution; the resulting solution does not exhibit a blue color.

(3) Coat a small amount of L-Ornithine Hydrochloride on a copper net, and ignite in a colorless flame; it exhibits a green color.

Optical rotation $[\alpha]_D^{20}$: Between + 23.0° and + 25.0° (after drying, 4 g, 6 mol/L hydrochloric acid TS, 100 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Weight 0.5 g of L-Ornithine Hydrochloride, dissolve in 10 mL of water. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy using water as the control solution, and determine the transmission rate at a wavelength of 430 nm; the transmission rate NLT 98.0%.

(2) ***Sulfate***—Proceed with 1.0 g of L-Ornithine Hydrochloride according to the Sulfate and perform the test. Prepare the control solution with 0.4 mL of 0.005 mol/L sulfuric acid (NMT 0.019%).

(3) ***Ammonium***—Proceed with 1.0 g of L-Ornithine Hydrochloride according to the Ammonium and perform the test. Prepare the control solution with 2.0 mL of ammonium standard solution (NMT 0.002%).

(4) ***Heavy metals***—Proceed with 1.0 g of L-Ornithine Hydrochloride according to Method 3 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Iron***—Put 1.50 g of L-Ornithine Hydrochloride into a 100-mL Nessler tube, add 10 mL of dilute hydrochloric acid (1 in 5), and use this solution as the test solution. Pipet 1.5 mL of iron standard solution, transfer into a 100-mL Nessler tube, add 10 mL of dilute hydrochloric acid (1 in 5), and use this solution as the standard solution. Add 3 mL of 20% hydroxylamine hydrochloride solution to the test solution and the standard solution, warm on a steam bath for 10 minutes, cool, add 5 mL of 0.3% *o*-phenanthroline TS, shake to mix, and add water to make about 70 mL. Add 20 mL of 20% sodium acetate solution and water to make 100 mL, shake to mix, and observe from above or side of the Nessler tube against a white background. The color of the test solution is not more intense than that of the condition solution (NMT 10 ppm).

(6) ***Arsenic***—Proceed with 1.0 g of L-Ornithine Hydrochloride according to Method 3 and perform the test. Prepare the control solution with 1.0 mL of arsenic standard solution (NMT 1 ppm).

(7) ***Other amino acids***—Dissolve 0.2 g of L-Ornithine Hydrochloride in a small amount of ammonia TS (1 in 2), add water to make 100 mL, and use this solution as the test solution. Perform the test with 5 µL of the test solution as directed under the Thin Layer Chromatography. Spot each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of 1-propanol and ammonia water (2 : 1) to a distance of about 10 cm, and air-dry the plate. Spray ninhydrin TS evenly on the plate, air-dry, heat at 80 ℃ for 10 minutes; any spot other than the principal spot does not appear.

Loss on drying NMT 0.2% (2 g, 105 ℃, 3 hours).

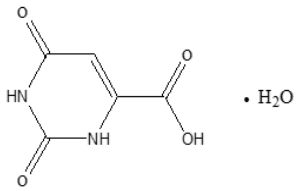
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 90 mg of L-Ornithine Hydrochloride, previously dried, dissolve in 3 mL of formic acid and 50 mL of acetic acid(100) for non-aqueous titration, add 3 mL of mercury(II) acetate TS for non-aqueous titration, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 8.431 mg of $C_5H_{12}N_2O_2 \cdot HCl$

Packaging and storage Preserve in tight containers.

Orotic Acid Hydrate
오로트산수화물



$C_5H_4N_2O_4 \cdot H_2O$: 174.11

1,2,3,6-Tetrahydro-2,6-dioxo-4-pyrimidinecarboxylic acid hydrate, [*65-86-1*, anhydrous]

Orotic Acid Hydrate contains NLT 98.0% and NMT 101.0% of orotic acid ($C_5H_4N_2O_4$: 156.10), calculated on the anhydrous basis.

Description Orotic Acid Hydrate occurs as a colorless or white crystal, or a crystalline powder, which is odorless. It is sparingly soluble in dimethylformamide, very slightly soluble in water, and practically insoluble in ethanol(95), ether and chloroform.
It dissolves in sodium hydroxide TS. The pH of a saturated solution of Orotic Acid Hydrate is between 2.0 and 3.0.

Identification (1) Add 1 drop of iron(III) chloride TS to 5 mL of a saturated solution of Orotic Acid Hydrate; the solution exhibits a deep red color.

(2) To 0.1 g of Orotic Acid Hydrate, add 20 mL of 0.01 mol/L hydrochloric acid TS, shake vigorously to mix, and filter it. To 10 mL of the filtrate, add 5 drops of bromine TS, shake to mix for 10 seconds, and add a very small amount of sodium thiosulfate to decolorize. Warm at 56 ℃ on a steam bath for 3 minutes; the solution exhibits an orange color.

(3) Determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy with a solution of Orotic Acid Hydrate in 0.01 mol/L sodium hydroxide (1 in 100000); it exhibits a maximum between 283 and 287 nm.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Orotic Acid Hydrate in 5 mL of water and 10 mL of sodium hydroxide TS; the resulting solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Orotic Acid Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Weigh 1.0 g of Orotic Acid Hydrate and perform the test according to Method 3 under the Arsenic (NMT 2 ppm).

Water Between 4.3% and 11.5% (0.2 g, volumetric titration, direct titration).

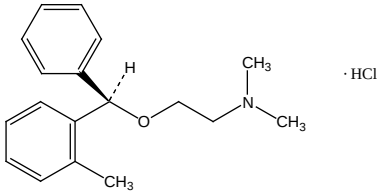
Residue on ignition NMT 0.10% (1 g).

Assay Weigh accurately about 0.35 g of Orotic Acid Hydrate, and dissolve in 8 mL of 0.5 mol/L sodium hydroxide. To this solution, add 30 mL of water, and titrate the excess sodium hydroxide with 0.1 mol/L hydrochloric acid VS (indicator: 3 drops of phenolphthalein TS). Perform a blank test in the same manner.

Each mL of 0.5 mol/L sodium hydroxide VS
= 78.05 mg of C5H4N2O4

Packaging and storage Preserve in tight containers.

Orphenadrine Hydrochloride
오르페나드린염산염



and enantiomer

$C_{18}H_{23}NO \cdot HCl$: 305.84

N,*N*-Dimethyl-2-[(2-methylphenyl)(phenyl) methoxy]ethanamine hydrochloride [*341-69-5*]
Orphenadrine Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of orphenadrine hydrochloride ($C_{18}H_{23}NO \cdot HCl$).

Description Orphenadrine Hydrochloride occurs as a white crystalline powder.
It is freely soluble in water or ethanol(95).

Identification (1) Determine the infrared spectra of Orphenadrine Hydrochloride and orphenadrine hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Orphenadrine Hydrochloride (1 in 50) responds to the Qualitative Analysis (2) for chloride.

Melting point About 160 °C.

Purity (1) ***Clarity and color of solution***—Weight 0.7 g of Orphenadrine Hydrochloride, dissolve in ethanol(95) to make exactly 10 mL; the solution is clear and the absorbance measured at the wavelength of 436 nm as directed under the Ultraviolet-visible Spectroscopy is NMT 0.050.

(2) ***Heavy metals***—Proceed with 2.0 g of Orphenadrine Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead

standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 0.300 g of Orphenadrine Hydrochloride in water to make 50 mL, add 2 mL of ammonia water(28) to this solution, and extract 3 times with each of 10 mL of toluene. Combine the extracts, add anhydrous sodium sulfate, shake, filter, and concentrate the filtrate under reduced pressure at a temperature NMT 50 °C. Dissolve the residue in toluene to make exactly 20 mL, and use the resulting solution as the test solution. Dissolve 20 mg of orphenadrine hydrochloride RS and 20 mg of orphenadrine related substance I {(*RS*)-*N*,*N*-dimethyl-2-[(3-methylphenyl)phenylmethoxy]ethanamine} RS in 20 mL of water, add 1 mL of ammonia water(28), and extract 3 times with each of 5 mL of toluene. Combine the extracts, add anhydrous sodium sulfate, shake, filter, and concentrate the filtrate under reduced pressure at a temperature NMT 50 °C. Dissolve the residue in toluene to make exactly 20 mL, and use the resulting solution as the standard solution. Perform the test with 2 μL of the test solution as directed under the Gas Chromatography according to the following conditions, and measure each peak area; the amount of each related substance other than the major peak is NMT 0.3% and the total amount of related substances is NMT 1.0%. However, exclude any related substances whose amount is NMT 0.02%.

$$\text{Content (\%) of related substances} = 100 \times \frac{A_i}{A_S}$$

A_i: Peak area of each related substance

A_S: Sum of each peak area obtained from the test solution

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A glass column about 0.32 mm in internal diameter and 60 m in length, coated the inside with poly(dimethyl)(diphenyl)siloxane in a thickness of 1 μm.

Split ratio: About 1 : 25.

Column temperature: 240 °C

Sample injection port temperature: 290 °C

Detector temperature: 290 °C

Carrier gas: Helium

Flow rate: 1 mL/min

System suitability

System performance: Proceed with 2 μL of the standard solution according to the above conditions; the resolution between the peaks of the related substance I and orphenadrine is NLT 1.5.

Time span of measurement: About 1.3 times the retention time of orphenadrine.

Loss on drying NMT 0.5% (1 g, 105 °C, 3 hours).

Residue on ignition NMT 0.1% (1 g).

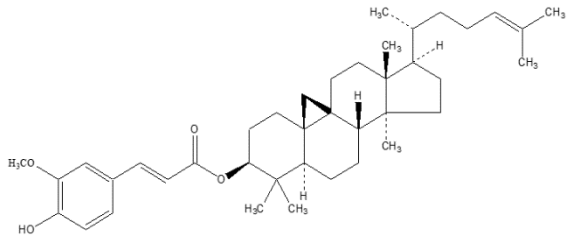
Sterility Meets the requirements. However, this test is applied when Orphenadrine Hydrochloride is used in the manufacture of sterile preparations without undergoing a sterilization process.

Assay Weigh accurately about 0.25 g of Orphenadrine Hydrochloride, previously dried, dissolve in 50 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 30.59 mg of $C_{18}H_{23}NO \cdot HCl$

Packaging and storage Preserve in light-resistant, well-closed containers or light-resistant, hermetic containers.

γ-Oryzanol
γ-오리자놀



$C_{40}H_{58}O_4$: 602.89

(3β)-9,19-Cyclolanost-24-en-3-ol 3-(4-hydroxy-3-methoxyphenyl)-2-propenoate, [*11042-64-1*]

γ-Oryzanol, when dried, contains NLT 98.0% and NMT 101.0% of γ-oryzano ($C_{40}H_{58}O_4$).

Description γ-Oryzanol occurs as white to pale yellow crystals or a crystalline powder and is odorless.
It is freely soluble in acetone, chloroform or propylene glycol, sparingly soluble in ether or petroleum ether, slightly soluble in methanol and very slightly soluble in water. It is freely soluble in potassium hydroxide-ethanol TS.

Melting point—About 165 °C.

Identification (1) Dissolve 10 mg of γ-Oryzanol in 10 mL of potassium hydroxide-ethanol TS; the resulting solution exhibits a yellow color.

(2) Dissolve 0.1 g of γ-Oryzanol in 20 mL of acetone, add 30 mL of a solution of iron(III) chloride in ethanol (1 in 50); the color of the solution turns green.

(3) Weigh 0.1 g of γ-Oryzanol, dissolve in 10 mL of hexane, and use this solution as the test solution. Weigh 0.1 g of γ-oryzanol RS, dissolve in 10 mL of hexane, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a

mixture of hexane and ethyl acetate (5 : 1) and air-dry the plate. Examine the plate under ultraviolet light; the R_f values of the spots obtained from the test and solution and the standard solution are same.

(4) Determine the absorption spectra of the test solution obtained in the Assay as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima at around the wavelengths of 231 nm, 291 nm and 315 nm.

Purity (1) ***Clarity and color of solution***—Add 5 mL of freshly boiled ad cooled water to 0.5 g of γ-Oryzanol, heat in a water while shaking occasionally; the resulting solution does not exhibit a yellow color.

(2) ***Heavy metals***—Proceed with 1.0 g of γ-Oryzanol according to Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of γ-Oryzanol according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Free ferulic acid***—Dissolve 0.1 g of γ-Oryzanol in 10 mL of Hexane, and perform the test with this solution as the test solution under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Then, develop the plate with a mixture of ethyl acetate and hexane (1 : 1) to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light; any spot other than the principal spots obtained from the test solution does not appear.

Loss on drying NMT 3.0% (0.5 g, in vacuum, phosphorus pentoxide, 80 ℃, 3 hours).

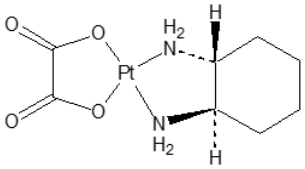
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 10 mg of γ-Oryzanol, dissolve in 60 mL of n-heptane, add n-heptane additionally to make 100 mL, pipet 10.0 mL of the resulting solution, and add n-heptane to make 100 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance of this solution, *A*, at the wavelength of 315 nm.

$$\text{Amount (mg) of γ-oryzanol } (C_{40}H_{58}O_4) = A / 359 \times 10{,}000$$

Packaging and storage Preserve in tight containers.

Oxaliplatin
옥살리플라틴



$C_8H_{14}N_2O_4Pt$: 397.29

[(1*R*,2*R*)-Cyclohexane-1,2-diamine](ethanedioato-*O*,*O'*)platinum(II) [*61825-94-3*]

Oxaliplatin contains NLT 98.0% and NMT 102.0% of oxaliplatin ($C_8H_{14}N_2O_4$), calculated on the dried basis.

Description Oxaliplatin occurs as a white crystalline powder.
It is slightly soluble in water, very slightly soluble in methanol and practically insoluble in ethanol(95).

Identification Determine the infrared spectra of Oxaliplatin and oxaliplatin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +74.5° and +74.8° (after drying, 0.250 g, water, 50 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g of Oxaliplatin in water to make 50 mL; the resulting solution is clear and colorless.

(2) ***Acidity or alkalinity***—Dissolve 0.10 g of Oxaliplatin in water to make 50 mL; when adding 0.5 mL phenolphthalein TS, the resulting solution is colorless; when adding 0.01 mol/L sodium hydroxide TS, the resulting solution exhibits pink and the amount used is NMT 0.6 mL.

(3) ***Related substances***—(i) Related substance I: Weigh accurately 0.10 g of Oxaliplatin, add water, shake vigorously to mix, sonicate for a very short time, and add water to make 50 mL. Use this solution as the test solution. Separately, weigh accurately 14.0 mg of Oxaliplatin related substance I {Oxalic acid}, dissolve in water to make exactly 250 mL, and use this solution as the standard stock solution. Add water to 5.0 mL of the standard stock solution to make exactly 200 mL; use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions; the peak area of related substance I from the test solution is not greater than 3 times the major peak area of the standard solution (0.15%). Inject the test solution within 20 minutes after preparing the test solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with base-deactivated octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of pH 6.0 phosphate buffer solution and acetonitrile (8 : 2).

Flow rate: 2 mL/min

System suitability

System performance: Dissolve 12.5 mg of sodium nitrate in water to make 250 mL; to 2.0 mL of this solution, add 25.0 mL of standard stock solution and add water to make 100 mL. Proceed with 20 μL of this solution according to the above conditions; the resolution between the peaks of nitrate and related substance I is NLT 9. Proceed with 20 μL of the standard solution according to the above conditions; the signal-to-noise ratio of the peak of related substance I is NLT 10.

Time span of measurement: About 2 times the retention time of related substance I.

pH 6.0 phosphate buffer solution—Dissolve 1.36 g of potassium dihydrogen phosphate in 10 mL of 32% tetrabutylammonium hydroxide solution, add water to make 1000 mL, and adjust pH to 6.0 with phosphoric acid.

(ii) Related substance II: Weigh accurately 0.10 g of Oxaliplatin, add water, shake well, sonicate for a very short time, and add water to make exactly 50 mL. Use this solution as the test solution. Separately, weigh accurately 5 mg of oxaliplatin related substance II {(*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-κ*N*,κ*N'*]platinum (diaquaaminocyclohexane platinum)} RS, dissolve in 25 mL of methanol, add water to make exactly 100.0 mL, and sonicate for about 1 hour and 30 minutes until dissolved. Use this solution as the standard stock solution. Add water to 3.0 mL of this solution to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions; the peak area of oxliplatin related substance II from the test solution is not greater than 4 times the major peak area from the standard solution (NMT 0.15%). Inject the test solution within 20 minutes after preparing the test solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with base-deactivated octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of pH 3.0 phosphate buffer solution and acetonitrile (8 : 2).

Flow rate: 2 mL/min

System suitability

System performance: Add 0.02% sodium hydroxide solution to 50.0 mL of the standard solution to adjust pH to 6.0. Heat the solution for 4 hours at 70 °C, then cool (Related substance V is created). Proceed with 20 μL of this solution according to the above conditions; the resolution between the peaks of related substances II and V is NLT 7. Proceed with 20 μL of the standard solution according to the above conditions; signal-to-noise ratio of related substance II is NLT 10.

Relative retention time: The relative retention times of related substance II and related substance V are about 4.3 and 6.4, respectively.

Time span of measurement: About 2.5 times the retention time of related substance II.

pH 3.0 phosphate buffer solution—Dissolve 1.36 g of potassium dihydrogen phosphate and 1 g of sodium 1-heptanesulfonate in 1000 mL of water and adjust pH to 3.0 ± 0.05 with phosphoric acid.

(iii) Related substance III and other related substances: Weigh accurately 0.10 g of Oxaliplatin, add water, shake well, sonicate for a very short time to dissolve, and then add water to make 50 mL. Use this solution as the test solution. Separately dissolve 5.0 mg of oxaliplatin related substance III {(*OC*-6-33)-[(1*R*,2*R*)-cyclohexane-1,2-diamine-κ*N*,κ*N'*][ethanedioato(2-)-κ*O*,κO^2]dihydroxyplatinum} RS and 5.0 mg of oxaliplatin RS in water to make exactly 100 mL, and use this solution as the standard solution (i). To 1.0 mL of the standard solution (i), add water to make exactly 100 mL, and use this solution as the standard solution (ii). Dissolve 50.0 mg of oxaliplatin RS in water to make exactly 50 mL and use this solution as the standard solution (iii). Dissolve 5 mg of dichlorodiaminocyclohexane platinum RS in the standard solution (iii) to make exactly 50 mL; use this solution as the standard solution (iv). Add water to 5 mL of the standard solution (iv) to make exactly 50 mL, and use this solution as the standard solution (v). Add 1 mL of the standard solution (i) to 0.10 g of Oxaliplatin and dissolve in water to make exactly 50 mL, and use this solution as the standard solution (vi). Perform the test with 10 μL each of the test solution, the standard solution (ii), the standard solution (v), and the standard solution (vi) as directed under the Liquid Chromatography according to the following conditions; the peak area of related substance III from the test solution is not greater than 3/4 times the peak area of related substance III from the standard solution (vi) (0.15%); the peak areas of the other individual related substances are not greater than 2 times the peak area of oxaliplatin from the standard solution (ii) (0.1%); and the total area of the individual peaks is not greater than 3 times the peak area of oxaliplatin from the standard solution (ii) (0.15%). Disregard the peak area of oxaliplatin from the standard solution (ii) and peaks with a retention time NMT 2 minutes. Introduce the test solution within 20 minutes after preparing the test solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: A mixture of a solution prepared by adding 0.6 mL of dilute phosphoric acid to 1000 mL of water, shaking to mix, and adjusting to pH 3.0 with sodium hydroxide TS or phosphoric acid and acetonitrile (99 : 1).

Flow rate: 1.2 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution (5) according to the above conditions; the resolution between the dichlorodiaminocyclohexane platinum peak and oxaliplatin peak is NLT 2. Proceed with 10 μL of the standard solution (2) according to the above conditions; the signal-to-noise ratio of the peak for related substance III is NLT 50, and the signal-to-noise ratio of the peak for oxaliplatin is NLT 10.

Time span of measurement: About 3 times the retention time of oxaliplatin.

(iv) Total related substances: The total amount of related substances I, II and III and other related substances is NMT 0.30%.

(4) ***Related substance IV***—Weigh accurately 30 mg of oxaliplatin and dissolve in methanol to make exactly 50 mL; use this solution as the test solution. Weigh exactly 5.0 mg of oxaliplatin related substance IV {(*SP*-4-2)-[(1*S*,2*S*)-cyclohexane-1,2-diamine-κ*N*,κ*N*′][ethanediato(2-)-κO^1,κO^2]platinum} RS and dissolve in methanol to make exactly 100 mL; use this solution as the standard solution (i). To 15.0 mL of the standard solution (i), add methanol to make exactly 50 mL, and use this solution as the standard solution (ii). Dissolve 75 mg of oxaliplatin RS in methanol to make exactly 100 mL, and use this solution as the standard solution (iii). To 5.0 mL of the standard solution (iii), add methanol to make exactly 100 mL, and use this solution as the standard solution (iv). To 40 mL of the standard solution (iii), add 1.0 mL of the standard solution (ii) and add methanol to make exactly 50 mL, and use this solution as the standard solution (v). Add 5.0 mL of the standard solution (iv) to 4.0 mL of the standard solution (i) and add methanol to make exactly 50 mL, and use this solution as the standard solution (vi). Proceed with 20 μL each of the test solution, the standard solution (v) and the standard solution (vi) as directed under the Liquid Chromatography according to the following conditions; the peak height of related substance IV from the test solution is not greater than 3 times the peak height of related substance IV from the standard solution (v) (0.15%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with silica gel OC for chiral separations for liquid chromatography.

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: A mixture of methanol and ethanol(99.5) (7 : 3).

Flow rate: 0.3 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution (vi) according to the above conditions; the resolution between peaks of oxaliplatin and related substance IV is NLT 1.5. Proceed with 20 μL of the standard solution (i) according to the above conditions; the signal-to-noise ratio of the peaks of related substance IV is NLT 10.

Time span of measurement: About 2 times the retention time of oxaliplatin.

(5) ***Silver***—Weigh accurately 0.1000 g of oxaliplatin and dissolve in water to make exactly 50 mL. Pipet 20 μL of this solution, add 0.5 mol/L nitric acid TS to make exactly 40 μL, and use this solution as the test solution. Weigh accurately 1.575 g of nitric acid, dissolve in 0.5 mol/L nitric acid TS to make exactly 1000 mL, take a suitable amount of this solution, and dilute with 0.5 mol/L nitric acid TS to obtain a solution contining 10 ppb of silver per mL. Use this solution as the standard solution (i). To 20 μL of the test solution, add 8 μL of the standard solution (i) and add 0.5 mol/L nitric acid TS to make 40 mL, and use this solution as the standard solution (ii). To 20 μL of the test solution, add 16 μL of the standard solution (i) and add 0.5 mol/L nitric acid TS to make 40 μL, and use this solution as the standard solution (iii). Perform the test with the test solution and the standard solutions according to the standard addition method under the Atomic Absorption Spectroscopy, and determine the concentration of silver in the test solution and quantify (NMT 5 ppm).

Gas: Air–acetylene or hydrogen

Lamp: Silver hollow-cathode lamp

Wavelength: 328.1 nm

Loss on drying NMT 0.5% (1.0 g, 105 ℃, 2 hours).

Bacterial endotoxins Less than 1.0 EU per mg of Oxaliplatin (when used for preparation of sterile preparations without additional processes to remove endotoxin).

Assay Weigh accurately about 50 mg each of Oxaliplatin and oxaliplatin RS, dissolve in water to make exactly 500 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution according to the operating conditions for testing Related

substance III and other related substances, and determine the peak areas A_T and A_S of oxaliplatin.

$$\text{Amount (mg) of oxaliplatin } (C_8H_{14}N_2O_4Pt) = 500 \times C \times \frac{A_T}{A_S}$$

C: Concentration of oxaliplatin in the standard solution (mg/mL)

Operating conditions

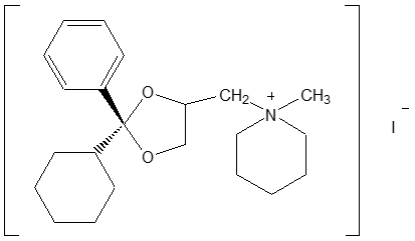
System suitability

System performance: Weigh 5 mg of dichlorodiaminocyclohexane platinum RS and dissolve to make 50 mL in a solution of 50 mg of oxaliplatin RS dissolved in water to make 500 mL. Proceed with 20 μL of this solution according to the above conditions; the resolution between the peaks of dichlorodiaminocyclohexane platinum and oxaliplatin is NLT 2.0.

System repeatability: Repeat the test 5 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of oxaliplatin is NMT 2.0%.

Packaging and storage Preserve in hermetic containers (when the label states that it does not contain bacterial endotoxins).

Oxapium Iodide
옥사피움요오드화물



and enantiomer

$C_{22}H_{34}INO_2$: 471.42

1-[(2-Cyclohexyl-2-phenyl-1,3-dioxolan-4-yl)methyl]-1-methylpiperidin-1-ium iodide [*6577-41-9*]

Oxapium Iodide, when dried, contains NLT 98.5% and NMT 101.0% of oxapium iodide ($C_{22}H_{34}INO_2$).

Description Oxapium Iodide occurs as a white crystalline powder.

It is soluble in methanol, ethanol(95) or acetonitrile, slightly soluble in acetic anhydride or acetic acid(100), and practically insoluble in ether.

A solution of Oxapium Iodide in methanol (1 in 100) shows no optical rotation.

Identification (1) Dissolve 0.1 g of Oxapium Iodide in 10 mL of methanol and add 2 mL of dilute nitric acid and silver nitrate TS; greenish yellow precipitates are produced.

(2) Determine the infrared spectra of Oxapium Iodide and oxapium iodide RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 198 and 203 ºC.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Oxapium Iodide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 50 mg of Oxapium Iodide in 100 mL of a mixture of water and acetonitrile (1 : 1), and use this solution as the test solution. Pipet 1 mL of the test solution, add a mixture of water and acetonitrile (1 : 1) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of the solutions by the automatic integration method; the sum of the peak areas other than the major peak obtained from the test solution is not greater than the area of the major peak from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature between 20 and 30 ℃.

Mobile phase: Add 57 mL of acetic acid(100) and 139 mL of triethylamine to water to make 1000 mL. To 50 mL of this solution, add 500 mL of acetonitrile, 10 mL of dilute acetic acid and 440 mL of water.

Flow rate: Adjust the flow rate so that the retention time of oxapium is about 4 minutes.

System suitability

Detection sensitivity: Adjust the sensitivity so that the peak height of oxapium obtained from 50 μL of the standard solution is between 5% and 15% of the full scale.

System performance: Dissolve 50 mg of Oxapium Iodide and 3 mg of benzophenone in 100 mL of the mobile phase. Proceed with 20 μL of this solution according to the above operating conditions; oxapium and benzophenone are eluted in this order with the resolution being NLT 5.

Time span of measurement: Approximately 6 times the retention time of oxapium after the peak of Iodide ion.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

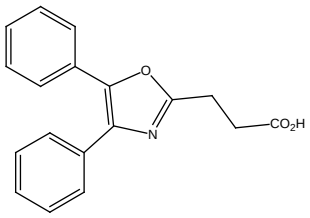
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.7 g of Oxapium Iodide, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (9 : 1), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry, platinum electrode). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 47.14 mg of $C_{22}H_{34}INO_2$

Packaging and storage Preserve in light-resistant, tight containers.

Oxaprozin
옥사프로진



$C_{18}H_{15}NO_3$: 292.32
3-(4,5-Diphenyl-1,3-oxazol-2-yl)propanoic acid [*82419-36-1*]

Oxaprozin, when dried, contains NLT 98.5% and NMT 101.0% of oxaprozin ($C_{18}H_{15}NO_3$).

Description Oxaprozin occurs as a white to yellowish white crystalline powder.
It is sparingly soluble in methanol or ethanol(95), slightly soluble in ether, and practically insoluble in water.
It is gradually affected by light.

Melting point—About 265 °C (with decomposition).

Identification Determine the infrared spectra of Oxazolam and oxazolam RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 161 and 165 ºC.

Absorbance $E_{1cm}^{1\%}$ (285 nm): Between 455 and 495 (10 mg after drying, methanol, 1000 mL).

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Oxaprozin according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Proceed with 2.0 g of Oxaprozin according to Method 3 and perform the test (NMT 1 ppm).

(3) ***Related substances***—Dissolve 0.1 g of Oxazolam in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution (1). Pipet 5 mL, 3 mL and 1 mL each of the test solution, add methanol to make 10 mL, and use these solutions as the standard solutions (2), (3) and (4), respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution, the standard solutions (1), (2), (3) and (4), on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate and acetic acid(100) (99 : 1) to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the total intensity of the spots other than the principal spot obtained from the test solution is NMT 1.0% compared to the spots from the standard solutions (1), (2), (3) and (4).

Loss on drying NMT 0.3% (1 g, 105 ℃, 2 hours).

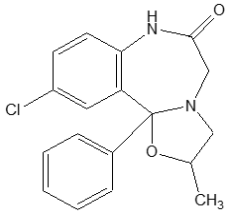
Residue on ignition NMT 0.3% (1 g).

Assay Weigh accurately about 0.5 g of Oxazolam, previously dried, dissolve in 50 mL of ethanol(95), and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Separately, perform a blank test and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 29.33 mg of $C_{18}H_{15}NO_3$

Packaging and storage Preserve in light-resistant, tight containers.

Oxazolam
옥사졸람



$C_{18}H_{17}ClN_2O_2$: 328.79
10-Chloro-2-methyl-11b-phenyl-2,3,7,11b-tetrahydrobenzo[f]oxazolo[3,2-d][1,4]diazepin-6(5H)-one [*24143-17-7*]

Oxazolam, when dried, contains NLT 99.0% and NMT 101.0% of oxazolam ($C_{18}H_{17}ClN_2O_2$).

Description Oxazolam occurs as white crystals or a crystalline powder and is odorless and tasteless.
It is very soluble in acetic acid(100), soluble in 1,4-dioxane or dichloromethane, slightly soluble in ethanol(95) or ether, and practically insoluble in water.
It dissolves in dilute hydrochloric acid.
It is gradually colored by light.

Melting point—About 187 °C (with decomposition).

Identification (1) To 10 mg of Oxazolam, add 10 mL of ethanol(95), heat to dissolve, add 1 drop of hydrochloric acid; the resulting solution exhibits a yellow color. Expose to ultraviolet light (main wavelength: 365 nm); the solution exhibits a yellowish green fluorescence. Add 1 mL of sodium hydroxide TS to the solution; the color and fluorescence of the solution disappear immediately.

(2) To 10 mL of Oxazolam, add 5 mL of dilute hydrochloric acid, dissolve by heating on a steam bath for 10 minutes, and cool. 1 ml of the resulting solution responds to the Qualitative Analysis for primary aromatic amines.

(3) Transfer 2 g of Oxazolam to a 200-mL flask, add 50 mL of ethanol(95) and 25 mL of 6 mol/L hydrochloric acid TS, connect the flask to a reflux condenser, and heat the resulting solution under a reflux condenser for 5 hours After cooling, neutralize the solution with sodium hydroxide solution (1 in 4), and extract with 30 mL of dichloromethane. Dehydrate the extract with 3 g of anhydrous sodium sulfate, filter, and evaporate the dichloromethane of the filtrate. Dissolve the residue in 20 mL of methanol by heating on a steam bath, and cool in iced water rapidly. Collect the crystals, dry in vacuum at 60 ℃ for 1 hour, and determine its melting point; the melting point is 96 to 100 ℃.

(4) Determine the absorption spectra of the solutions of Oxazolam and oxazolam RS in ethanol(95) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(5) Perform the test with Oxazolam as directed under the Flame Coloration (2); it exhibits a green color.

Absorbance $E_{1cm}^{1\%}$ (246 nm): Between 410 and 430 (1 mg after drying, ethanol(95), 100 mL).

Purity (1) ***Chloride***—To 1.0 g of Oxazolam, add 50 mL of water, allow to stand for 1 hour with occasional shaking, and filter. Pipet 25 mL of the filtrate, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.20 mL of 0.01 mol/L hydrochloric acid (NMT 0.014%).

(2) ***Heavy metals***—Proceed with 1.0 g of Oxazolam according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Weigh 1.0 g of Oxazolam, place into a Kjeldahl flask, add 5 mL of sulfuric acid and 5 mL of nitric acid, and then heat gently. Continue heating until the solution becomes colorless to light yellow, adding 2 mL - 3 mL of nitric acid occasionally. After cooling, add 15 mL of saturated ammonium oxalate, and heat until dense white smokes are produced to concentrate to the volume of 2 mL to 3 mL. After cooling, add water to make 10 mL, and perform the test with this solution as the test solution (NMT 2 ppm).

(4) ***Related substances***—Dissolve 50 mg of Oxazolam in 10 mL of dichloromethane and use this solution as the test solution. Pipet 1 mL of this solution, add dichloromethane to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of toluene and acetone (8 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Observe the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

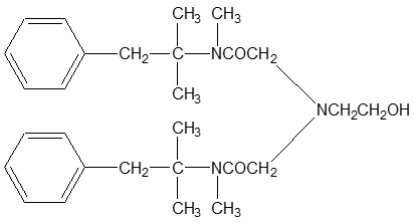
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.65 g of Oxazolam, previously dried, dissolve in 100 mL of a mixture of acetic acid(100) and 1.4-dioxane (1 : 1), and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of methylosaniline chloride TS). The endpoint of the titration is when the color the solution changes from violet through blue to bluish green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 32.879 mg of $C_{18}H_{17}ClN_2O_2$

Packaging and storage Preserve in light-resistant, tight containers.

Oxethazaine
옥세타자인



$C_{28}H_{41}N_3O_3$: 467.64

2,2'-[(2-Hydroxyethyl)imino]*bis*[*N*-methyl-*N*-(2-methyl-1-phenyl-2-propanyl)acetamide] [*126-27-2*]

Oxethazaine, when dried, contains NLT 98.5% and NMT 101.0% of oxethazaine ($C_{28}H_{41}N_3O_3$).

Description Oxethazaine occurs as a white to pale yellowish white crystalline powder.
It is very soluble in acetic acid(100), freely soluble in methanol or ethanol(95), sparingly soluble in ether, and practically insoluble in water.

Identification (1) Determine the absorption spectra of

solutions of Oxethazaine and oxethazaine RS in ethanol(95) (1 in 2500) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Oxethazaine and oxethazaine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 101 and 104 ℃.

Purity (1) ***Chloride***—Dissolve 1.0 g of Oxethazaine in 20 mL of ethanol(95), add 6 mL of dilute nitric acid and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid, 20 mL of ethanol(95), 6 mL of dilute nitric acid and water to make 50 mL (NMT 0.011%).

(2) ***Heavy metals***—Proceed with 2.0 g of Oxethazaine according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 0.40 g of Oxethazaine in 10 mL of ethanol(95) and use this solution as the test solution. Pipet 1 mL of this solution, add ethanol(95) to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of isopropyl ether, tetrahydrofuran, methanol and ammonia water(28) (24 : 10 : 5 :1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

(4) ***2-aminoethanol***—Dissolve 1.0 g of Oxethazaine in methanol to make exactly 10 mL. To this solution, add 0.1 mL of a solution of 1-fluoro-2,4-dinitrobenzene in methanol (1 in 26) and shake to mix, then warm for 20 minutes at 60 ℃; the color of the solution is not more intense than that of the following control solution.

Control solution—Dissolve 0.10 g of 2-aminoethanol in methanol to make exactly 200 mL, pipet 1 mL of this solution and add methanol to make exactly 10 mL. Proceed in the same manner as directed above.

Loss on drying NMT 0.5% (1 g, in vacuum, 60 ℃, 3 hours).

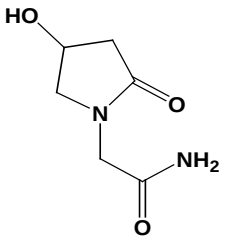
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.9 g of Oxethazaine, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of methylosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 46.76 mg of $C_{28}H_{41}N_3O_3$

Packaging and storage Preserve in tight containers.

Oxiracetam
옥시라세탐



$C_6H_{10}N_2O_3$: 158.16
4-Hydroxy-2-oxo-1-pyrrolidineacetamide, [*62613-82-5*]

Oxiracetam contains NLT 98.0% and NMT 102.0% of oxiracetam ($C_6H_{10}N_2O_3$), calculated on the anhydrous basis.

Description Oxiracetam occurs as a white crystalline powder and is odorless.
It is soluble in water and practically insoluble in acetone or ether.

Melting point—Between 167 and 170 ℃.

Identification (1) Determine the infrared spectra of Oxiracetam and oxiracetam RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve 0.5 g each of Oxiracetam and oxiracetam RS in 5 mL of water, respectively, and use these solutions as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate using a mixture of ethyl acetate, ethanol and acetic acid (10 : 9 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Place the plate in a suitable container containing between 2 g and 4 g of iodine crystal, cover with a lid and allow to stand for 3 to 5 minutes; the test solution and the standard solution show the same color spots at the same R_f value.

Purity (1) ***Chloride***—Perform the test with 2.0 g of Oxiracetam. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.005%).

(2) ***Ammonium***—Weigh accurately about 1 g of Oxiracetam, place in a test tube, and dissolve in 14 mL of water. If necessary, alkalize the test solution by adding 2

mol/L sodium hydroxide TS. Add water to make 15 mL and add 0.3 mL of Nessler's TS. Separately pipet 10 mL of ammonium standard solution, place in a test tube, and add 5 mL of water and 0.3 mL of Nessler's TS. Close the test tube and allow to stand for 5 minutes; the yellow color observed in the test solution is not more intense than the color of the control solution (NMT 0.001%).

Ammonium standard solution—Weigh accurately about 0.741 g of ammonium chloride and dissolve in water to make exactly 1000 mL. Pipet 1 mL of this solution and add water to make exactly 100 mL. Pipet 1 mL of this solution, add water to make exactly 25 mL, and use this solution as the ammonium standard solution (1 ppm NH_4).

Nessler's TS—Dissolve 11 g of potassium iodide and 15 g of mercury(II) iodide in water to make 100 mL. Separately dissolve 25 g of sodium hydroxide in water to make 100 mL. Prepare by mixing the two solutions at a ratio of 1 : 1; prepare before use.

(3) ***Heavy metals***—Weigh 1.0 g of Oxiracetam according to Method 2 as directed under the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Water NMT 1.0% (2 g, volumetric titration, direct titration)

Assay Weigh accurately about 50 mg of Oxiracetam and oxiracetam RS, dissolve in 5 mL of water, add 40 mL of acetonitrile and 1.0 mL of the internal standard solution, and then add the mobile phase to make 50 mL. Use these solutions as the test solution and the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of oxiracetam to the peak area of the internal standard.

Amount (mg) of oxiracetam ($C_6H_{10}N_2O_3$)
= Amount (mg) of oxiracetam RS × Q_T / Q_S

Internal standard solution—A solution of caffeine anhydrous in the mobile phase (1 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

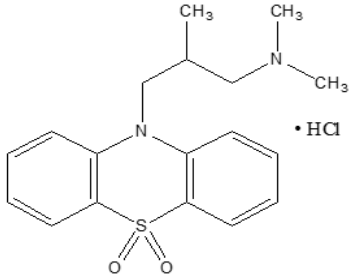
Column: A stainless steel column about 4.0 mm in internal diameter and 30 cm in length, packed with aminopropylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and water (97 : 3).

Flow rate: 1.2 mL/min

Packaging and storage Preserve in well-closed containers.

Oxomemazine Hydrochloride
옥소메마진염산염



$C_{18}H_{22}N_2O_2S·HCl$: 366.91

N,*N*,β-Trimethyl-10*H*-phenothiazine-10-propylamine 5,5-dioxide monohydrochloride, [*4784-40-1*]

Oxomemazine Hydrochloride, when dried, contains NLT 98.0% and NMT 101.0% of oxomemazine hydrochloride ($C_{18}H_{22}N_2O_2S·HCl$).

Description Oxomemazine Hydrochloride occurs as a fine white powder and is odorless.
It is freely soluble in water or methanol, practically insoluble in ether or ethyl acetate, and sparingly soluble in ethanol, acetone or chloroform.

Identification (1) Weigh 0.5 g of Oxomemazine Hydrochloride, place in a separatory funnel, and dissolve in 10 mL of water. Add 1 mL of 40% sodium hydroxide solution, then extract 2 times with 10 mL of chloroform each time. Collect the chloroform layer in another separatory funnel, wash 2 times with 5 mL of water each time, then combine the chloroform. Add 0.5 g of anhydrous potassium carbonate, shake to mix, then filter. Evaporate the filtrate to dryness on a steam bath, then dry the residue in vacuum to a constant mass. Remove from the desiccator and crystallize using an agitator, then measure as directed under the Melting Point; the melting point is between 113 and 118 ℃.

(2) Add 1 mL of sulfuric acid to 50 mg of Oxomemazine Hydrochloride; the solution exhibits a light pink color. Add 2 mL of water and 0.5 mL of nitric acid to 50 mg of Oxomemazine Hydrochloride; the solution exhibits a light yellow color.

(3) Weigh an appropriate amount of Oxomemazine Hydrochloride and dissolve in 0.1 mol/L hydrochloric acid TS to prepare a 20 mg/L solution. Determine the absorption spectra of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima at around 268 nm, 296 nm and 330 nm.

pH Between 4.0 and 6.0 (3% aqueous solution).

Purity (1) ***Clarity and color of solution***—Dissolve 1 g of Oxomemazine Hydrochloride in 10 mL of water; the solution is clear or slightly turbid, and is not more intense than 0.0001 mol/L iodine TS.

(2) ***Heavy metals***—Proceed with 1.0 g of Oxomemazine Hydrochloride as directed under Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Loss on drying NMT 0.5% (2 g, between 100 and 105 ℃, constant mass).

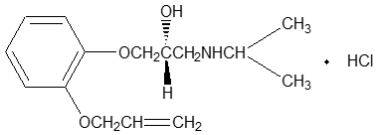
Residue on ignition NMT 0.1% (2 g).

Assay Weigh accurately 0.7 g of Oxomemazine Hydrochloride, previously dried, dissolve in 100 mL of water, and titrate with 0.1 mol/L silver nitrate VS (potentiometric titration under the Titrimetry) (electrode: silver electrode). Perform a blank test and make any necessary correction.

Each mL of 0.1 mol/L silver nitrate VS
= 36.691 mg of $C_{18}H_{22}N_2O_2S \cdot HCl$

Packaging and storage Preserve in tight containers.

Oxprenolol Hydrochloride
옥스프레놀롤염산염



and enantiomer

$C_{15}H_{23}NO_3 \cdot HCl$: 301.81
1-(Propan-2-ylamino)-3-(2-prop-2-enoxyphenoxy)propan-2-ol hydrochloride [*6452-73-9*]

Oxprenolol Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of oxprenolol hydrochloride ($C_{15}H_{23}NO_3 \cdot HCl$).

Description Oxprenolol Hydrochloride occurs as a white crystalline powder.
It is very soluble in water, freely soluble in ethanol(95) or acetic acid(100), slightly soluble in acetic anhydride, and practically insoluble in ether.

Identification (1) To 2 mL of an aqueous solution of Oxprenolol Hydrochloride (1 in 100), add 1 drop of copper(II) sulfate TS and 2 mL of sodium hydroxide TS; the solution exhibits a bluish purple color. Add 1 mL of ether to this solution, shake well to mix and allow to stand; the ether layer exhibits a purple color, and the water layer exhibits a bluish purple color.

(2) Add 3 drops of Reinecke salt TS to 3 mL of an aqueous solution of Oxprenolol Hydrochloride (1 in 150); a pale red precipitate is formed.

(3) Determine the infrared spectra of Oxprenolol Hydrochloride and oxprenolol hydrochloride RS, previously dried, as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) An aqueous solution of Oxprenolol Hydrochloride (1 in 50) responds to the Qualitative Analysis for chloride.

Melting point Between 107 and 110 ℃.

pH Dissolve 1.0 g of Oxprenolol Hydrochloride in 10 mL of water. The pH of this solution is between 4.5 and 6.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Oxprenolol Hydrochloride in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 2.0 g of Oxprenolol Hydrochloride as directed under Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Oxprenolol Hydrochloride as directed under Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.25 g of Oxprenolol Hydrochloride in 10 mL of water, and use this solution as the test solution. Pipet 4 mL of this solution and add water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, in a developing chamber saturated with ammonia vapor, develop the plate with a mixture of chloroform and methanol (9 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 80 ℃, 3 hours).

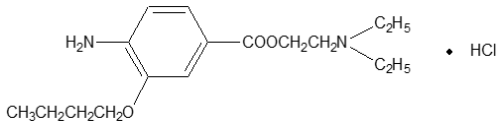
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.6 g of Oxprenolol Hydrochloride, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 30.181 mg of $C_{15}H_{23}NO_3 \cdot HCl$

Packaging and storage Preserve in tight containers.

Oxybuprocaine Hydrochloride
옥시부프로카인염산염



Benoxinate Hydrochloride

$C_{17}H_{28}N_2O_3 \cdot HCl$: 344.88

2-(Diethylamino)ethyl 4-amino-3-butoxybenzoate hydrochloride [*5987-82-6*]

Oxybuprocaine Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of oxybuprocaine hydrochloride ($C_{17}H_{28}N_2O_3 \cdot HCl$).

Description Oxybuprocaine Hydrochloride occurs as white crystals or a crystalline powder.
It is odorless, has a salty taste, and paralyzes the tongue.
It is very soluble in water, freely soluble in ethanol(95) and chloroform, and practically insoluble in ether.
It is gradually colored by light.
Dissolve 1.0 g of Oxybuprocaine Hydrochloride in 10 mL of water; the pH of this solution is between 5.0 and 6.0.

Identification (1) Dissolve 10 mg of Oxybuprocaine Hydrochloride in 1 mL of dilute hydrochloric acid and 4 mL of water; the solution responds to the Qualitative Analysis for primary aromatic amines.

(2) Dissolve 0.1 g of Oxybuprocaine Hydrochloride in 8 mL of water and add 3 mL of ammonium thiocyanate TS; an oil-like substance forms, and a white crystal is precipitated when the wall of the vessel is scratched with a glass rod. Separately take this crystal, recrystallize with water, and dry for 5 hours in a desiccator (vacuum, phosphorus pentoxide); the melting point is between 103 and 106 ℃.

(3) Determine the absorption spectra of aqueous solution of Oxybuprocaine Hydrochloride and oxybuprocaine hydrochloride RS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) An aqueous solution of Oxybuprocaine Hydrochloride (1 in 10) responds to the Qualitative Analysis for chloride.

Melting point Between 158 and 162 ºC.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of oxybuprocaine hydrochloride in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of oxybuprocaine hydrochloride according to Method 1.and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve 0.25 g of Oxybuprocaine Hydrochloride in 10 mL of chloroform and use this solution as the test solution. Pipet 1.0 mL of the test solution and add chloroform to make exactly 20 mL. Pipet 1 mL of this solution, add chloroform to make exactly 50 mL and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, ethanol(95) and formic acid (7 : 2 : 1) to about 10 cm, and air-dry the plate. Spray evenly *p*-dimethylaminobenzaldehyde TS for spray on the plate; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

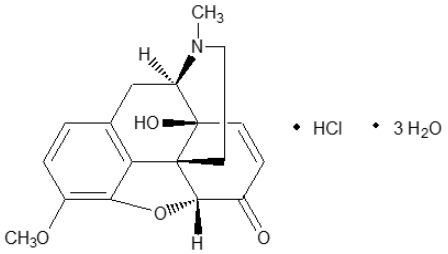
Residue on ignition NMT 0.1% (1 g).

Assay Weigh exactly about 0.6 g of Oxubyprocaine Hydrochloride, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 34.488 mg of $C_{17}H_{28}N_2O_3 \cdot HCl$

Packaging and storage Preserve in light-resistant, well-closed containers.

Oxycodone Hydrochloride Hydrate
옥시코돈염산염수화물



Oxycodone Hydrochloride

$C_{18}H_{21}NO_4 \cdot HCl \cdot 3H_2O$: 405.87

(1*S*,5*R*,13*R*,17*S*)-17-Hydroxy-10-methoxy-4-methyl-12-oxa-4-azapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}] octadeca-7(18),8,10-trien-14-one trihydrate hydrochloride [*591229-40-2*]

Oxycodone Hydrochloride Hydrate contains NLT 98.0% and NMT 101.0% of oxycodone hydrochloride ($C_{18}H_{21}NO_4 \cdot HCl$: 351.83), calculated on the anhydrous basis.

Description Oxycodone Hydrochloride Hydrate occurs as a white crystalline powder.
It is freely soluble in water, methanol or acetic acid(100), sparingly soluble in ethanol(95), slightly soluble in acetic

anhydride and practically insoluble in ether.
Dissolve 1.0 g of Oxycodone Hydrochloride Hydrate in 10 mL of water; the pH of this solution is 3.8 to 5.8.
It is affected by light.

Identification (1) Determine the absorption spectra of aqueous solutions of Oxycodone Hydrochloride Hydrate and oxycodone hydrochloride hydrate RS (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelength.

(2) Determine the infrared spectra of Oxycodone Hydrochloride Hydrate and oxycodone hydrochloride hydrate RS according to the potassium bromide disk method as directed under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) An aqueous solution of Oxycodone Hydrochloride Hydrate (1 in 50) responds to the Qualitative Analysis (2) for chloride.

Optical rotation $[\alpha]_D^{20}$: Between -140° and -149° (0.5 g calculated on the anhydrous basis, water, 25 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Oxycodone Hydrochloride Hydrate in 10 mL of water; the solution is clear and colorless.

(2) ***Morphine***—Dissolve 10 mg of Oxycodone Hydrochloride Hydrate in 1 mL of water, add 5 mL of 1-nitroso-2-naphthol TS and 2 mL of potassium nitrate (1 in 10), and warm at 40 ℃ for 2 minutes. Then, add 1 mL of sodium nitrate solution (1 in 5000), and warm at 40 ℃ for 5 minutes. After cooling, add 10 mL of chloroform, shake to mix, centrifuge, and collect the aqueous layer; the color of the resulting solution is not more intense than pale bright red.

(3) ***Codeine***—Dissolve 10 mg of Oxycodone Hydrochloride Hydrate in 5 mL of sulfuric acid, add 1 drop of iron(III) chloride TS, and warm; the solution does not exhibit a blue color. Add 1 more drop of nitric acid; the solution does not exhibit a red color.

(4) ***Thebaine***—Dissolve 0.1 g of Oxycodone Hydrochloride Hydrate in 2 mL of diluted hydrochloric acid (1 in 10), heat the solution on a steam bath for 25 minutes, cool, add 0.5 mL of hydrochloric acid-4-aminoantipyrine TS and 0.5 mL of potassium hexacyanoferrate(III) TS, shake to mix, add 2 mL of ammonia TS and 3 mL of chloroform, and shake to mix; the chloroform layer does not exhibit a red color.

Water Between 12% and 15% (0.2 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately about 0.5 g of Oxycodone Hydrochloride Hydrate, calculated on the anhydrous basis, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 35.182 mg of $C_{18}H_{21}NO_4 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Oxygen
산소

O_2 : 32.00

[*7782-44-7*]

Prepare Oxygen with air through the air-liquifaction process.

Oxygen contains NLT 99.5 vol% and NMT 101.0 vol% of oxygen (O_2).

Description Oxygen occurs as a colorless gas and is odorless.
1 mL of Oxygen dissolves in about 32 mL of water or about 7 mL of ethanol(95) at 20 ℃ and 101.3 kPa.
1000 mL of Oxygen is about 1.429 g at 0 ℃ and 101.3 kPa.

Identification Perform the test with Oxygen as directed under the Assay; it shows a paramagnetic signal equal to the standard oxygen gas.

Purity The amount of Oxygen is collected after maintaining the container at between18 and 22 ℃ for NLT 6 hours before performing the test, and converted to the volume at the pressure of 101.3 kPa at 20 ℃.

(1) ***Carbon dioxide***—Transfer 50 mL of barium hydroxide TS to a Nessler tube. Place the end of the gas injection tube (about 1 mm in internal diameter) 2mm away from the floor and pass 1000 mL of Oxygen through the Nessler tube; the turbidity of the solution is not more intense than the following control solution.

Control solution—Transfer 50 mL of barium hydroxide TS to a Nessler tube and add 1 mL of a solution dissolved 0.1 g of sodium bicarbonate in 100 mL of newly boiled and cooled water.

(2) ***Nitrogen***—Take 1.0 mL of Oxygen into a gas flowmeter for gas chromatography or a syringe through a PVC injection tube directly from a pressure-resistant metal hermetic container with a pressure-reducing valve. Perform the test with this as directed under the Gas Chromatography according to the following conditions and calculate the peak area, AT, of nitrogen. Separately, take 0.50 mL of nitrogen in a gas mixture dispenser, add the carrier gas to make the total volume to exactly 100 mL, and mix well. Take 1.0 mL of this mixture, proceed in the same manner as in the preparation of Oxygen, and

calculate the peak area, AS of nitrogen; AT is not greater than AS.

Operating conditions

Detector: A thermal conductivity detector

Column: A column about 3 mm in internal diameter and about 3 m in length, packed with zeolite for gas chromatography (250 μm to 355 μm in particle diameter, 0.5 nm in pore diameter).

Column temperature: A constant temperature of about 50 °C.

Carrier gas: Hydrogen or helium

Flow rate: Adjust the flow rate so that the retention time of nitrogen is about 5 minutes.

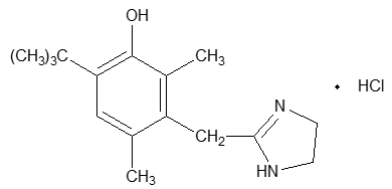
Selection of column: Take 0.5 mL of nitrogen in a gas mixture dispenser, add Oxygen to make 100 mL, and mix well. Proceed with 1.0 mL of this mixture according to the above conditions; oxygen and nitrogen are eluted in this order and each peak is completely separated.

(3) ***Carbon monoxide***—Connect a tube with a sufficient length to a carbon monoxide container so that all liquid contents are vaporized passing through the tube when opening the valve of the container, and prevent the inlet tube connected to the detector tube from frosting. Through the tube (previously replace the air in the apparatus with Oxygen), pass 1000 ± 50 mL of Oxygen in the form of vapor through the carbon monoxide detector tube at an appropriate flow rate, and determine carbon monoxide concentration; NMT 0.001%. But, to prevent contamination, connect the gas volumetric apparatus to the bottom of the detector tube during measurement.

Assay Use Oxygen as the sample gas. Separately, quantify standard nitrogen gas and standard oxygen gas with a magnetic analyzer as directed under the Oxygen assay.

Packaging and storage Preserve in pressure-resistant metal hermetic containers at NMT 40 ℃.

Oxymetazoline Hydrochloride
옥시메타졸린염산염



$C_{16}H_{24}N_2O \cdot HCl$: 296.84

6-*tert*-Butyl-3-(4,5-dihydro-1*H*-imidazol-2-ylmethyl)-2,4-dimethylphenol hydrochloride [*2315-02-8*]

Oxymetazoline hydrochloride contains NLT 98.5 and NMT 101.5% of oxymetazoline hydrochloride ($C_{16}H_{24}ClN_2O \cdot HCl$), calculated on the dried basis.

Description Oxymetazoline hydrochloride occurs as a white, fine crystalline powder.

It is soluble in water or ethanol(95), and practically insoluble in benzene, chloroform or ether.

It is hygroscopic.

Melting point—About 300 °C (with decomposition).

Identification (1) Determine the absorption spectra of aqueous solutions of Oxymetazoline Hydrochloride and oxymetazoline hydrochloride RS (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths, and the difference of each absorbance of Oxymetazoline Hydrochloride and Oxymetazoline Hydrochloride RS at the absorbance maximum wavelength at about 279 nm is NMT 3.0%.calculated on the dried basis.

(2) Determine the infrared spectra of Oxymetazoline Hydrochloride and oxymetazoline hydrochloride RS, previously dried, as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit maximum of absorption at the same wave numbers.

(3) To a solution of 50 mg of Oxymetazoline Hydrochloride dissolved in 3 mL of water, add 1 mL of ammonia TS and filter. Acidify the filtrate with nitric acid; the filtrate responds to the Qualitative Analysis for chloride.

pH Dissolve 1.0 g of Oxymetazoline Hydrochloride in 20 mL of water; the pH of this solution is between 4.0 and 6.5.

Purity ***Heavy metals*—**Proceed with 1.0 g of Oxymetazoline Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

Loss on drying NMT 1.0% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 25 mg of Oxymetazoline Hydrochloride, and dissolve in the mobile phase to make exactly 50 mL. Separately, weigh an appropriate amount of oxymetazoline hydrochloride RS, previously dried at 105 ℃ for 3 hours, dissolve in the mobile phase to prepare a solution containing 0.5 mg per mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of oxymetazoline hydrochloride, A_T and A_S, in each solution.

$$\text{Amount (mg) of oxymetazoline hydrochloride } (C_{16}H_{24}N_2O \cdot HCl) = 50 \times C \times \frac{A_T}{A_S}$$

C: Concentration (mg/mL) of the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with porous silica gel coated with strongly acidic cation exchange resin for liquid chromatography (10 μm in particle diameter).

Mobile phase: A mixture of water, methanol, 1 mol/L sodium acetate TS and acetic acid(100) (46 : 40 : 10 : 4).

Flow rate: 1 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution under the above operating conditions; the symmetry factor is NMT 2.0.

System repeatability: Repeat the test 6 times according to the above conditions with 20 μL of the standard solution; the relative standard deviation of the peak area is NMT 2.0%

Packaging and storage Preserve in tight containers.

Oxymetazoline Hydrochloride Nasal Solution
옥시메타졸린염산염 점비액

Oxymetazoline Hydrochloride Nasal Solution contains NLT 90.0% and NMT 110.0% of the labeled amount of oxymetazoline hydrochloride ($C_{16}H_{24}O_2$: 296.84).

Method of preparation Prepare as directed under Nasal Solutions, with Oxymetazoline Hydrochloride.

Description Oxymetazoline Hydrochloride Nasal Solution occurs as a clear, colorless liquid.

Identification Weigh accurately the amount equivalent to 2.5 mg of oxymetazoline hydrochloride according to the labeled amount of Oxymetazoline Hydrochloride Nasal Solution, add water 10 to make 10 mL, then add 2 mL of sodium carbonate solution (1 in 10), and extract with 10 mL of chloroform. Take the chloroform layer and extract with 10 mL of 0.1 mol/L hydrochloric acid. Take 8 mL of the hydrochloric acid layer and place in a test tube, neutralize with a small amount of 1 mol/L sodium hydroxide solution, add 1 more drop of 1 mol/L sodium hydroxide solution and mix, then add a few drops of sodium pentacyanonitrosylferrate(III) TS and 2 drops of sodium hydroxide solution (15 in 100), and allow to stand for 10 minutes. To this solution, add 0.1 mol/L hydrochloric acid to adjust pH to between 8 and 9, then allow to stand for 10 minutes; the solution exhibits a purple color.

pH Between 4.0 and 6.5.

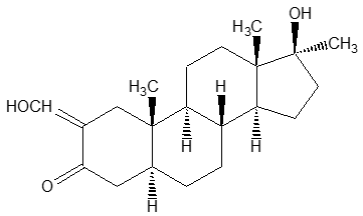
Assay Use Oxymetazoline Hydrochloride Nasal Solution as the test solution. Separately, weigh oxymetazoline hydrochloride RS, previously dried at 105 ℃ for 3 hours, and dissolve in the mobile phase to make the same concentration as the test solution. Use this solution as the standard solution. Perform the test solution with the test solution and the standard solution as directed under the Assay under Oxymetazoline Hydrochloride.

$$\text{Amount (mg) of oxymetazoline hydrochloride } (C_{16}H_{24}N_2O\cdot HCl) = C \times \frac{A_T}{A_S}$$

C: Concentration (mg/mL) of the standard solution

Packaging and storage Preserve in tight containers.

Oxymetholone
옥시메톨론



$C_{21}H_{32}O_3$: 332.48

17β-Hydroxy-2-hydroxymethylidene-17α-methyl-3-androstanone [*434-07-1*]

Oxymetholone, when dried, contains NLT 97.0% and NMT 103.0% of oxymetholone ($C_{21}H_{32}O_3$).

Description Oxymetholone occurs as a white to pale yellowish crystalline powder and is odorless.

It is freely soluble in chloroform, soluble in 1,4-dioxane, sparingly soluble in methanol, ethanol(95) or acetone, slightly soluble in ether, and practically insoluble in water.

It is gradually colored and decomposed by light.

Identification (1) Dissolve 2 mg of Oxymetholone in 1 mL of ethanol(95) and add 1 drop of iron(III) chloride TS; the resulting solution exhibits a violet color.

(2) Dissolve 0.01 g of Oxymetholone and oxymetholone RS in methanol to make 50 mL. Take 5 mL of these solutions, and add 5 mL of sodium hydroxide-methanol TS and add methanol to make 50 mL. Determine the absorption spectra of both solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Oxymetholone and oxymetholone RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wave numbers.

Optical rotation $[\alpha]_D^{20}$: Between +29° and +33° (0.1 g after drying, acetone, 10 mL, 100 mm).

Melting point Between 175 and 182 ºC.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Oxymetholone in 25 mL of ethanol(99.5); the solution is clear and colorless to pale yellow.

(2) ***Related substances***—Dissolve 50 mg of Oxymetholone in 5 mL of chloroform and use this solution as the test solution. Pipet 1 mL of the test solution, add chloroform to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Air-dry the plate, and immediately develop the plate with a mixture of toluene and ethanol(99.5) (49 : 1) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Spray vanillin-sulfuric acid TS evenly on the plate, then heat for 3 to 5 minutes at 100 ℃; spots other than the principal spot and the spot from the starting point from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 1.0% (0.5 g, in vacuum, phosphorus pentoxide, 4 hours).

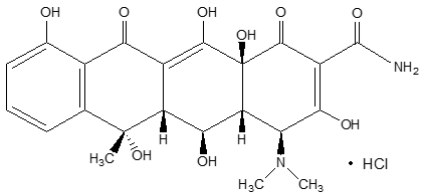
Residue on ignition NMT 0.15% (0.5 g).

Assay Weigh accurately about 40 mg of Oxymetholone, previously dried, and dissolve in methanol to make exactly 50 mL. Pipet 5 mL of this solution and add methanol to make exactly 50 mL. Pipet 5 mL of this solution, and add 5 mL of sodium hydroxide-methanol TS and methanol to make exactly 50 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy using a solution prepared by adding methanol to 5 mL of sodium hydroxide-methanol TS to make 50 mL as the control solution, and measure the absorbance, *A*, at the absorbance maximum wavelength of about 315 nm.

$$\text{Amount (mg) of oxymetholone } (C_{21}H_{32}O_3) = \frac{A}{541} \times 50000$$

Packaging and storage Preserve in light-resistant, tight containers.

Oxytetracycline Hydrochloride
옥시테트라사이클린염산염



$C_{22}H_{24}N_2O_9 \cdot HCl$: 496.89

(4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-(dimethylamino)-3,5,6,10,11,12a-hexahydroxy-6-methyl-1,12-dioxo-1,4,4a,5,5a,6,12,12a-octahydrotetracene-2-carboxamide hydrochloride [*2058-46-0*]

Oxytetracycline Hydrochloride is the hydrochloride of a tetracycline compound having antibacterial activity produced by the growth of *Streptomyces rimosus*.

Oxytetracycline Hydrochloride contains NLT 880 μg and NLT 945 μg (potency) of oxytetracycline ($C_{22}H_{24}N_2O_9$: 460.43) per mg, calculated on the dried basis.

Description Oxytetracycline Hydrochloride occurs as yellow crystals or a crystalline powder.
It is freely soluble in water and slightly soluble in ethanol(99.5).

Identification (1) Determine the absorption spectra of solutions of Oxytetracycline Hydrochloride and oxytetracycline hydrochloride RS in 0.1 mol/L hydrochloric acid TS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Weigh 20 mg of Oxytetracycline Hydrochloride, dissolve in 3 mL water, and add 1 drop of silver nitrate TS; the resulting solution is turbid.

Optical rotation $[\alpha]_D^{20}$: Between -188° and -200° (0.25 g calculated on the dried basis, 0.1 mol/L hydrochloric acid, 25 mL, 100 mm).

pH Dissolve 0.1 g of Oxytetracycline Hydrochloride in 10 mL of water; the pH of this solution is between 2.0 and 3.0.

Absorbance Weigh accurately about 50 mg each of Oxytetracycline Hydrochloride and oxytetracycline hydrochloride RS and dissolve each in 0.1 mol/L hydrochloric acid TS to make exactly 250 mL. Pipet 10 mL each of these solutions, add 0.1 mol/L hydrochloric acid TS to make exactly 100 mL, and use these solutions as the test and standard solutions. With the test and standard solutions, measure the absorbance A_T and A_S at 353 nm as directed under the Ultraviolet-visible Spectroscopy, using 0.1 mol/L hydrochloric acid TS as the control solution (92.5 ± 4.3%).

$$\text{Absorbance ratio (\%)} = \frac{A_T}{A_S} \times \frac{Potency\ (\mu g)\ in\ amount\ of\ Oxytetracycline\ Hydrochloride\ RS\ taken}{Amount\ (mg)\ of\ Oxytetracycline\ Hydrochloride\ taken}$$

$$\times \frac{100}{(100-m)}$$

m: Water (%) of sample

Purity (1) ***Heavy metals***—Proceed with 0.5 g of Oxytetracycline Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.5 mL of lead standard solution (NMT 50 ppm).

(2) ***Related substances***—Weigh accurately about 20 mg of Oxytetracycline Hydrochloride, dissolve in 0.01 mol/L hydrochloric acid TS to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of 4-epioxytetracycline, dissolve in 0.01 mol/L hydrochloric acid TS to make exactly 25 mL, and use the resulting solution as the 4-epioxytetracycline stock solution. Further, dissolve about 20 mg of tetracycline hydrochloride in 0.01 mol/L hydrochloric acid TS to make exactly 25 mL, and use the resulting solution as the tetracycline hydrochloride stock solution. Weigh accurately about 8 mg of β-apoxytetracycline, dissolve in 5 mL of 0.01 mol/L sodium hydroxide TS, add 0.01 mol/L hydrochloric acid TS to make exactly 100 mL, and use the resulting solution as the β-apoxytetracycline stock solution. Pipet 1 mL of 4-epioxytetracycline stock solution, 4 mL of tetracycline hydrochloride stock solution and 40 mL of β-apoxytetracycline stock solution, add 0.01 mol/L hydrochloric acid TS to make exactly 200 mL, and use the resulting solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and measure the peak areas of each solution using the automatic integration method; the peak areas of 4-epioxytetracycline and tetracycline from the test solution are not larger than the respective peak areas from the standard solution, and the total area for the peak of α-apoxytetracycline, the peak of β-apoxytetracycline and the peaks between these two is not greater than the peak area of β-apoxytetracycline from the standard solution. Further, the peak area of 2-acetyl-2-decarboxamide oxytetracycline eluted after the major peak of the test solution is not greater than 4 times the peak area of 4-epioxytetracycline from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with styrene-divinylbenzene copolymer for liquid chromatography (8 μm in particle diameter).

Column temperature: A constant temperature of about 60 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: Mix 60 mL of 0.33 mol/L potassium dihydrogen phosphate TS, 100 mL of tetrabutylammonium hydrogen sulfate (1 in 100), 10 mL of ethylenediamine tetraacetic acid disodium salt dihydrate solution (1 in 2500) and 200 mL of water, and adjust pH to 7.5 with 2 mol/L sodium hydroxide TS. Add 30 g of *t*-butyl alcohol and add water to make 1000 mL.

Mobile phase B: Mix 60 mL of 0.33 mol/L potassium dihydrogen phosphate TS, 50 mL of tetrabutylammonium hydrogen sulfate (1 in 100), 10 mL of ethylenediamine tetraacetic acid disodium salt dihydrate solution (1 in 2500) and 200 mL of water, and adjust pH to 7.5 with 2 mol/L sodium hydroxide TS. Add 100 g of *t*-butyl alcohol and add water to make 1000 mL.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 20	70 → 10	30 → 90
20 - 35	10 → 20	90 → 80

Flow rate: 1.0 mL/min

System suitability

Test for required detectability: To exactly 1 mL of 4-epioxytetracycline stock solution, add 0.01 mol/L hydrochloric acid TS to make exactly 200 mL. Pipet 4 mL of this solution and add 0.01 mol/L hydrochloric acid TS to make exactly 20 mL. Confirm the peak area of 4-epioxytetracycline obtained from 20 μL of this solution is between 14% and 26% of the peak area of 4-epioxytetracycline from the standard solution.

System performance: Weigh accurately about 8 mg of α-apoxytetracycline and dissolve in 5 mL of 0.01 mol/L sodium hydroxide TS, add 0.01 mol/L hydrochloric acid TS to make exactly 100 mL, and use the resulting solution as the α-apoxytetracycline stock solution. Pipet 3 mL of the test solution, 2 mL of the 4-epioxytetracycline stock solution, 6 mL of the tetracycline hydrochloride stock solution, 6 mL of the β-apoxytetracycline stock solution and 6 mL of the α-apoxytetracycline stock solution, and add 0.01 mol/L hydrochloric acid TS to make exactly 50 mL. Proceed with 20 μL of this solution according to the above conditions; 4-epioxytetracycline, oxytetracycline, tetracycline, α-apoxytetracycline and β-apoxytetracycline are eluted in this order, with the resolutions between 4-epioxytetracycline and oxytetracycline, between oxytetracycline and tetracycline and between α-apoxytetracycline and β-apoxytetracycline being NLT 4, NLT 5 and NLT 4, respectively, and the symmetry factor of oxytetracycline being NMT 1.3.

System repeatability: Pipet 1 mL of 4-epioxytetracycline stock solution and add 0.01 mol/L hydrochloric acid TS to make exactly 200 mL. Repeat the test 6 times with 20 μL each of these solutions according to the above operating conditions; the relative standard deviation of the peak areas of 4-epioxytetracycline is NMT 2.0%.

Relative retention time: The relative retention time of α-apoxytetracycline with respect to oxytetracycline is about 2.1.

Time span of measurement: About 3.5 times the retention time of oxytetracycline after the solvent peak.

0.33 mol/L potassium dihydrogen phosphate—TS Dissolve 4.491 g of potassium dihydrogen phosphate in water to make 100 mL.

Loss on drying NMT 2.0% (1 g, in vacuum, 60 ℃, 3 hours).

Residue on ignition NMT 0.5% (1 g).

Sterility It meets the requirements when used in sterile preparations. However, it is excluded in cases where there is a final sterilization process in the manufacturing of a sterile preparation.

Bacterial endotoxins It is less than 0.4 EU per mg (potency) of oxytetracycline when used for the manufacturing of sterile preparations.

Histamine It meets the requirements when used in sterile preparations. Proceed with an appropriate amount of Oxytetracycline Hydrochloride to prepare a solution containing 5.0 mg (potency) per mL, and use the solution as the test solution. Use 0.6 mL of the test solution for the test.

Assay Weigh accurately about 50 mg (potency) of Oxytetracycline Hydrochloride and dissolve in 25 mL of 0.1 mol/L hydrochloric acid TS, add water to make exactly 250 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg (potency) of oxytetracycline RS, dissolve in 25 mL of 0.1 mol/L hydrochloric acid TS, add water to make exactly 250 mL, and use this solution as the standard solution. Store the standard solution at below 5℃ and use it within 7 days. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of oxytetracycline from each solution.

$$\text{Potency (μg) of oxytetracycline } (C_{22}H_{24}N_2O_9) = \text{Potency (μg) of oxytetracycline RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 50 g of *t*-butyl alcohol in water to make 200 mL, add 60 mL of phosphate buffer solution, pH 7.5, 50 mL of *t*-butylammoniumhydrogensulfate and 10 mL of edetate TS, and add water to make 1000 mL.

Flow rate: 1.4 mL/min

System suitability

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of erythromycin is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Oxytetracycline Hydrochloride Capsules
옥시테트라사이클린염산염 캡슐

Oxytetracycline Hydrochloride Capsules contain NLT 90.0% and NMT 120.0% of the labeled amount of oxytetracycline ($C_{22}H_{24}N_2O_9$: 460.44).

Method of preparation Prepare as directed under Capsules, with Oxytetracycline Hydrochloride.

Identification Weigh an amount of the content of Oxytetracycline Hydrochloride Capsules, previously powdered, equivalent to about 10 mg of oxytetracycline hydrochloride, dissolve in 20 mL of water, add 1 mL of sodium carbonate solution (1 in 100) to 1 mL of this solution, and then add 1 mL of diazobenzenesulfonic acid TS; the resulting solution exhibits an orangey red color.

Loss on drying NMT 5.0% (0.1 g, 0.7 kPa, 60 ℃, 3 hours).

Dissolution Perform the test with 1 capsule of Cefalexin Capsule at 75 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take the dissolved solution 60 minutes after starting the dissolution test, filter, and discard the first 10 mL of the filtrate. Pipet *V* mL of the subsequent filtrate, add water to make exactly *V*□ mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of oxytetracycline RS, dissolve in 5 mL of 0.1 mol/L hydrochloric acid, then add the dissolution medium to make it the same concentration as the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength of around 273 nm, as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as a control solution. It meets the requirements when the dissolution rate of Oxytetracycline Hydrochloride Capsules in 60 minutes is NLT 80% (Q).

$$\text{Dissolution rate (\%) of the labeled amount of oxytetracycline } (C_{22}H_{24}N_2O_9) = Cs \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 90000$$

Cs: Concentration [mg (potency)/mL] of the standard solution

C: Labeled amount [mg (potency)] of oxytetracycline ($C_{22}H_{24}N_2O_9$) per capsule

Uniformity of dosage units Meets the requirements.

Assay Take NLT 20 capsules of Oxytetracycline Hydrochloride Capsules, weigh accurately the mass of the content equivalent to about 50 mg (potency) according to the labeled potency, dissolve in 25 mL of 0.1 mol/L hydrochloric acid TS, add water to make exactly 250 mg, and use this solution as the test solution. Separately, weigh accurately about 50 mg (potency) of oxytetracycline RS, dissolve in 25 mL of 0.1 mol/L hydrochloric acid TS, add water to make exactly 250 mL, and use this solution as the standard solution. Store the standard solution at below 5 °C and use it within 7 days. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of oxytetracycline hydrochloride in the test solution and the standard solution.

$$\text{Potency (μg) of oxytetracycline } (C_{22}H_{24}N_2O_9) = \text{Potency (μg) of oxytetracycline RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

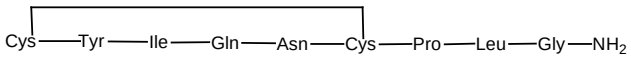
Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 50 g of *t*-butyl alcohol in water to make 200 mL, then add 60 mL of phosphate buffer solution, pH 7.5, 50 mL of *t*-butylammonium hydrogen sulfate and 10 mL of edetate TS, and add water to make 1000 mL.

Flow rate: 1.4 mL/min

Packaging and storage Preserve in tight containers.

Oxytocin
옥시토신



$C_{43}H_{66}N_{12}O_{12}S_2$: 1007.19

1-({(4*R*,7*S*,10*S*,13*S*,16*S*,19*R*)-19-amino-7-(2-amino-2-oxoethyl)-10-(3-amino-3-oxopropyl)-16-(4-hydroxybenzoyl)-13-[(1S)-1-methylpropyl]-6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17-pentaaza-cycloicosan-4-yl}carbonyl)-L-prolyl-L-leucyl-glycinamide [*50-56-6*]

Oxytocin is a synthetic peptide having the property of causing the contraction of uterin.

Oxytocin contains NLT 540 and NMT 600 oxytocin units per mg of peptide, calculated on the anhydrous and acetic acid-free basis.

Description Oxytocin occurs as a white powder.
It is very soluble in water and freely soluble in ethanol(99.5).
It is soluble in hydrochloric acid TS.
The pH of a solution prepared by dissolving 0.10 g of oxytocin in 10 ml of freshly boiled and cooled water is between 4.0 and 6.0.
It is hygroscopic.

Identification Determine the absorption spectra of solutions of Oxytocin and oxytocin RS (1 in 2000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Constituent amino acids Weigh accurately about 1 mg of Oxytocin, transfer to a test tube for hydrolysis, dissolve in 6 mol/L hydrochloric acid TS for nitrogen substitution, then seal in vacuum, and heat at 110 ℃ - 115 ℃ for 16 hours. Cool, remove the stopper, evaporate the hydrolysate to dryness in vacuum, dissolve the residue in 2 mL of 0.02 mol/L hydrochloric acid TS, and use this solution as the test solution. Separately weigh accurately about 24 mg of L-asparaginate, about 24 mg of L-threonine, about 21 mg of L-serine, about 29 mg of L-glutamic acid, about 23 mg of L-proline, about 15 mg of glycine, about 18 mg of L-alanine, about 23 mg of L-valine, about 48 mg of L-cystine, about 30 mg of methionine, about 26 mg of L-isoleucine, about 26 mg of L-leucine, about 36 mg of L-tyrosine, about 33 mg of phenylalanine, about 36 mg of L-lysine hydrochloride, about 42 mg of L-histidine hydrochloride hydrate and about 42 mg of L-arginine hydrochloride, dissolve in 10 mL of 1 mol/L hydrochloric acid TS, and add water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the respective molar ratios with respect to leucine; between 0.95 and 1.05 for asparaginic acid, between 0.95 and 1.05 for glutamic acid, between 0.95 and 1.05 for proline, between 0.95 and 1.05 for glycine, between 0.80 and 1.10 for isoleucine, between 0.80 and 1.05 for tyrosine, between 0.80 and 1.05 for cystine, and NMT 0.01 for each of the other amino acids.

Operating conditions

Detector: A visible absorption photometer (wavelengths: 440 nm and 570 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 8 cm in length, packed with strongly acidic ion exchange resin for liquid chromatography (sodium type) where polystyrene (3 μm in particle diameter) is bonded to a sulfonic acid group.

Column temperature: A constant temperature of about 57 °C.

Chemical reactor: A constant temperature of about 130 ℃.

Color development time: About 1 minute.

Mobile phase: Control the mixing ratio of mobile phase A, mobile phase B and mobile phase C stepwise or via the gradient elution as follows.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)	Mobile phase C (vol%)
0 - 9	100	0	0
9 - 25	0	100	0
25 - 61	0	100 →0	0 →100
61 - 80	0	0	100

Prepare mobile phase A, mobile phase B and mobile phase C according to the following table.

	Mobile phase A	Mobile phase B	Mobile phase C
Citric acid	19.80	22.00	6.10
Monohydrate Sodium citrate	6.19	7.74	26.67
Dihydrate Sodium chloride	5.66	7.07	54.35
Ethanol (99.5)	260.0 mL	20.0 mL	-
Benzyl alcohol	-	-	5.0 mL
Thiodiglycol	5.0 mL	5.0 mL	
Lauromacrogol Solution (1 in 4)	4.0 mL	4.0 mL	4.0 mL
Caprylic acid	0.1 mL	0.1 mL	0.1 mL
Water	A sufficient quantity	A sufficient quantity	A sufficient quantity
Total volume	2000 mL	1000 mL	1000 mL
pH	3.3	3.2	4.9

Mobile phase flow rate: About 0.26 mL/min.
Reaction TS flow rate: About 0.3 mL/min.
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; asparaginic acid, threonine, serine, glutamic acid, proline, glycine, alanine, valine, cystine, methionine, isoleucine, leucine, tyrosine, phenylalanine, lysine, hystidine and arginine are eluted in this order, and the resolutions between threonine and serine, between glycine and alanine, and between isoleucine and leucine are NLT 1.5, 1.4 and 1.2, respectively.

System repeatability: Repeat the test 3 times with 20 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of asparaginic acid, proline, valine and arginine are NMT 2.0%, respectively.

Reaction TS—Mix 407 g of lithium acetate dihydrate, 245 mL of acetic acid(100) and 801 mL of 1-methoxy-2-propanol, add water to make 2000 mL, then stir to mix while passing nitrogen for at least 10 minutes, use the resulting solution as solution A. Separately add 77 g of ninhydrin and 0.134 g of sodium borohydride in 1957 mL of 1-methoxy-2-propanol and stir to mix while passing nitrogen for about 30 minutes, and use the resulting solution as solution B. Mix solution A and solution B when using.

Purity (1) ***Acetic acid***—Weigh accurately about 15 mg of Oxytocin, dissolve in internal standard solution to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately about 1 g of acetic acid(100), dissolve in internal standard solution to make exactly 100 mL. Pipet 2 mL of the resulting solution, add the internal standard solution to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S of the peak area of oxytocin to that of the internal standard; the amount of acetic acid is between 6.0% and 10.0%.

$$\text{Content (\%) of acetic acid } (CH_3COOH)\ (\%) = \frac{Q_T}{Q_S} \times \frac{W_S}{W_T} \times \frac{1}{10}$$

W_S: Amount (mg) of acetic acid(100) taken
W_T: Amount (mg) of Oxytocin taken

Internal standard solution—A solution of propionic acid in the mobile phase (1 in 10000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Add 900 mL of water to 0.7 mL of phosphoric acid, adjust the pH to 3.0 with 8 mol/L sodium hydroxide TS, then add water to make 1000 mL. Add 50 mL of methanol to 950 mL of this solution.

Flow rate: Adjust the flow rate so that the retention time of acetic acid is about 3 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; acetic acid and propionic acid are eluted in this order with the resolution being NLT 14.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of acetic acid to those the internal standard is NMT 2.0%.

(2) ***Related substances***—Dissolve 25 mg of Oxytocin in 100 mL of mobile phase A and use this solution as the test solution. Perform the test with 50 μL of the test solution as directed under the Liquid Chromatography according to the following conditions, measure the individual peak areas according to the automatic integration

method, and find the individual peak areas according to the percentage peak area method; the amount of the each peak other than oxytocin is NMT 1.5%. The sum of the peaks other than oxytocin is NMT 5.0%.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed under the Operating conditions under the Assay.

System suitability

Test for required detectability: Pipet 1 mL of the test solution, add the mobile phase to make exactly 100 mL, and use this solution as the system suitability solution. Pipet 1.0 mL of this solution and add the mobile phase A to make exactly 10 mL. Confirm the peak area of oxytocin obtained from 50 mL of this solution is between 5% and 15% of the peak area of oxytocin obtained from the system suitability solution.

System performance: Take a sufficient amount of Oxytocin and vasopressin and dissolve in mobile phase A to prepare solutions containing 0.1 mg per mL each. Proceed with 50 μL of these solutions according to the above operating conditions; vasopressin and oxytocin are eluted in this order with the resolution being NLT 14 and the symmetry factor of the oxytocin peaks is NMT 1.5.

System repeatability: Repeat the test 6 times with 50 μL of the system suitability solution according to the above conditions; the relative standard deviation of the ratios of the peak area of oxytocin is NMT 2.0%.

Time span of measurement: About 2.5 times the retention time of oxytocin.

Water NMT 5.0% (50 mg, coulometric titration).

Assay Weigh accurately an amount of Oxytocin, equivalent to about 13000 units, add the mobile phase A to make exactly 100 mL, and use this solution as the test solution. Separately, dissolve 1 vial of oxytocin RS in the mobile phase A to make a clear solution containing about 130 units per mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of oxytocin from each solution.

$$\text{Number of units in 1 mg of Oxytocin, calculated on the anhydrous and acetic acid-free basis} = \frac{A_T}{A_S} \times \frac{W_S}{W_T} \times 100$$

W_S: Number of units in 1 mL of the standard solution

W_T: Amount (mg) of Oxytocin taken, calculated on the anhydrous and acetic acid-free basis

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: Dissolve 15.6 g of Sodium phosphate dibasic, dihydrate in 1000 mL of water.

Mobile phase B: A mixture of water and acetonitrile (1 : 1).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 30	70 →40	30 →60
30 - 30.1	40→70	60 →30
30.1 - 45	70	30

Flow rate: 1.0 mL/min

System suitability

System performance: Take a sufficient amount of Oxytocin and vasopressin and dissolve in mobile phase A to prepare solutions containing 0.1 g per mL each. Proceed with 25 μL of these solutions according to the above operating conditions; vasopressin and oxytocin are eluted in this order with the resolution being NLT 14 and the symmetry factor of the oxytocin peaks is NMT 1.5.

System repeatability: Repeat the test 6 times with 25 μL of the standard solution according to the above conditions; the relative standard deviation of the peak areas of oxytocin is NMT 1.0%.

Packaging and storage Preserve in tight containers at a temperature at 2 to 8 °C.

Oxytocin Injection
옥시토신 주사액

Oxytocin Injection is an aqueous injection and contains NLT 90.0% and NMT 110.0% of the oxytocin units as labeled.

Method of preparation Prepare as directed under injections, with synthesized Oxytocin.

Description Oxytocin Injection occurs as a clear, colorless liquid.

pH Between 2.5 and 4.5.

Sterility It meets the requirements when tested according to the membrane filtration method.

Bacterial endotoxins Less than 10 EU per 1 unit of oxytocin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Take an appropriate amount of Oxytocin Injection according to the labeling unit, and add the diluent to prepare a solution containing about 1 unit per mL. Use this solution as the test solution. Separately, dissolve 1 vial of oxytocin RS in mobile phase A to make exactly 20 mL. Take an appropriate amount of this solution, and add the diluent to prepare a solution containing about 1 unit per mL. Use this solution as the standard solution. Perform the test with 100 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area, A_T and A_S of oxytocin from each of the solutions.

$$\text{Number of units per mL of Oxytocin Injection} = W_S \times \frac{A_T}{A_S} \times \frac{b}{a}$$

W_S: Number of units per mL of the standard solution

a: Amount (mL) of Oxytocin Injection taken

b: Total volume (mL) after adding diluent to prepare the test solution

Diluent—Dissolve 5 g of chlorobutanol, 1.1 g of sodium acetate trihydrate, 5 g of acetic acid(100) and 6 mL of ethanol(95) in water to make 1000 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: Dissolve 15.6 g of sodium dihydrogen phosphate dihydrate in 1000 mL of water.

Mobile phase B: A mixture of water and acetonitrile (1 : 1).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 30	70 → 40	30 → 60
30 - 30.1	40 → 70	60 → 30
30.1 - 45	70	30

Flow rate: 1.0 mL/min

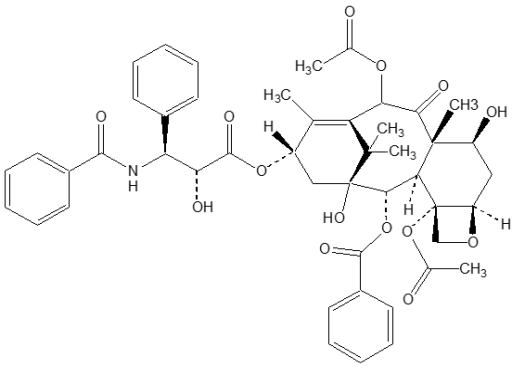
System suitability

System performance: Weigh an appropriate amount of oxytocin and vasopressin and dissolve in mobile phase A to prepare a solution containing 20 μg per mL, respectively. Proceed with 100 μL of this solution under the above operating conditions; vasopressin and oxytocin are eluted in this order with the resolution being NLT 14, and the symmetry factor of oxytocin is NMT 1.5.

System repeatability: Repeat the test 6 times with 100 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of oxytocin is NMT 2.0%.

Packaging and storage Preserve in hermetic containers in a cold place, avoiding freezing.

Paclitaxel
파클리탁셀



$C_{47}H_{51}NO_{14}$: 853.91

(1*S*,2*S*,3*R*,4*S*,7*R*,9*S*,10*S*,12*R*,15*S*)-4,12-*bis*(acetyloxy)-1,9-dihydroxy-15-{[(2*R*,3*S*)-2-hydroxy-3-phenyl-3-(phenylformamido)propanoyl]oxy}-10,14,17,17-tetramethyl-11-oxo-6-oxatetracyclo[11.3.1.0^{3,10}.0^{4,7}]heptadec-13-en-2-yl benzoate [*33069-62-4*]

Paclitaxel contains NLT 97.0% and not more 102.0% of paclitaxel ($C_{47}H_{51}NO_{14}$), calculated on the anhydrous basis and solvent-free basis.

Description Paclitaxel occurs as a white powder.
It is soluble in ethanol(95) and practically insoluble in water.

Identification (1) Determine the infrared spectra of Paclitaxel and paclitaxel RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Optical rotation $[\alpha]_D^{20}$: Between -49.0° and -55.0° (0.2

g calculated on the anhydrous basis, methanol, 20 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Paclitaxel according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—(i) If it is indicated as being dissociated from a natural product, weigh accurately about 10 mg of Paclitaxel, add a mixture of methanol and acetic acid(100) (200:1). And if necessary, sonicate to dissolve, make exactly 10 mL, and use this solution as the test solution. Perform the test with 15 μL of the test solution as directed under the Liquid Chromatography according to the following conditions, and determine the content (%) of each related substance; the amounts (%) of related substances in Table 1 are not greater than the amounts in Table 1, the amount of each related substance is NMT 0.1%, and the amount of total related substances is NMT 2.0%.

$$\text{Content (\%) of each related substance} = 100 \times \frac{FA_{\text{i}}}{A_U}$$

F: Relative correction factor for the peak of each related substance

(See Table 1)

A_{i}: Peak area of each related substance

A_{u}: Peak area of paclitaxel

Table 1

Relative retention Time	Relative correction factor(F)	Name	Limit (%)
0.24	1.29	Baccatine III	0.2
0.53	1.00	10-deacetylpaclitaxel	0.5
0.57	1.00	7-xylosil paclitaxel	0.2
0.78	1.26	Cephalomannine (Paclitaxel related substance I)	a_1[1]
0.78	1.26	2",3"-dehydrocephalomannin	a_2[1]
0.86	1.00	10-deacetyl-7-epipaclitaxel (paclitaxel related substance II)	0.5
1.10	1.00	Benzyl analogue[3]	b_1[2]
1.10	1.00	3",4"-dehydropaclitaxel C	b_2[2]
1.40	1.00	7-epicephalomannine	0.3
1.85	1.00	7-epipaclitaxel	0.5

[1] Depending on the relative amounts present, separation of these peaks may be incomplete. The sum of a_1 and a_2 is NMT 0.5%.

[2] Depending on the relative amounts present, separation of these peaks may be incomplete. The sum of b_1 and b_2 is NMT 0.5%.

[3] This related substance is identified as (2*R*,3*S*)-2-hydroxy-3-phenyl-3-(2-phenylacetylamino) propanoic acid ester at position 13 of baccatin III.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 227 nm).

Column: A stainless-steel column with about 4.6 mm in internal diameter and 25 cm in length, packed with pentafluorophenyl propyl silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: Acetonitrile

Mobile phase B: Water

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 35	35	65
35 - 60	35 → 80	65 → 20
60 - 70	80 → 35	20 → 65
70 - 80	35	65

Flow rate: 2.6 mL/min

System suitability

System performance: Weigh 10 mg each of paclitaxel related substances I (cephalomannine) RS and paclitaxel related substance II (10-deacetyl-7-epipaclitaxel) RS, and dissolve in methanol to make 100 mL. Take 5 mL of this solution and add methanol to make 50 mL. Then, to 5.0 mL of this solution, add a mixture of methanol and acetic acid(100) (200:1) to make 50 mL. Proceed with 15 μL of this solution according to the above operating conditions; the relative retention time for the peaks of paclitaxel related substance I and paclitaxel related substance II are about 0.78 and 0.86, respectively with the resolution between these peaks being NLT 1.0.

System repeatability: Weigh about 10 mg of paclitaxel RS, add a mixture of methanol and acetic acid(100) (200:1), if necessary, sonicate to dissolve, and make 100 mL. Pipet 5 mL of this solution, add a mixture of methanol and acetic acid(100) (200 : 1) to make 100 mL. Repeat the test 5 times with 15 μL each of this solution; the relative standard deviation of the peak areas of the paclitaxel is NMT 2.0%.

(ii) If it is indicated as being manufactured through a semi-synthetic process, weigh about 10 mg of Paclitaxel, add a mixture of methanol and acetic acid(100) (200:1), if necessary, sonicate to dissolve, make exactly 10 mL, and use this solution as the test solution. Take 15 μL each of the mixture of methanol and acetic acid(100) (200:1) and the test solution, and perform the test as directed under the Liquid Chromatography, determine the content (%) of each related substance excluding all peaks obtained from the mixture of methanol and acetic acid(100) (200:1); the amounts (%) of related sub-

stances in Table 2 are not greater than the amounts in Table 2, the amount of each related substance is NMT 0.1%, and the amount of total related substances is NMT 2.0%.

$$\text{Content (\%) of each related substance} = 100 \times \frac{FA_i}{A_S}$$

F: Relative correction factor for the peak of each related substance

(See Table 2)

A_i: Peak area of each related substance

A_S: Total area of all peaks obtained from the test solution

Table 2

Relative retention time	Relative correction factor (F)	Name	Limit (%)
0.11	1.24	10-deacetylbaccatine III	0.1
0.20	1.29	Baccatine III	0.2
0.42	1.39	Photodegradation product[2]	0.1
0.47	1.00	10-deacetylpaclitaxel	0.5
0.80	1.00	2-devenzoyl paclitaxel-2-pentenoate	0.7
0.92[1]	1.00	Oxetane ring, acetyl and benzoyl[2]	x_1
0.92[1]	1.00	10-acetoacetylpaclitaxel	x_2
0.94[1]	1.00	10-deacetyl-7-epipaclitaxel (paclitaxel related substances II)	x_3
1.37	1.00	7-epipaclitaxel	0.4
1.45	1.00	10,13-bis side chain paclitaxel[2]	0.5
1.54	1.00	7-acetylpaclitaxel	0.6
1.80	1.75	13-tes-baccatine III	0.1
2.14	1.00	7-tes-paclitaxel	0.3

[1] Depending on the relative amounts present, separation of these peaks may be incomplete. The sum of x_1, x_2 and x_3 is NMT 0.4%.

[2] The chemical names of these related substances are as follows:

Photodegradation product: (1*R*,2*R*,4*S*,5*S*,7*R*,10*S*,11*R*,12*S*,13*S*,15*S*,16*S*)-2-10-diacetyloxy-5,13-hydroxy-4,16,17,17-tetramethyl-8-oxa-3-oxo-12-phenylcarbonyloxypentacyclo [11.3.1.0.^{1,11}.O^{4,11}.O^{7,10}] heptadec-15-yl (2*R*,3*S*)-2-hydroxy-3-phenyl-3-(phenylcarbonylamino) propanoate

Oxetane ring, acetyl and benzoyl group transfer: (1*S*,2*S*,3*R*,4*S*,5*S*,7*R*,8*S*,10*R*,13*S*)-5-10-diacetyloxy-1,2,4,7-tetrahydroxy-8,12,15,15-tetramethyl-9-oxo-4-(phenylcarbonyloxymethyl) tricyclo [9.3.1.0.^{3,8}] pentadec-11-en-13-yl (2*R*,3*S*)-2-hydroxy-3-phenyl-3-(phenylcarbonylamino) propanoate

10,13-bis side chain paclitaxel: (2*R*,3*S*)-2-hydroxy-3-phenyl-3-(phenylcarbonylamino) propanoic acid esters at position 13 of baccatin III and (2*R*,3*S*)-2-hydroxy-3-phenyl-3-(phenylcarbonylamino) propanoic acid esters at position 10 of baccatin III

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 227 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: A mixture of water and acetonitrile (3 : 2).

Mobile phase B: Acetonitrile

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 20	100	0
20 - 60	100 → 10	0 → 90
60 - 62	10 → 100	90 → 0
72 - 70	100	0

Flow rate: About 1.2 mL/min

System suitability

System performance: Weigh 96 mg of paclitaxel RS, add a mixture of methanol and acetic acid(100) (200 : 1), shake to dissolve, make exactly 10 mL, and use this solution as the standard solution (1). Weigh 8 mg of paclitaxel related substances II RS, add a mixture of methanol and acetic acid(100) (200 : 1), shake to dissolve, make exactly 100 mL, and use this solution as the standard solution (2). Take 5.0 mL each of standard solution (1) and standard solution (2), add a mixture of methanol and acetic acid(100) (200:1) to make exactly 50 mL, and use this solution as the system suitability solution. Proceed with 15 μL of this solution according to the above operating conditions; the relative retention time of the peaks of paclitaxel related substance II and paclitaxel are about 0.94 and 1.0, respectively, with the resolution between these peaks being NLT 1.2.

System repeatability: Repeat the test 5 times with 15 μL each of the system suitability solution according to the above conditions; the relative standard deviation of the peak areas of paclitaxel is NMT 2.0%.

Water NMT 4.0% (0.1 g, coulometric titration).

Residue on ignition NMT 0.2% (1 g).

Microbiological examination of non-sterile products The total aerobic microbial count is NMT 100 CFU and the total combined yeasts/molds count is NMT 100 CFU per g of Paclitaxel. Also, *Escherichia coli*, *Salmonella*, *Pseudomonas aeruginosa* and *Staphylococcus* aureus are

not detected.

Bacterial endotoxins Paclitaxel contains less than 0.4 EU/mg of bacterial endotoxins.

Assay Weigh accurately about 10 mg each of Paclitaxel and paclitaxel RS, add a mixture of methanol and acetic acid(100) (200 : 1) each, if necessary, sonicate to dissolve, make exactly 10 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with exactly 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of paclitaxel from each solution.

$$\text{Amount (mg) of paclitaxel } (C_{47}H_{51}NO_{14}) = \text{Amount (mg) of paclitaxel RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 227 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 25 cm in length, packed with pentafluorophenyl propyl silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of water and acetonitrile (11 : 9).

Flow rate: 1.5 mL/min

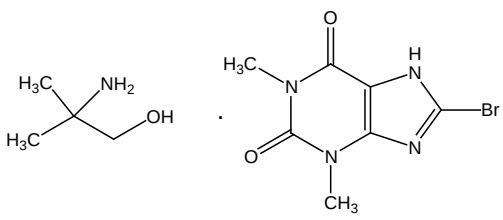
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the symmetry factor for paclitaxel peak is NLT 0.7 and NMT 1.3.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of paclitaxel is NMT 1.5%.

Packaging and storage Preserve in light-resistant, tight containers at 20 to 25 ℃.

Pamabrom
파마브롬



$C_{11}H_{18}BrN_5O_3$: 348.20

2-Amino-2-methylpropan-1-ol ; 8-bromo-1,3-dimethyl-7*H*-purine-2,6-dione [*606-04-2*]

Pamabrom contains NLT 72.2% and NMT 76.6% of 8-bromotheophylline ($C_7H_7BrN_4O_2$) and NLT 24.6% and NMT 26.6% of 2-amino-2-methyl-1-propanol ($C_4H_{11}NO$), calculated on the anhydrous basis.

Description Pamabrom occurs as a white powder.
It is sparingly soluble in water.

Identification Weigh 25 mg of Pamabrom, dissolve in 25 mL of water while shaking, add methanol while mixing to make exactly 100 mL; and use this solution as the test solution. Separately, weigh 20 mg of 8-bromotheophylline RS, add 25 mL of water, 50 mL of methanol and a small amount of dilute ammonia TS, shake gently to dissolve, add methanol to make 100 mL; and use this solution as the standard solution. Spot 10 μL each of the test solution and the standard solution onto a plate made of silica gel with fluorescent indicator for thin-layer chromatography, develop the plate with a mixture of xylene, methanol and acetic acid(100) (11 : 2 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the R_f values of the principal spots obtained from the test solution and the standard solution are the same.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Pamabrom according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Theophylline***—Weigh accurately about 0.2 g of Pamabrom, add 50 mL of a mixture of water and methanol (70 : 30), sonicate for 5 minutes to dissolve. After cooling, add a mixture of water and methanol (70 : 30) to make exactly 200 mL, and use this solution as the test solution. Weigh accurately about 0.1 g of theophylline RS, add a mixture of water and methanol (70 : 30), shake to dissolve, add 3 drops of ammonia water(28), and add a mixture of water and methanol (70 : 30) to make exactly 100 mL. Pipet 1.0 mL of this solution, add a mixture of water and methanol (70 : 30) to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the conditions under the Assay, and determine the peak areas, A_T and A_S, of theophylline from each solution, respectively (NMT 0.5%).

$$\text{Content (\%) of theophylline} = 20 \times \frac{C}{W} \times \frac{A_T}{A_S}$$

C: Concentration (μg/mL) of theophylline RS in the standard solution

W: Amount (mg) of sample taken

Water NMT 3.0% (1.0 g, volumetric titration, direct titration).

Assay (1) ***8-vromotheophylline***—Weigh accurately about 0.2 g of Pamabrom, add 50 mL of a mixture of water and methanol (70 : 30) and 2 drops of ammonia

water(28), sonicate for 5 minutes to dissolve. After cooling, add a mixture of water and methanol (70 : 30) to make exactly 200 mL. To 5.0 mL of this solution, add 10.0 mL of the internal standard solution and the mobile phase to make exactly 100 mL, filter, and use this filtrate as the test solution. Weigh accurately about 75 mg of 8-bromotheophylline RS, add a mixture of water and methanol (70 : 30), shake to dissolve, add 2 drops of ammonia water(28), and add a mixture of water and methanol (70 : 30) to make exactly 100 mL. To 5.0 mL of this solution, add 10.0 mL of the internal standard solution and the mobile phase to make exactly 100 mL, filter and use this filtrate as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of peak area of 8-bromotheophylline to that of the internal standard from each solution.

$$\text{Amount of 8-bromotheophylline } (C_7H_7BrN_4O_2) \text{ (mg)} = 4000 \times C \times \frac{Q_T}{Q_S}$$

C: Concentration of 8-bromotheophylline RS in the standard solution (mg/mL)

Internal standard solution—Weigh about 12.5 mg of caffeine, add a mixture of water and methanol (70 : 30) to make exactly 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm - 10 μm in particle diameter).

Mobile phase: A mixture of water, methanol and acetic acid(100) (69 : 30 : 1).

System suitability

System performance: Proceed with 20 μL of the standard solution under the above operating conditions; the relative retention times of caffeine and 8-bromotheophylline are about 0.6 and 1.0, and the resolution is NLT 2.0.

System repeatability: Repeat the test 5 times with 20 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of 8-bromotheophylline is NMT 2.0%.

(2) ***2-amino-2-methyl-1-propanol***—Weigh accurately about 1 g of Pamabrom, add 10 mL of water, and gently heat on a steam bath until completely dissolved. Cool it down and titrate with 0.5 mol/L hydrochloric acid VS (indicator: methyl orange TS) Separately, perform a blank test and make any necessary correction.

Each mL of 0.5 mol/L hydrochloric acid VS
= 44.57 mg of $C_4H_{11}NO$

Packaging and storage Preserve in well-closed containers.

Pancreas
판크레아스

Pancreas is prepared from pancreas of *Sus scrofa* Linné *var. domesticus* Gray (*Suidae*), and contains NLT 1.55 FIP units/mg of protein digestion activity, NLT 18.62 FIP units/mg of starch digestive activity and NLT 38 FIP units/mg of fat digestion activity.

Description Pancreas occurs as a milky white amorphous powder and has a slight characteristic odor.

Identification Perform the test as direct under the Assay; the result is positive.

Loss on drying NMT 2.0% (1 g, phosphorus pentoxide, 80°C, 4 hours).

Assay (1) ***Fat digestion activity***—Weigh accurately an amount of Pancreas, equivalent to about 500 FIP, put it in a mortar, add 1 mL of cold buffer solution for lipase suspension, and grind well to mix. Then quantitatively put it in a 200-mL volumetric flask, wash the mortar using cold buffer solution for lipase suspension, and combine the washings to the solution in the flask. Make a very fine suspension, fill it up to the gauge line with cold buffer solution for lipase suspension, mix well to dilute. After about 10 minutes, place the flask in iced water and use it for the quantitative test. Separately, weigh accurately an amount of lipase RS, equivalent to about 500.0 FIP, (for reference standards stored in the refrigerator, first allow them to reach room temperature, and then open the package), put them in a mortar, proceed them in the same manner as the test solution, and use this solution as the standard solution. Put 29.5 mL of the substrate solution in a 100-mL beaker, warm to 37 ℃ in a thermostat at 37 ± 0.1°C. Set up a beaker with a pH meter whose pH has been previously adjusted with a standard buffer solution, a stirrer, and a micro buret containing 0.1 mol/L sodium hydroxide. While stirring with a stirrer, adjust pH to 9.0 with 0.1 mol/L sodium hydroxide, then add 0.5 mL of standard lipase solution, previously mixed well. After exactly 1 minute with a stopwatch, determine the volume (mL) of 0.1 mol/L sodium hydroxide consumed. Test multiple times to obtain an average volume(mL) consumed (S). The average volume(mL) consumed is about 0.12 mL. Proceed with the potency of the lipase in the test solution in the same way as the standard lipase solution. In the case of potency, if the volume(mL) of 0.1 mol/L sodium hydroxide consumed from the test solution is not the same as that of the standard lipase solution, dilute the test solution or make the test solution again to make it the same, and determine the volume(mL) of 0.1 mol/L sodium hydroxide consumed (M).

Fat digestion activity (FIP unit/mg)
= Potency of the lipase RS (FIP unit/mg)
$$\times \frac{M}{S} \times \frac{G_s}{G_m}$$

G_s: Amount (mg) of lipase RS
G_m: Amount (mg) of the sample

Definition of FIP units—Under the conditions described in the above procedure, one unit is the amount of enzymes that releases 1 μmole of fatty acid per minute at 37°C and pH 9.0.

(2) ***Starch digestive activity***—Weigh accurately about 0.5 g of Pancreas, put it in a mortar, wash the container well with 0.2 mol/L phosphate buffer (pH 6.8, 0 5 °C), and put the washings into a volumetric flask. Place the volumetric flask in an ice water bath, fill up to the gauge line and mix. Dilute this solution again with cooled 0.2 mol/L phosphate buffer solution to make about 10 FIP units/mL. Perform a potency test after about 10 minutes using this solution as the test solution. Put 25.0 mL of substrate solution in a test tube (22 mm × 200 mm), add 10 mL of 0.2 mol/L phosphate buffer solution and 1 mL of 0.2 mol/L sodium chloride solution, and allow it to stand in a thermostat at 25 °C. When the substrate solution reaches 25 °C, add 1.0 mL of the test solution and mix. After exactly 10 minutes (use a stopwatch), wash the test tube with 2 mL of 1 mol/L hydrochloric acid, combine the washings with the solution, and add 10 mL of 0.05 mol/L iodine and 45 mL of 0.1 mol/L sodium hydroxide while stirring. Allow to stand in a dark place for 15 minutes, then add 4 mL of 20% sulfuric acid, and titrate with 0.1 mol/L sodium thiosulfate VS. Perform a blank test in the same manner and make any necessary correction.

Starch digestive activity (FIP unit/mg)
$$= \frac{5(V_b - B_m)}{[1 - 0.03(V_b - B_m)] \times G_m}$$

V_m: volume(mL) of 0.1 mol/L sodium thiosulfate solution consumed in the test solution.
V_b: volume(mL) of 0.1 mol/L sodium thiosulfate solution consumed in the control solution.
G_m: Amount of the sample (mg)

Definition of FIP unit—Under the conditions described in the above procedure, one unit is the amount of enzymes that is required to hydrolyze 1 μmol of glycosidic bond per minute.

(3) ***Protein digestion activity***—Weigh accurately about 0.1 g of Pancreas, grind it with the cooled calcium chloride solution in a mortar, and add it quantitatively to a 100-mL volumetric flask. Wash the mortar with the calcium chloride solution, combine the washings to make 100 mL, use the solution as the test solution, and mark it as P. Separately, weigh accurately about 0.1 g of protease RS and proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution.

(i) Free protease: Dilute the test solution (P) with buffer solution to a potency equivalent to the standard solution and mark it as P_1.

(ii) Total protease: Take 10.0 mL of the test solution, add 10 mL of enterokinase solution, activate at 35 °C for 90 minutes, dilute to a potency equivalent to the standard solution, and mark it as P_2. Label two test tubes for the standard solution as S_1, S_2, and S_3, and label two test tubes for the control solution as S_1B, S_2B, and S_3B. Also, label two test tubes with the test solution as P and two test tubes with a control solution as PB.
Add 2.0 mL of the buffer solution into the test tube S_1 and 1.0 mL of the buffer solution into the test tubes S_2 and P, respectively.
Put 1.0 mL of the standard solution into the test tube S_1, 2.0 mL into the test tube S_2, and 3.0 mL into the test tube S_3, and put 2.0 mL of the test solution into the test tube P, respectively. In the same way, fill the control test tubes S_1B, S_2B, S_3B and PB, respectively. Then add 5.0 mL of trichloroacetic acid solution into the control test tubes, and shake to mix. Place all test tubes on a steam bath at 35 °C, add 2 mL of substrate solution to the control test tube, and mix. Stop the reaction by adding 2 mL of the substrate solution, previously warmed on a steam bath, to test tubes S_1, S_2, S_3, and P, respectively, at precise time intervals and mixing. Take each test tube out of the water bath, allow them to stand at room temperature for 20 minutes, and filter the content of two test tubes each using the same type of filter paper. Make sure the filtrate is free from bubbles and test it as directed under the Ultraviolet-visible Spectroscopy using test tube B as the control tube, and determine the absorbance at a layer length of 10 mm and a wavelength of 275 nm. For test tube B, add 5.0 mL of trichloroacetic acid to 3 mL of buffer solution, and proceed in the same manner.
Create a calibration curve from the absorbance for the concentration of each standard solution. At this time, the absorbance should be between 0.150 and 0.600. Obtain the concentration of the test solution from the plotted calibration curve.

Protein digestion activity (FIP unit/mg)
= Potency of the protease RS (FIP unit/mg)
$$\times \frac{V_m \times a}{G_m}$$

V_m: Dilution factor of the sample
a: Amount of sample obtained from the calibration curve (mg)
G_m: Amount of the sample (mg)

Definition of potency—Under the above test conditions, one unit is the amount of enzymes that releases the peptide from casein to produce an absorbance equivalent to 1 μmol of tyrosine at 275 nm per minute.

Adjustment of filter paper (for the Assay for protein

digestion activity)—Filter 5 mL of trichloroacetic acid through filter paper, and using the filtrate as the test solution and the unfiltered trichloroacetic acid as the control solution, determine the absorbance at a wavelength of 280 nm as directed under the Ultraviolet-visible Spectroscopy; it can be used if the absorbance is less than 0.04.

Packaging and storage Preserve in well-closed containers.

Pancreatin
판크레아틴

Pancreatin is an enzyme mainly prepared from pancreas of *Sus scrofa* Linné *var. domesticus* Gray (*Suidae*), and has starch digestive activity, protein digestive activity and fat digestion activity. Pancreatin contains NLT 90.0% of digestive activity units of the labeled amount. It is typically diluted with suitable diluents.

Description Pancreatin occurs as a white to pale yellow or pale yellowish brown powder and has a characteristic odor.

Identification Perform the test according to the Assay; Pancreatin shows a positive reaction.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Pancreatin according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 2.0 g of Pancreatin according to Method 2 and perform the test (NMT 1 ppm).

(3) ***Fats***—To 1.0 g of Pancreatin, add 20 mL of ether, shake occasionally to mix, extract for 30 minutes, and filter. Wash the residue with 10 mL of ether, combine the filtrate and the washings, evaporate ether, and dry the residue at 105℃ for 2 hours; the amount of the residue is NMT 20 mg.

Loss on drying NMT 4.0% (1 g, in vacuum, phosphorus pentoxide, 24 hours).

Residue on ignition NMT 5.0% (1 g).

Assay (1) ***Assay for amylase activity***—(i) Test solution: Dissolve Pancreatin in water cooled with ice, adjust to contain 0.4 units/mL to 0.8 units/mL of starch saccharifying activity, and use this solution as the test solution.

(ii) Substrate solution: Use potato starch solution TS for starch digestibility test. Add 10 mL of the phosphate buffer solution for pancreatin instead of 10 mL of 1 mol/L acetic acid-sodium acetate buffer solution, pH 5.0.

(iii) Procedure: Proceed as directed in (1) starch saccharifying activity test of the Starch digestibility test under the Digestive Power

(2) ***Assay for protein digestive activity***—(i) Test solution: Dissolve Pancreatin in an appropriate amount of water cooled with ice, adjust to contain 15 units/mL to 25 units/mL of protein digestive activity, and use this solution as the test solution.

(ii) Substrate solution: Use the substrate solution 2 in the Assay for the Protein digestive activity under the Digestion test. However, adjust the pH of solution to 8.5.

(iii) Procedure: Proceed as directed under the Assay for the Protein digestive activity under the Digestion test. However, use trichloroacetic acid B as the precipitation TS.

(3) ***Assay for fat digestive activity***—(i) Test solution: Dissolve Pancreatin in an appropriate amount of water cooled with ice, adjust to contain 1 unit/mL to 5 units/mL of fat digestive activity, and use this solution as the test solution.

(ii) Emulsifier: Prepare with 18 g of polyvinyl alcohol I and 2 g of polyvinyl alcohol II according to the Fat digestive activity under the Digestion test.

(iii) Substrate solution: Prepare the substrate solution according to the Fat digestive activity under the Digestion test.

(iv) Procedure: Proceed according to the Fat digestive activity as directed under the Digestion test. Prepare the buffer solution with phosphate buffer solution of pH 8.0.

Packaging and storage Preserve in tight containers and store at below 30℃.

Pancreatin II
판크레아틴II

Pancreatin II is obtained from the pancreas of pigs (*Sus scrofa* Linné *var. domesticus* Gray, in the *Suidae* family) or cattle (*Bos taurus* Linné, in the *Bovidae* family), and contains NLT 20,000 FIP units of starch digestibility, 35,000 FIP units of fat digestion activity, and 2,000 FIP units of protein digestion activity per g.

Description Pancreatin II occurs as a white to pale yellow powder. It has a characteristic odor.

Identification Perform the test with Pancreatin II as directed in the potency test; the result is positive.

Loss on drying NMT 5%.

Fat To 1 g of Pancreatin II, add 20 mL of ether, and mix occasionally. After extracting for about 30 minutes, filter. Wash with 10 mL of ether, combine filtrate and washings, evaporate ether to dryness, and dry the residue at 105 ℃ for 2 hours; the amount is NMT 30 mg (NMT 3%).

Microbiological examination of non-sterile products When tested with 10 g of Pancreatin II as directed under

the Microbiological Examination of Non-sterile Products, *Salmonella* bacteria is not detected.

Potency test (1) ***Starch digestibility test***—Weigh accurately 300 mg of Pancreatin II, transfer to a 500-mL volumetric flask, and shake to mix well. Add 0.2 mol/L phosphate buffer solution to the gauge line, mix at room temperature with a magnetic stirrer for 20 minutes, and filter. Use the filtrate as the test solution. Immediately, proceed to the next procedure. To each of 4 Erlenmeyer flasks, add 25 mL of 1% soluble starch solution, 10 mL of 0.2 mol/L phosphate buffer solution (pH 6.8), and 1 mL of 0.2 mol/L sodium chloride solution, mix, and allow to stand on a steam bath at 25 ± 0.1 ℃ for 10 minutes. To each of 2 Erlenmeyer flasks, add 1.0 mL each of the test solution at 1 minute interval, and exactly after 10 minutes, add 2 mL of hydrochloric acid to stop the reaction. Add 10 mL of 0.05 mol/L iodine, immediately add 45 mL of 0.1 mol/L sodium hydroxide, close the stopper, and allow to stand in the dark for 15 minutes. Add 4 mL of 20% sulfuric acid, and titrate 0.1 mol/L sodium thiosulfate VS. To the remaining 2 Erlenmeyer flasks, previously add 2 mL of 1 mol/L hydrochloric acid solution, add 1.0 mL each of the test solution at 1 minute interval, and proceed as described above.

$$\text{Starch digestibility of 1 g of Pancreatin II (FIP unit)} = 500 \times [5(V_B - V_L) - 0.006] \times \frac{1}{\text{amount (g) of sample taken}}$$

V_L: Average volume (mL) of 0.1 mol/L sodium thiosulfate consumed in the test solution

V_B: Average volume (mL) of 0.1 mol/L sodium thiosulfate consumed to the blank test

500: Dilution factor of the test solution

5: 50/10 (50: μmol of glucoside binding corresponding to 1 mL of 0.05 mol/L I_2 solution, 10: elapsed time (minutes))

(2) ***Fat digestion activity***—Weigh accurately about 25 mg of lipase RS for pancreatin assay (corresponding to about 1000 FIP units of fat digestion activity), grind with a small amount of water using a cold mortar to make a powder, and add water to the gauge line (preserve at 0 ℃). Weigh accurately about 25 mg of Pancreatin II, proceed in the same manner as the standard solution below, and use this solution as the test solution (preserve at 0 ℃). Immediately, proceed to the next procedure. To 250-mL beaker, add 25 mL of olive oil emulsion, 20 mL of tris buffer solution, 5 mL of 8% sodium taurocholate solution, and 22.5 mL of water in this order, mix with stirrer on a steam bath at 37 ± 0.1 ℃, and allow to stand for isothermal solution. Add 0.1 mol/L sodium hydroxide to adjust the pH to exactly 9.0, add 5.0 mL of the test solution or the standard solution, and titrate with 0.1 mol/L sodium hydroxide VS exactly for 5 minutes until the pH of the solution becomes 9.0.

$$\text{Fat digestion activity of 1 g of Pancreatin II (FIP unit)} = \text{Potency (FIP unit/g) of lipase RS} \times \frac{V_T}{T_S} \times \frac{Amount\ (mg)\ of\ RS}{Amount\ (mg)\ of\ sample}$$

V_T: Volume (mL) of 0.1 mol/L sodium thiosulfate consumed in the test solution

V_S: Volume (mL) of 0.1 mol/L sodium thiosulfate consumed to the standard solution

(3) ***Protein digestion activity***—Weigh accurately about 25 mg of protease RS for pancreatin assay (corresponding to about 75 FIP units of protein digestion activity), add cold 0.02 mol/L calcium chloride solution to make 25 mL, take 4.0 mL of this solution, and add pH 7.5 borate buffer solution to make 100 mL. Use this solution as the standard solution [0.040 mg (0.0660 FIP units) /mL] (storage: prepare at 0 ℃ in an ice bath and use within 1 hour). Weigh accurately 100 mg of Pancreatin II, and add 0.02 mol/L calcium chloride solution to make 100 mL. Add 10.0 mL of the above solution to the 50-mL Erlenmeyer flask, add 10 mL of enterokinase solution, close the stopper, and activate for 15 minutes by shaking to mix with a magnetic stirrer on a steam bath at 35 ± 0.1 ℃. After activating, cool the solution at about 0 ℃ in ice, take 6.0 mL of this solution, and add pH 7.5 borate buffer solution to make 100 mL (0.03 mg/mL) (storage: prepare at 0 ℃ in ice and use within 1 hour).
With 17 test tubes, label 2 each as S_1, S_2, S_3, S_{1B}, S_{2B}, S_{3B}, U, and U_B, and for the remaining 1, label it as R_L. According to the table below, sequentially add the labeled amounts of test solution (mL) into the designated test tubes.

	S_1	S_2	S_3	U	S_{1B}	S_{2B}	S_{3B}	U_B	R_L
pH 7.5 borate Buffer solution	2	1	-	1	2	1	-	1	3
Standard solution	1	2	3	-	1	2	3	-	-
Test solution	-	-	-	2	-	-	-	2	-
5% trichloroacetic acid solution	-	-	-	-	5	5	5	5	5

After completing the procedure, mix, take 2.0 mL of casein solution, previously maintained at 35 ± 0.1 ℃, and add at regular intervals. After exactly 30 minutes, take 5 mL of 5% trichloroacetic acid solution, and add to S_1, S_2, S_3, and U to stop the reaction. After removing from the water bath, allow to stand at room temperature for 20 minutes, filter by stacking two suitable filter papers, and determine the absorbance at the wavelength of 275 nm using R_L as the control solution. Calculate the average absorbance for each pair, S_1-S_{1B}, S_2-S_{2B}, and S_3-S_{3B}, and plot these absorbance values on the x-axis and the volume of the standard solution used in mL on the y-axis to prepare a calibration curve.

Protein digestion activity per g of Pancreatin II (FIP unit/g)

$$= \frac{V_R \times C_R \times 1000 \times 40}{P_P}$$

V_R: Volume(mL) corresponding to the standard solution of the test solution obtained from the calibration curve

C_R: The protease FIP units per mg of reference standards

P_P: μg of the sample in 10 mL of the final test solution

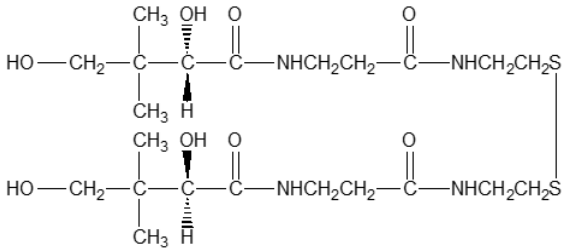
40: μg of reference standards in 1 mL of the standard solution

Filter paper—Determine the absorbance of the filtrate obtained by filtering a 5% trichloroacetic acid solution through a filter paper at the wavelength of 275 nm, using the unfiltered 5% trichloroacetic acid solution as the control solution, as directed under the Ultraviolet-visible Spectroscopy; it can be used when the absorbance is NMT 0.02.

Packaging and storage Preserve in tight containers.

Pantethine

판테틴



$C_{22}H_{42}N_4O_8S_2$: 554.72

N-[3-[2-[2-[3-[(2,4-Dihydroxy-3,3-dimethylbutanoyl)amino]propanoylamino]ethyldisulfanyl]ethylamino]-3-oxopropyl]-2,4-dihydroxy-3,3-dimethylbutanamide [*16816-67-4*]

Pantethine is an aqueous solution containing 80.0% of pantethine.

It contains NLT 98.0% and NMT 101.0% of pantethine ($C_{22}H_{42}N_4O_8S_2$), calculated on the anhydrous basis.

Description Pantethine occurs as a colorless to pale yellow, clear, and viscous liquid.
It is miscible with water, methanol, or ethanol(95).
It is decomposed by light.

Identification (1) To 0.7 g of Pantethine, add 5 mL of sodium hydroxide TS, shake to mix, and add 1 to 2 drops of copper(II) sulfate TS; the resulting solution exhibits a bluish purple color.

(2) To 0.7 g of Pantethine, add 3 mL of water, shake to mix, add 0.1 g of zinc powder and 2 mL of acetic acid(100), and boil for 2 to 3 minutes. After cooling, add 1 to 2 drops of sodium nitroprusside TS; the resulting solution exhibits a purple color.

(3) To 1.0 g of Pantethine, add 500 mL of water, and shake to mix. To 5 mL of this solution, add 3 mL of 1 mol/L hydrochloric acid TS, and heat on a steam bath for 30 minutes. After cooling, add 7 mL of a solution of hydroxylamine hydrochloride in sodium hydroxide TS (3 in 140), and allow to stand for 5 minutes. Add 3 drops of 2,4-dinitrophenol TS, add dropwise 1 mol/L hydrochloric acid TS until the color of the solution becomes colorless, and add 1 mL of iron(III) chloride TS; the resulting solution exhibits a purple color.

Optical rotation $[a]_D^{20}$: Between +15.0° and +18.0° (1 g, calculated on the anhydrous basis, water, 25 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Pantethine according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Proceed with 2.0 g of Pantethine according to Method 3 and perform the test (NMT 1 ppm).

(3) ***Related substances***—Dissolve 0.6 g of Pantethine in 10 mL of water, and use this solution as the test solution. Pipet 2 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with water-saturated methyl ethyl ketone as the developing solvent to a distance of about 10 cm, and air-dry the plate. Allow the plate to stand for 10 minutes in iodine vapor; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

(4) ***Mercapto compounds***—Add 20 mL of water to 1.5 g of Pantethine, shake to mix, and add 1 drop of ammonia TS and 1 to 2 drops of sodium nitroprusside TS; the resulting solution does not exhibit a red color.

Water Between 18% and 22% (0.2 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (2 g).

Assay Weigh accurately about 0.3 g of Pantethine, and add water to make exactly 20 mL. Pipet 5 mL of this solution, transfer to an iodine bottle, add exactly 25 mL of 0.05 mol/L bromine, and put 100 mL of water again. Rapidly add 5 mL of diluted sulfuric acid (1 in 5), immediately close the stopper, and heat at 40 ℃ - 50 ℃ for 15 minutes while occasionally stirring to mix. After cooling, carefully add 5 mL of potassium iodide solution (2 in 5), immediately close the stopper, shake to mix, and add 100 mL of water. Titrate free iodine with 0.1 mol/L sodium thiosulfate VS (indicator: 2 mL of starch TS). Per-

form a blank test in the same manner.

Each mL of 0.05 mol/L bromine VS
= 5.547 mg of $C_{22}H_{42}N_4O_8S_2$

Packaging and storage Preserve in light-resistant, tight containers at NMT 10 ℃.

D-Panthenol Injection
D-판테놀 주사액

D-Panthenol Injection contains NLT 90.0% and NMT 130.0% of the labeled amount of D-panthenol ($C_9H_{19}NO_4$: 205.25).

Method of preparation Prepare as directed under Injections, with D-Panthenol.

Identification Perform the test with D-Panthenol Injection as directed under the Analysis for Vitamins.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.6 EU per mg of D-Panthenol.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Perform the test with D-Panthenol Injection as directed under the Analysis for Vitamins.

Packaging and storage Preserve in hermetic containers.

D-Panthenol Ointment
D-판테놀 연고

D-Panthenol Ointment contains NLT 90.0% and NMT 150.0% of the labeled amount of D-panthenol ($C_9H_{19}NO_4$: 205.25).

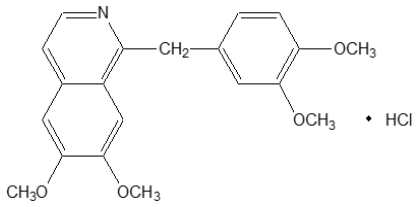
Method of preparation Prepare as directed under Ointments, with D-Panthenol.

Identification Perform the test with D-Panthenol Ointment as directed under the Analysis for Vitamins.

Assay Perform the test with D-Panthenol Ointment as directed under the Analysis for Vitamins.

Packaging and storage Preserve in tight containers.

Papaverine Hydrochloride
파파베린염산염



$C_{20}H_{21}NO_4 \cdot HCl$: 375.85
1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxyisoquinoline hydrochloride [*61-25-6*]

Papaverine Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of papaverine hydrochloride ($C_{20}H_{21}NO_4 \cdot HCl$).

Description Papaverine Hydrochloride occurs as white crystals or a crystalline powder.
It is sparingly soluble in water or acetic acid(100), slightly soluble in ethanol(95), and practically insoluble in acetic anhydride or ether.
Dissolve 1.0 g of Papaverine Hydrochloride in 50 mL of water; the pH of the solution is between 3.0 and 4.0.

Identification (1) To 1 mg of Papaverine Hydrochloride, add 1 drop of formaldehyde solution-sulfuric acid TS; the resulting solution is colorless to pale yellowish green, and then gradually turns dark red to brown.

(2) Dissolve 20 mg of Papaverine Hydrochloride in 1 mL of water and add 3 drops of sodium acetate TS; a white precipitate is formed.

(3) Dissolve 1 mg of Papaverine Hydrochloride with 3 mL of acetic anhydride and 5 drops of sulfuric acid, heat on a steam bath for 1 minute, and examine the solution under ultraviolet light (main wavelength: 365 nm); the solution exhibits a yellowish green fluorescence.

(4) Dissolve 0.1 g of Papaverine Hydrochloride in 10 mL of water, make the solution alkaline with ammonia TS, and shake to mix with 10 mL of ether. Separate the ether layer, wash with 5 mL of water, and filter. Evaporate the filtrate on a steam bath, dry the residue at 105℃ for 3 hours; the residue melts between 145 and 148 ℃.

(5) Make an aqueous solution of Papaverine Hydrochloride (1 in 50) alkaline with ammonia TS, discard the produced precipitate by filtering, and acidify the filtrate with dilute nitric acid; the resulting solution responds to the Qualitative Analysis (2) for chloride.

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Papaverine Hydrochloride in 10 mL of water; the resulting solution is clear and colorless.

(2) ***Related substances***—Dissolve about 20 mg of Papaverine Hydrochloride, weighed accurately, in diluent to make exactly 10 mL, and use this solution as the test solution. Pipet 1.0 mL of the test solution, add the diluent

to make exactly 100 mL. Pipet 1.0 mL of this solution, add the diluent to make exactly 10 mL, and use this solution as the standard solution (1). Separately, weigh accurately 12 mg of noscapine RS, dissolve in 1.0 mL of the test solution, add diluent to make 100 mL, and use this solution as the standard solution (2). Perform the test with 10 μL each of the test solution and the standard solutions (1), (2) as directed under the Liquid Chromatography according to the following conditions. Determine each peak area from each solution by the automatic integration method, and measure the amount of each related substance; the amounts of papaverine related substances I {tetrahydropapaverine}, papaverine related substances II {dihydropapaverine}, papaverine related substances III {papaverinol}, noscapine, papaverine related substance IV {2-(3,4-dimethoxyphenyl)-*N*-[2-(3,4-dimethoxyphenyl)-ethyl] acetamide}, papaverine related substance V {papaveraldine } are NMT 0.1%, respectively. In addition, the peak areas ofindividual related substances other than the above related substances are not larger than the major peak area obtained from standard solution (1) (NMT 0.1%), and the peak area of total related substances is not larger than 5 times the major peak area of standard solution (1) (NMT 0.5%). Exclude any peaks smaller than 0.5 times the major peak area obtained from standard solution (1) (NMT 0.05%). However, determine the peak areas of papaverine related substances II, noscapine and papaverine related substances V by multiplying the peak areas obtained by the automatic integration method by the correction factors 2.7, 6.2 and 0.5, respectively.

Diluent—A mixture of mobile phase A and acetonitrile (80 : 20).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 238 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octylsilane silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Control the mixing ratio of mobile phase A, mobile phase B and mobile phase C stepwise or via the gradient elution as follows.

Mobile phase A: Dissolve 3.4 g of potassium dihydrogen phosphate in 1000 mL of water, adjust the pH to 3.0 with dilute phosphoric acid.

Mobile phase B: Acetonitrile

Mobile phase C: Methanol

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)	Mobile phase C (vol%)
0 - 5	85	5	10
5 - 12	85 → 60	5	10 → 35
12 - 20	60	5	35
20 - 24	60 → 40	5 in 20	35 → 40
24 - 27	40	20	40
27 - 32	40 → 85	20 in 5	40 → 10
32 - 40	85	5	10

Flow rate: 1 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution (2) under the above operating conditions; the resolution of noscapine and papaverine are NLT 1.5. The relative retention times of papaverine related substances I, II and III, noscapine, papaverine related substances IV and V to that of papaverine (approximate retention time of 23.4 minutes) are 0.7, 0.75, 0.8, 0.9, 1.1 and 1.2, respectively.

(3) ***Morphine***—Dissolve 10 mg of Papaverine Hydrochloride in 1 mL of water, add 5 mL of 1-nitroso-2-naphthol TS and 2 mL of potassium nitrate (1 in 10), and warm at 40 ℃ for 2 minutes. Then, add 1 mL of sodium nitrate (1 in 5000) and warm at 40 ℃ for 5 minutes. After cooling, add 10 mL of chloroform, shake to mix, centrifuge, and collect the aqueous layer; the color of the resulting solution is not more intense than light red.

(4) ***Readily carbonizable substances***—Perform the test with 0.12 g of Papaverine Hydrochloride. The color of the solution is not more intense than that of the matching fluid for color S or P.

Loss on drying NMT 1.0% (1 g, 105 ℃, 4 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.5 g of Papaverine Hydrochloride, previously dried, add 100 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and warm to dissolve. After cooling, titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 37.585 mg of $C_{20}H_{21}NO_4 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Papaverine Hydrochloride Injection
파파베린염산염 주사액

Papaverine Hydrochloride Injection is an aqueous solution for injection. It contains NLT 95.0% and NMT 105.0% of the labeled amount of papaverine hydrochloride ($C_{20}H_{21}NO_4 \cdot HCl$: 375.85).

Method of preparation Prepare as directed under Injections, with Papaverine Hydrochloride.

Description Papaverine hydrochloride injection occurs as a clear, colorless liquid.

pH—Between 3.0 and 5.0.

Identification (1) Add 3 drops of sodium acetate TS to 1 mL of papaverine hydrochloride injection; a white precipitate is formed.

(2) Dilute a volume of Papaverine Hydrochloride Injection, equivalent to 0.1 g of Papaverine Hydrochloride according to the labeled amount, with water to make 10 mL, render the solution alkaline with ammonia TS and shake with 10 mL of ether. Separate the ether layer, wash with 5 mL of water, then filter. Evaporate the filtrate on a steam bath to dryness and dry the residue at 105 ℃ for 3 hours: the residue so obtained melts between 145 and 148 ℃.

(3) Weight 1 mg of the residue from (2) and perform the test as directed under Identification (1) and (3) for Papaverine hydrochloride.

(4) Alkalify 2 mL of Papaverine Hydrochloride Injection with ammonia TS, filter the precipitate off and acidify the filtrate with dilute nitric acid: the solution responds to the Qualitative Tests (2) for chloride.

Sterility Meets the requirements.

Bacterial endotoxins Less than 6.0 EU per mg of papaverine hydrochloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

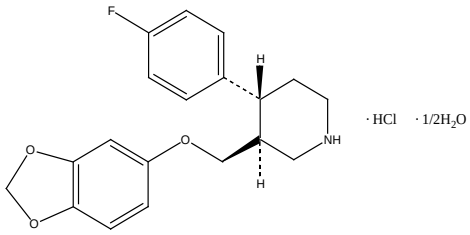
Extractable volume of injections Meets the requirements.

Assay Pipet an amount of papaverine hydrochloride injection equivalent to about 0.2 g of papaverine hydrochloride ($C_{20}H_{21}NO_4 \cdot HCl$), add water to make 10 mL, alkalize by adding ammonia TS, and extract with 20 mL, 15 mL, 10 mL and 10 mL of chloroform. Combine the chloroform extracts, wash with 10 mL of water, and extract the washings twice with 5 mL of chloroform, respectively. Combine all of the chloroform extracts, evaporate the chloroform on a steam bath, dissolve the residue in 30 mL of acetic acid(100), and titrate with 0.05 mol/L perchloric acid (indicator: 2 drops of methylrosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L perchloric acid VS
= 18.793 mg of $C_{20}H_{21}NO_4 \cdot HCl$

Packaging and storage Preserve in light-resistant, hermetic containers.

Paroxetine Hydrochloride Hydrate
파록세틴염산염수화물



Paroxetine Hydrochloride

$C_{19}H_{21}ClFNO_3 \cdot ½H_2O$: 374.84

(3*S*,4*R*)-3-[(2*H*-1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine [*110429-35-1*]

Paroxetine Hydrochloride Hydrate contains NLT 97.5% and NMT 102.0% of paroxetine hydrochloride ($C_{19}H_{21}ClFNO_3$: 365.84), calculated on the anhydrous basis.

Method of preparation If there is any possibility of 4-(4-fluorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine [4-(4-fluorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine] to be inserted as the potential impurities according to the manufacturing process of Paroxetine Hydrochloride Hydrate, take caution with starting material, manufacturing process, and intermediate material control to minimize the residue of impurities in consideration of risk assessment results. If needed, the manufacturing process can be justified by the test data proving that there is no quality risk in final drug substances.

Description Paroxetine Hydrochloride Hydrate occurs as a white crystalline powder.
It is freely soluble in methanol, sparingly soluble in ethanol(95) and dichloromethane, and slightly soluble in water.

Identification (1) Put about 0.16 g of Paroxetine Hydrochloride Hydrate in a test tube, add 0.2 g of potassium dichromate and 1 mL of sulfuric acid, and place a filter paper soaked in 1,5-diphenylcarbonohydrazide TS at the mouth of the test tube; the filter paper turns purple.

(2) Determine the infrared spectra of Paroxetine Hydrochloride Hydrate and paroxetine hydrochloride hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If the absorption spectra are different, dissolve Paroxetine Hydrochloride Hydrate and paroxetine hydrochloride hydrate RS in a mixture of 2-propanol and water (9 : 1) to make a 10% solution, recrystallize. Then determine the spectra again using the residue obtained.

(3) Perform the test with the test solution and the standard solution (3) obtained in the related substance I, as directed under the Liquid Chromatography according to the test conditions in the related substance I; the reten-

tion times of the major peaks obtained are the same.

Purity (1) ***Heavy metals***—Weigh 1.0 g of Paroxetine Hydrochloride Hydrate, put it in a platinum crucible, and perform the test according to Method 2. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances I***—Weigh accurately about 0.1 g of Paroxetine Hydrochloride Hydrate, dissolve in 20 mL of methanol, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Add the mobile phase to 1.0 mL of the test solution to make exactly 100 mL. To 1.0 mL of this solution add the mobile phase to make exactly 10 mL, and use this solution as the standard solution (1). Separately, dissolve 5 mg of paroxetine related substances I {(3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidin((+)-trans-paroxetine)} RS and 5 mg of paroxetine hydrochloride hydrate RS in 2 mL of methanol, add the mobile phase to make exactly 100 mL; and use this solution as the standard solution (2). Dissolve 10 mg of paroxetine hydrochloride hydrate RS in 2 mL of methanol, add the mobile phase to make exactly 10 mL; and use this solution as standard solution (3). Perform the test with 10 μL each of the test solution, the standard solution (1) and the standard solution (2) according to the following conditions as directed under the Liquid Chromatography; the peak area equivalent to related substance I obtained from the test solution is not more than twice the major peak area obtained from the standard solution (1) (NMT 0.2%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 295 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 10 cm in length, packed with silica gel AGP for liquid chromatography (5 μ*m* in particle diameter).

Mobile phase: A mixture of 0.58% sodium chloride solution and methanol (8 : 2).

Flow rate: About 0.5 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution (2) according to the above conditions; the resolution between the peaks of related substance I and of paroxetine are NLT 2.2.

Time span of measurement: About 2.5 times the retention time of paroxetine.

(3) ***Related substances II***—Dissolve 50.0 mg of Paroxetine Hydrochloride Hydrate in a mixture of water and tetrahydrofuran (9 : 1) to make exactly 50 mL, and use this solution as the test solution. To 5.0 mL of the test solution, add a mixture of water and tetrahydrofuran (9 : 1) to make exactly 50 mL, and use this solution as the standard solution (1). Separately, dissolve 2 mg of paroxetine related substance II {(3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-ethoxyphenyl)piperidine} RS in a mixture of water and tetrahydrofuran (9 : 1) to make exactly 20 mL, and use this solution as the standard solution (2). To 2.0 mL of the standard solution (1), add 2.0 mL of the standard solution (2) and a mixture of water and tetrahydrofuran (9 : 1) to make exactly 20 mL, and use this solution as the standard solution (3). To 2.0 mL of the standard solution, add a mixture of water and tetrahydrofuran (9 : 1) to make exactly 200 mL, and use this solution as the standard solution (4). Dissolve 2 mg of paroxetine related substance III {(3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-phenylpiperidine (desfluoroparoxetine)} RS in a mixture of water and tetrahydrofuran (9 : 1) to make exactly 20 mL, and use this solution as the standard solution (5). Take 20 μL each of the test solution, the standard solutions (3), (4) and (5), and perform a test under the Liquid Chromatography according to the following conditions; the peak area equivalent to related substance III obtained from the test solution is not larger than 3 times the major peak area obtained from the standard solution (4) (0.3%), the individual peak area of each related substance other than the related substance III is not larger than the major peak area obtained from the standard solution (4) (0.1%), and the total area ofthese peaks is not larger than 5 times the major peak area obtained from the standard solution (4) (0.5%). However, exclude any peak having an area smaller than half the area of the major peak from the standard solution (4).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 295 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 25 cm in length, packed with octylsilane silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: A mixture of water, tetrahydrofuran and trifluoroacetic acid (900 : 100 : 5).

Mobile phase B: A mixture of acetonitrile, tetrahydrofuran and trifluoroacetic acid (900 : 100 : 5).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 30	80	20
30 - 50	80 → 20	20 → 80
50 - 60	20	80
60 - 65	20 → 80	80 → 20
65 - 70	80	20

Flow rate: 1.0 mL/min

System suitability

System performance: Take 2.0 mL of the standard solution (1) and 1.0 mL of the standard solution (5), mix, and add a mixture of water and tetrahydrofuran (9 : 1) to make 20 mL. Proceed with 20 μL of this resulting solution according to the above conditions; the relative retention time of related substances III with respect to the re-

tention time of paroxetine peak is about 0.8. Proceed with 20 μL of the standard solution (3) according to the above conditions; the resolutions between the peak of related substance II and the peak of paroxetine are NLT 3.5.

Time span of measurement: About 2.5 times the retention time of paroxetine.

Water Between 2.2% and 2.7% (0.3 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg each of Paroxetine Hydrochloride Hydrate and paroxetine hydrochloride hydrate RS, dissolve in water to make exactly 100 mL, and use these solutions as the test solution and the standard solution. Perform the test with exactly 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of paroxetine from each solution.

Amount (mg) of paroxetine hydrochloride ($C_{19}H_{21}ClFNO_3$)
= Amount (mg) of paroxetine hydrochloride, calculated on the anhydrous basis, in paroxetine hydrochloride hydrate RS $\times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 295 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and about 25 cm in length, packed with trimethylsilyl silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 3.85 g of ammonium acetate in 500 mL of water, adjust the pH to 5.5 with acetic acid(100), then add water to make 600 mL. Next, gently add acetonitrile, mix, add 10 mL of triethylamine, and then adjust the pH to 5.5 by adding acetic acid(100) again.

Flow rate: 1 mL/min

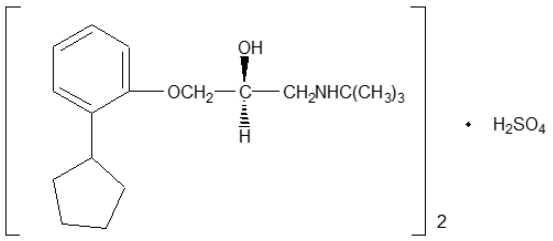
System suitability

System performance: Weigh accurately 5.0 mg each of Paroxetine Hydrochloride Hydrate and paroxetine related substance III RS, dissolve in water to make exactly 10 mL. Proceed with 10 μL of this solution according to the above conditions; the resolution between the peaks of paroxetine related substance III and of paroxetine is NLT 2.0.

Time span of measurement: About 2 times the retention time of paroxetine.

Packaging and storage Preserve in light-resistant, well-closed containers.

Penbutolol Sulfate
펜부톨롤황산염



$(C_{18}H_{29}NO_2)_2 \cdot H_2SO_4$: 680.94

(2*S*)-1-(*tert*-Butylamino)-3-(2-cyclopentylphenoxy)propan-2-ol;sulfuric acid [*38363-32-5*]

Penbutolol Sulfate, when dried, contains NLT 98.5% and NMT 101.0% of penbutolol sulfate [$(C_{18}H_{29}NO_2)_2 \cdot H_2SO_4$].

Description Penbutolol Sulfate occurs as a white crystalline powder.
It is very soluble in acetic acid(100), freely soluble in methanol, sparingly soluble in ethanol(95), slightly soluble in water, and practically insoluble in acetic anhydride or ether.

Identification (1) Determine the absorption spectra of solutions of Penbutolol Sulfate and penbutolol sulfate RS in methanol (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Penbutolol Sulfate and penbutolol sulfate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) To 0.1 g of Penbutolol Sulfate, add 25 mL of water, warm to dissolve, and cool; the resulting solution responds to the Qualitative Analysis for sulfate.

Optical rotation $[\alpha]_D^{20}$: Between -23° and -25° (0.2 g after drying, methanol, 20 mL, 100 mm).

Melting point Between 213 and 217 ℃.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Penbutolol Sulfate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—P Proceed with 1.0 g of Penbutolol Sulfate according to Method 4 and perform the test (NMT 2 ppm).

(3) ***Related substances***—Dissolve 0.8 g of Penbutolol Sulfate in 10 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot

10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of 2-propanol, ethanol(95) and ammonia water(28) (85 : 12 : 3) to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (0.5 g, 105 ℃, 3 hours).

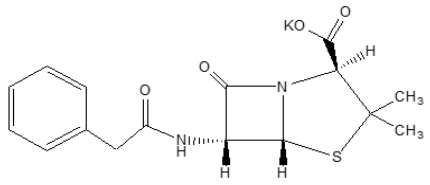
Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.8 g of Penbutolol Sulfate, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 68.09 mg of $(C_{18}H_{29}NO_2)_2 \cdot H_2SO_4$

Packaging and storage Preserve in well-closed containers.

Penicillin G Potassium
페니실린G칼륨



Benzylpenicillin Potassium $C_{16}H_{17}N_2KO_4S$: 372.48
Potassium(2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-[(2-phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylate [*113-98-4*]

Penicillin G Potassium is the potassium salt of a penicillin compound with antibacterial activity produced by the growth of the *Penicillium* genus.
Penicillin G Potassium contains NLT 1430 units (potency) and NMT 1630 units (potency) of penicillin G ($C_{16}H_{18}N_2O_4S$: 334.39) per mg (potency), calculated on the dried basis. 1 unit is equivalent to 0.57 μg of penicillin G potassium.

Description Penicillin G Potassium occurs as white crystals or a crystalline powder. It is very soluble in water and slightly soluble in ethanol(99.5).

Identification (1) Determine the absorption spectra of solutions of Penicillin G Potassium and penicillin G potassium RS (1 in 1000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelength.

(2) Determine the infrared spectra of Penicillin G Potassium and penicillin G potassium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

(3) Penicillin G Potassium responds to the Qualitative Analysis (1) for potassium salt.

Crystalline Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between +270° and +300° (1 g calculated on the dried basis, water, 50 mL, 100 mm).

pH Dissolve 1.0 g of Penicillin G Potassium in 100 mL of water; the pH of this solution is between 5.0 and 7.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Penicillin G Potassium in 10 mL of water; the solution is clear and colorless to bright yellow.

(2) ***Heavy metals***—Proceed with 2.0 g of Penicillin G Potassium according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Penicillin G Potassium according to Method 4 and perform the test. However, transfer 10 mL of a solution of magnesium nitrate hexahydrate-ethanol (95) (1 in 10) into the porcelain crucible, add 1 mL of hydrogen peroxide(30), and ignite the ethanol to burn (NMT 2 ppm).

(4) ***Related substances***—Weigh accurately 40 mg of Penicillin G Potassium, add water to make exactly 20 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas from the respective solutions according to the automatic integration method; each peak area other than penicillin G from the test solution is not greater than the peak area of penicillin G from the standard solution. Also, the sum of peak areas other than penicillin G from the test solution is not greater than 3 times the peak area of penicillin G from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (7 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: To a mixture of dibasic ammonium phosphate (33 in 5000) and acetonitrile (19 : 6), add phosphoric acid to adjust the pH to 8.0.

Flow rate: Adjust the flow rate so that the retention

time of penicillin G is about 7.5 minutes.

Time span of measurement: About 5 times the retention time of penicillin G.

System suitability

Test for required detectability: Pipet 10 mL of the standard solution and add water to make exactly 100 mL. Confirm that the peak area of penicillin obtained from 20 μL of this solution is equivalent to 7% to 13% of that of penicillin from the standard solution.

System performance: Dissolve 40 mg of Penicillin G Potassium in 20 mL of water. Separately, dissolve 10 mg of methyl *p*-hydroxybenzoate in 20 mL of acetonitrile. To 1 mL of this solution, add water to make 20 mL. Take 1 mL each of these solutions, and add water to make 100 mL. Proceed with 20 μL of this solution according to the above conditions; penicillin G and methyl *p*-hydroxybenzoate are eluted in this order with the resolution between these peaks being NLT 8.

System repeatability: Repeat the test 5 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of penicillin G is NMT 2.0%.

Loss on drying NMT 1.0% (3 g, NMT 0.67 kPa, 60 ℃, 3 hours).

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, it is excluded in cases where there is a final sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins Less than 0.01 EU per 100 units (potency) of penicillin G when used in the manufacturing of sterile preparations.

Thermal stability Based on the assay results, weigh accurately about 50000 units (potency) of Penicillin G Potassium (A units), store at 100 ± 1 ℃ for 96 hours (4 days), and determine the potency (B units) by conducting assay (loss of potency is NMT 10%).

$$\text{Loss of potency ratio} = \frac{A\ unit - B\ unit}{A\ unit} \times 100$$

Penicillin G potassium content (by weight ratio) Weigh accurately 60 mg to 70 mg of Penicillin G Potassium, transfer into a stoppered centrifuge tube, dissolve in 2.0 mL of water, and cool at 0 to 5 ℃. Add 2.0 mL of amyl acetate TS for penicillin cooled to 0 to 8 ℃ and 0.5 mL of diluted phosphoric acid (1 in 5), close the stopper tightly, vigorously shake for about 15 seconds to mix, and centrifuge for about 20 seconds to separate the two liquid layers. Extract as much of the amyl acetate layer as possible (about 1.7 mL to 1.8 mL) using a 2.0 mL syringe with an appropriate injection needle, transfer into a glass filter (about 10 mm in diameter) containing 0.1 g of anhydrous sodium sulfate, and filter with suction into a small test tube, cooled with ice around its perimeter. Pipet 1.0 mL of this solution, and transfer separately into the previously weighed test tubes with dimensions of about 15 × 15 mm and a flat bottom with 0.5 mL of *N*-ethylpiperidine TS for penicillin and 1.0 mL of acetone TS for penicillin, respectively. At this point, complete the procedure of acidifying the test solution and adding the following filtrate within 3 minutes. Place the test tubes described above in a stoppered weighing bottle, close the stopper, and allow to stand at 0 to 8 ℃ for NLT 2 hours. Carefully filter the precipitate with suction with the previously weighed glass filter (G4, about 10 mm in diameter), and wash the top with 1 mL of acetone TS for penicillin at 0 to 8 ℃ using a syringe. To the test tube described above, place a glass filter, dry at room temperature in vacuum for 1 hour, and weigh. (NLT 85.0%).

$$\text{Penicillin G potassium content (\%)} = \frac{Mass\ (mg)\ of\ N\text{-}ethylpiperidine\ penicillin\ precipitate \times 166.5}{Amount\ (mg)\ of\ \text{Penicillin G Potassium}\ taken}$$

Assay Weigh accurately about 60 mg of Penicillin G Potassium, dissolve in 1% phosphate buffer solution (pH 6.0), dilute with 1% phosphate buffer solution (pH 6.0) to make the solution containing 2000 units (potency) per mL, and use this solution as the test solution. Separately, weigh accurately about 40 mg of penicillin G potassium RS, dissolve in 1% phosphate buffer solution (pH 6.0), dilute with 1% phosphate buffer solution (pH 6.0) to make the solution containing 2000 units (potency) per mL, and use this solution as the standard solution. Pipet 2 mL each of the test solution and the standard solution, transfer into the 100-mL flask for iodine titration, add 2.0 mL of 1 mol/L sodium hydroxide TS, and allow to stand for 15 minutes. Add 2.0 mL of diluted hydrochloric acid (1 in 10) and 10.0 mL of 0.01 mol/L iodine VS, allow to stand for 15 minutes, add 5 mL of carbon tetrachloride if necessary, and shake to mix. Titrate with 0.01 mol/L sodium thiosulfate VS using a microburette (indicator: starch TS). Separately, pipet 2 mL each of the test solution and the standard solution, add 10.0 mL of 0.01 mol/L iodine VS, and perform a blank test in the same manner (however, do not allow it to stand for 15 minutes) as above and make any necessary correction. The amount (mL) of 0.01 mol/L iodine VS consumed in the test solution and the standard solution is denoted as V_T and V_S, respectively.

$$\text{Potency of penicillin G potassium in the test solution} = \text{Potency of penicillin G potassium RS} \times \frac{V_T}{V_S}$$

Packaging and storage Preserve in tight containers.

Penicillin G Potassium for Injection
주사용 페니실린G칼륨

Penicillin G Potassium for Injection is an injection dissolved before use. Penicillin G Potassium for Injection contains NLT 93.0% and NMT 107.0% of the labeled amount of penicillin G potassium ($C_{16}H_{17}KN_2O_4S$:

372.48).

Method of preparation Prepare as directed under Injections, with Penicillin G Potassium.

Description Penicillin G Potassium for Injection occurs as white crystals or a crystalline powder.

Identification Perform the test directed under the Identification (2) of Penicillin G potassium.

Crystallinity Meets the requirements.

pH Weigh an amount of Penicillin G Potassium for Injection, equivalent to 100000 units of penicillin G potassium, and dissolve in 10 mL of water; the pH of this solution is between 5.0 and 7.5.

Purity ***Clarity and color of solution***—Dissolve an amount of Penicillin G Potassium for Injection equivalent to 1.0×10^6 units of penicillin G potassium according to the labeled amount in water; the solution is clear. Determine the absorbance of this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at a wavelength of 400 nm is NMT 0.10.

Loss on drying NMT 1.2% (3 g, in vacuum at the pressure not exceeding·0.67 kPa, 60 °C, 3 hours).

Sterility Meets the requirements.

Bacterial endotoxin Less than 1.25×10^{-4} EU per unit penicillin G.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the contents of NLT 10 units of Penicillin G Potassium for Injection. Weigh accurately an amount equivalent to about 6 × 104 units of penicillin G potassium, dissolve in water to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately about 6 x 104 units of penicillin G potassium RS, dissolve in water to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area, A_T and A_S of penicillin G from each of the solutions.

Amount (unit) of penicillin G potassium ($C_{16}H_{17}KN_2O_4S$)
= Potency (μg) of penicillin G potassium RS$\times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (7 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Add phosphoric acid to a mixture of diammonium hydrogen phosphate solution (33 in 5000) and acetonitrile (19 : 6) to adjust the pH to 8.0.

Flow rate: Adjust the flow rate so that the retention time of penicillin G is about 7.5 minutes.

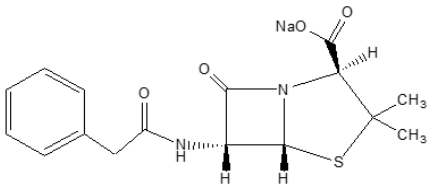
System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; the number of theoretical plates and the symmetry factor of the peak of benzylpenicillin are NLT 6000 and NMT 2.0, respectively.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of penicillin G potassium is NMT 1.0%.

Packaging and storage Preserve in hermetic containers.

Penicillin G Sodium
페니실린G나트륨



Benzylpenicillin Sodium $C_{16}H_{17}N_2NaO_4S$: 356.37
Sodium(2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-[(2-phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate [*69-57-8*]

Penicillin G Sodium is the sodium salt of a penicillin compound with antibacterial activity produced by the growth of the *Penicillium* genus. Penicillin G Sodium contains NLT 1500 units (potency) and NMT 1750 units (potency) of penicillin G sodium ($C_{16}H_{18}N_2O_4S$: 334.39) per mg, calculated on a dried basis.

Description Penicillin G Sodium occurs as white crystals or a crystalline powder. It is odorless or has a slightly characteristic odor.
It is very soluble in water and slightly soluble in acetone.
It is very soluble in Isotonic Sodium Chloride Injection and Glucose Injection.

Identification (1) Determine the infrared spectra of Penicillin G Sodium and penicillin G sodium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar inten-

sities of absorption at the same wavenumbers.

(2) Penicillin G Sodium responds to the Qualitative Analysis (1) for sodium salt.

Crystallinity Meets the requirements.

pH Dissolve 0.6 g of Penicillin G Sodium in 10 mL of water; the pH of this solution is between 5.0 and 7.5.

Loss on drying NMT 1.5% (0.1 g, in vacuum, 60 ℃, 3 hours).

Sterility It meets the requirements when used in the manufacturing of a sterile preparation. However, it is excluded in cases where there is a final sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins NMT 0.01 EU per 100 units (potency) of penicillin G when used in the manufacturing of sterile preparations.

Thermo stability Perform the test as directed under the Thermostability in Penicillin G Potassium (Loss potency NMT 10%).

Content of penicillin G sodium (by weight ratio) Perform the test as directed under the Content of penicillin G potassium in Penicillin G Potassium (NLT 85.0%). However, calculate as the following method.

$$\text{The content (\%) of penicillin G sodium} = \frac{Mass\ (mg)\ of\ N\text{-}ethylpiperidine\ penicillin\ precipitate \times 159.3}{Amount\ (mg)\ of\ Penicillin\ G\ Sodium\ taken}$$

Assay Weigh accurately about 10 mg (potency) of Penicillin G Sodium according to the labeled potency, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of penicillin G sodium RS, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Proceed with 10 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of penicillin G sodium in the test solution and the standard solution.

$$\text{Amount (unit) of penicillin G sodium } (C_{16}H_{17}N_2NaO_4S) = \text{Potency (unit) of penicillin G sodium RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

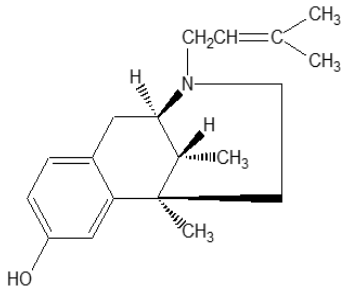
Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of 0.01 mol/L potassium dihydrogen phosphate solution and methanol (3 : 2).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Pentazocine
펜타조신



and enantiomer

$C_{19}H_{27}NO$: 285.42

(2*RS*,6*RS*,11*RS*)-6,11-Dimethyl-3-(3-methyl but-2-en-1-yl)-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocin-8-ol [*359-83-1*]

Pentazocine, when dried, contains NLT 99.0% and NMT 101.0% of pentazocine ($C_{19}H_{27}NO$).

Description Pentazocine occurs as a white to pale yellowish white crystalline powder and is odorless.
It is freely soluble in acetic acid(100) or chloroform, soluble in ethanol(95), sparingly soluble in ether, and practically insoluble in water.

Identification (1) To 1 mg of Pentazocine, add 0.5 mL of formaldehyde-sulfuric acid TS; the resulting solution exhibits a deep red color and immediately changes to a grayish brown color.

(2) Dissolve 5 mg of Pentazocine in 5 mL of sulfuric acid, add 1 drop of iron(III) chloride TS, and heat on a steam bath for 2 minutes; the color of the solution changes from pale yellow to deep yellow. Add 1 drop of nitric acid, and shake to mix; the resulting solution maintains a yellow color.

(3) Determine the absorption spectra of solutions of Pentazocine and pentazocine RS in 0.01 mol/L hydrochloric acid TS (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Melting point Between 150 and 158 ℃.

Absorbance $E_{1cm}^{1\%}$ (278 nm): Between 67.5 and 71.5 (0.1 g after drying, 0.01 mol/L hydrochloric acid TS, 1000 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g of Pentazocine in 20 mL of 0.1 mol/L hydrochloric acid TS; the resulting solution is colorless and clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Pentazocine according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution

(NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Pentazocine according to Method 3 and perform the test. However, use a solution of magnesium nitrate in ethanol(95) (1 in 10) (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.20 g of Pentazocine in 10 mL of chloroform, and use this solution as the test solution. Pipet 1 mL of this solution, add chloroform to make exactly 100 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, methanol and isopropylamine (94 : 3 : 3) as the developing solvent to a distance of about 13 cm, and air-dry the plate. Allow the plate to stand for 5 minutes in iodine vapor; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, phosphorus pentoxide, 60 ℃, 5 hours).

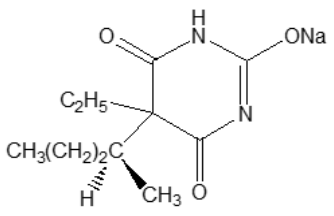
Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.5 g of Pentazocine, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of methylrosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 28.542 mg of $C_{19}H_{27}NO$

Packaging and storage Preserve in well-closed containers.

Pentobarbital Sodium
펜토바르비탈나트륨



$C_{11}H_{17}N_2NaO_3$: 248.25

Sodium 5-ethyl-4,6-dioxo-5-(pentan-2-yl)-1,4,5,6-tetrahydropyrimidin-2-olate [*57-33-0*]

Pentobarbital Sodium contains NLT 98.5% and NMT 101.0% of pentobarbital sodium ($C_{11}H_{17}N_2NaO_3$), calculated on the dried basis.

Description Pentobarbital Sodium occurs as a white crystalline grain or a powder. It is odorless or has a slightly characteristic odor and a slightly bitter taste.
It is very soluble in water, freely soluble in ethanol(95), and practically insoluble in ether.
An aqueous solution of Pentobarbital Sodium is decomposed when allowed to stand, and the decomposition is accelerated when heated.

Identification (1) Determine the absorption spectra of the test solution and the standard solution obtained from the Assay as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Ignite about 0.2 g of Pentobarbital Sodium, and dissolve the residue in acid; the solution responds to the Qualitative Analysis for sodium salt.

pH Dissolve 1.0 g of Pentobarbital Sodium in 100 mL of water; the pH of this solution is between 9.8 and 11.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Pentobarbital Sodium in 10 mL of freshly boiled and cooled water, and examine the solution after allowing to stand for 1 minute; the resulting solution is clear with no insoluble substances.

(2) ***Isomer***—Dissolve 300 ± 5 mg of Pentobarbital Sodium in 5 mL of water, add a solution prepared by dissolving 300 ± 5 mg of 4-nitrobromobenzyl in 10.0 mL of ethanol(95), shake to mix, and reflux for 30 minutes. After cooling to 25 ℃, filter in vacuum, wash the residue 4 times each with 5 mL of water, transfer the entire precipitate into the small flask, and reflux with 25 mL of ethanol(95) for 10 minutes; there are no insoluble substances. Cool this solution to 25 ℃, filter in vacuum, and dry the residue at 105 ℃ for 30 minutes; the melting point is between 136 and 146 ℃.

(3) ***Heavy metals***—Dissolve 2.0 g of Pentobarbital Sodium in 50 mL of water, add 5 mL of dilute hydrochloric acid, shake vigorously to mix, and warm on a steam bath for 2 minutes while occasionally shaking to mix. After cooling, add 25 mL of water, shake to mix, and filter. Discard the first 10 mL of the filtrate, take the subsequent 40 mL of the filtrate, add 1 drop of phenolphthalein TS, and add dropwise ammonia TS until the solution becomes pale red. Add 2 mL of dilute acetic acid and water to make 50 mL and use this solution as the test solution. Prepare the control solution by adding 2.5 mL of dilute hydrochloric acid, 1 drop of phenolphthalein TS, and dropwise ammonia TS until the solution becomes pale red, and adding 2 mL of dilute hydrochloric acid, 3.0 mL of lead standard solution, and water to make 50 mL (NMT 30 ppm).

(4) ***Related substances***—Weigh accurately about 0.11 g of Pentobarbital Sodium, add 80 mL of mobile phase, dissolve by sonicating, and add the mobile phase to make exactly 100 mL., Use this solution as the test solution. Separately weigh exactly about 0.1 mg of pentobarbital RS, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid

Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method and calculate the amount of each related substance in the test solution according to the following formula; pentobarbital related substance I {6-imino-5-ethyl-5-(1-methylbutyl)barbituric acid} is NMT 0.2%, pentobarbital related substance II {5-ethyl-5-(1-ethylpropyl)barbituric acid} is NMT 0.1%, and pentobarbital related substance III {5-ethyl-5-(1,3-dimethylbutyl)barbituric acid} is NMT 0.3%. Each amount of other related substances is NMT 0.1%, and the total amount of related substances is NMT 0.5%. However, determine the peak areas of related substance I and related substance III by dividing the peak areas obtained according to the automatic integration method by correction factors of 1.5 and 0.9, respectively.

$$\text{Content (\%) of related substances} = \frac{248.25}{226.27} \times 10000 \times \frac{C}{W} \times \frac{A_i}{A_S}$$

248.25: Molecular weight of pentobarbital sodium

226.27: Molecular weight of pentobarbital

C: Concentration (mg/mL) of pentobarbital in the standard solution

W: Amount (mg) of sample calculated on the anhydrous basis

A_i: Peak area of each related substance obtained from the test solution

A_S: Peak area of pentobarbital obtained from the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Flow rate: About 1.0 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the relative retention times for pentobarbital related substances I, II, and III to pentobarbital are about 0.39, about 0.93, and about 1.5, respectively. Also, the mass distribution ratio (k') is NLT 2.5, and the number of theoretical plates and the symmetry factor of the pentobarbital peak are NLT 15000 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of pentobarbital is NMT 15.0%.

Loss on drying NMT 3.5% (1 g, 105 ℃, 6 hours).

Assay Weigh accurately 25 mg of Pentobarbital Sodium, previously dried, dissolve in diluted ammonia water(28) (1 in 200) to make exactly 50 mL. Pipet 2 mL of this solution, add diluted ammonia water(28) (1 in 200) to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of pentobarbital RS, and dissolve in diluted ammonia water(28) (1 in 200) to make exactly 100 mL. Pipet 1 mL of this solution, add diluted ammonia water(28) (1 in 200) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy using the diluted ammonia water(28) (1 in 200) as the blank test solution, and determine the absorbances, A_T and A_S, at the wavelength of 240 nm.

$$\text{Amount (mg) of pentobarbital sodium } (C_{11}H_{17}N_2NaO_3) = \text{Amount (mg) of pentobarbital RS} \times \frac{A_T}{A_S} \times 1.097 \times \frac{1}{4}$$

Packaging and storage Preserve in tight containers.

Pentobarbital Sodium Capsules
펜토바르비탈나트륨 캡슐

Pentobarbital Sodium Capsules contain NLT 92.5% and NMT 107.5% of the labeled amount of pentobarbital sodium ($C_{11}H_{17}N_2NaO_3$: 248.25).

Method of preparation Prepare as directed under Capsules, with Pentobarbital Sodium.

Identification Weigh an amount of Pentobarbital Sodium Capsules, equivalent to about 0.1 g of pentobarbital sodium according to the labeled amount, transfer to a separatory funnel with 15 mL of water, add 2 mL of hydrochloric acid, shake well to mix and extract 5 times with 25 mL each of chloroform. Filter each extract through a suitable filter. Evaporate the filtrate to dryness on a steam bath with the aid of a current of air, add 10 mL of ether to the residue and evaporate to dryness again. Dry the residue recrystallized with heated ethanol at 105 ºC for 30 minutes. With the residue so obtained, proceed as directed under the Identification under Pentobarbital Sodium.

Dissolution Perform the test with 1 capsule of Pentobarbital Sodium Capsules at 100 revolutions per minute according to Method 1, using 900 mL of water as the dissolution medium. Take the dissolved solution after 45 minutes from starting the test and filter. Add freshly prepared diluted strong ammonia water (1 in 20) to obtain a solution having known concentration of about 10 μg of pentobarbital per mL and use this solution as the test solution. Separately, weigh accurately a suitable amount of pentobarbital RS, dissolve in freshly prepared diluted strong ammonia water (1 in 20) to obtain a solution having known concentration of about 10 μg of pentobarbital per mL and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using the diluted strong ammonia water (1 in 20) as a control solution, and determine the absorbance at

the absorbance maximum wavelength at around 240 nm. Multiply the amount of pentobarbital by 1.097 to obtain the amount of pentobarbital sodium.

It meets the requirements when the dissolution rate of Pentobarbital Sodium Capsules in 45 minutes is NLT 75%.

Uniformity of dosage units It meets the requirements when the Content uniformity test is performed according to the following procedure.

Transfer the contents of 1 capsule of Pentobarbital Sodium Capsules with 5 mL of ethanol to a 250-mL volumetric flask, add 10 mL of freshly prepared diluted strong ammonia water (1 in 200) and dilute immediately with the same solution to make 250 mL. Shake to mix and filter if necessary. Discard the first 20 mL of the filtrate and dilute the subsequent filtrate with diluted strong ammonia water (1 in 200) to obtain a solution having known concentration of about 10 μg of pentobarbital sodium per mL and use this solution as the test solution. Separately, weigh accurately a suitable amount of pentobarbital RS, dissolve in the diluted strong ammonia water (1 in 20) to obtain a solution having known concentration of 10 μg of pentobarbital per mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using the diluted ammonia water(28) (1 in 20) as a control solution, and determine the absorbances at the absorbance maximum wavelength at around 240 nm.

$$\text{Amount (mg) of pentobarbital sodium in 1 capsule} = \text{Labeled amount (mg) of pentobarbital sodium in 1 capsule} \times \frac{Concentration\left(\frac{\mu g}{mL}\right)of\ \text{pentobarbital of standard solution}}{Concentration\left(\frac{\mu g}{mL}\right)of\ \text{pentobarbital, calculated on the labled amount of test solution}} \times \frac{A_T}{A_S} \times 1.097$$

Assay Weigh accurately the mass of the contents of NLT 20 capsules of Pentobarbital Sodium Capsules and mix uniformly. Weigh accurately an amount of the contents, equivalent to about 50 mg of pentobarbital sodium ($C_{11}H_{17}N_2NaO_3$) and transfer to a separatory funnel. Add 15 mL of water and 1 mL of hydrochloric acid, shake to mix and extract five times with 25 mL each of chloroform. Filter the extract through about 15 g of anhydrous sodium sulfate placed on a funnel with glass wool. Wash anhydrous sodium sulfate with 15 mL of chloroform, combine the washings with the filtrate, add chloroform to make exactly 100 mL. To 2.0 mL of this solution, add 1.0 mL of internal standard solution and use this solution as the test solution. Separately, weigh accurately about 45 mg of pentobarbital RS, previously dried at 105 ℃ gel for 2 hours, dissolve in chloroform to make exactly 100 mL. To 2.0 mL of this solution, add 1.0 mL of internal standard solution and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Gas Chromatography and determine the peak area ratios, Q_T and Q_S of pentobarbital to the peak area of the internal standard.

$$\text{Amount (mg) of pentobarbital sodium } (C_{11}H_{17}N_2NaO_3) = \text{Amount (mg) of pentobarbital sodium RS} \times \frac{Q_T}{Q_S} \times 1.097$$

Internal standard solution—A solution of n-tricosane in chloroform (4 in 10000).

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A column about 4 mm in internal diameter and about 0.9 m in length, packed with diatomaceous earth for gas chromatography (149 μm to 177 μm in particle diameter), coated with polyamide at the ratio of 3%.

Column temperature: 200 ± 10 ℃

Sample injection port and detector temperature: About 225 ℃

Carrier gas: Nitrogen

Flow rate: Between 60 and 80 mL/min.

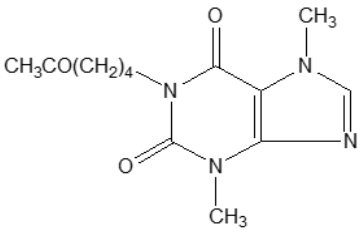
System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; n-tricosane and pentobarbital are eluted in this order with the resolution being NLT 2.3 and the symmetry factor being NMT 2.0.

System repeatability: Repeat the test 6 times with 5 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio is NMT 1.5%.

Packaging and storage Preserve in tight containers.

Pentoxifylline
펜톡시필린



$C_{13}H_{18}N_4O_3$: 278.31

3,7-Dimethyl-1-(5-oxohexyl)-1*H*-purine-2,6 (3*H*,7*H*)-dione [*6493-05-6*]

Pentoxifylline, when dried, contains NLT 98.0% and NMT 102.0% of pentoxifylline ($C_{13}H_{18}N_4O_3$).

Description Pentoxifylline occurs as a white crystalline powder. It has a characteristic odor and a bitter taste.

It is freely soluble in acetic acid(100), soluble in water, methanol, ethanol, or acetic anhydride, and slightly soluble in ether.

Identification (1) Determine the infrared spectra of Pentoxifylline and pentoxifylline RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention times of the major peaks obtained from the test solution and the standard solution in the Assay are the same.

Melting point Between 104 and 106 ℃.

pH The pH of an aqueous solution of Pentoxifylline (1 in 100) is between 5.0 and 7.5.

Absorption $E_{1cm}^{1\%}$ (274 nm): Between 360 and 376 (10 mg, water, 1000 mL).

Purity (1) ***Acid***—Dissolve 1 g of Pentoxifylline in 50 mL of freshly boiled and cooled water, and add 1 drop of bromothymol blue TS. The volume of 0.01 mol/L sodium hydroxide TS consumed until the color of this solution changes is NMT 0.2 mL.

(2) ***Chloride***—Dissolve 2.0 g of Pentoxifylline in 80 mL of hot water, cool rapidly to 20 ℃, and add water to make 100 mL. To 40 mL of this solution, add 6 mL of dilute nitric acid and water to make 50 mL, and use this solution as the test solution. Prepare the control solution by adding 6 mL of dilute nitric acid and water to 0.25 mL of 0.01 mol/L hydrochloric acid solution to make 50 mL (NMT 0.011%).

(3) ***Sulfate***—To 40 mL of the 100 mL solution from (2), add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 1 mL of dilute hydrochloric acid and water to 0.40 mL of 0.005 mol/L sulfuric acid to make 50 mL (NMT 0.024%).

(4) ***Heavy metals***—Proceed with 2.0 g of Pentoxifylline according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Arsenic***—Proceed with 2.0 g of Pentoxifylline according to Method 3 and perform the test (NMT 1 ppm).

(6) ***Related substances***—Weigh accurately about 35 mg of Pentoxifylline, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Weigh accurately about 7 mg of pentoxifylline RS and dissolve in the mobile phase to make exactly 100 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 100, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the area of the peak of each related substance obtained from the test solution, A_T, and the area of the pentoxifylline, A_S; the amount of each related substance from the test solution is NMT 0.2%, and the amount of total related substances is NMT 0.5%.

$$\text{Content (\%) of related substance} = (A_T / A_S) \times (C_S / C_T) \times 100$$

C_S: Concentration (mg/mL) of pentoxifylline in the standard solution

C_T: Concentration (mg/mL) of pentoxifylline in the test solution

Operating conditions

Proceed as directed under the operating conditions under the Assay.

Time span of measurement: NLT 5 times the retention time of pentoxifylline.

System suitability

System performance: Proceed with 20 μL of the system suitability solution according to the above conditions; the resolution between the caffeine peak and the pentoxifylline peak is NLT 10.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of pentoxifylline is NMT 5.0%.

System suitability solution—Weigh about 7 mg of caffeine, and dissolve in the mobile phase to make exactly 100 mL. Weigh accurately 1 mL of this solution and about 35 mg of pentoxifylline RS, transfer into a 100-mL volumetric flask, add the mobile phase to make 100 mL, and use this solution as the system suitability solution.

Loss on drying NMT 0.5% (1 g, in vacuum, phosphorus pentoxide, 60 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg of Pentoxifylline, and dissolve in the mobile phase to make 100 mL. Pipet 10 mL of this solution, and add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 5 mg of pentoxifylline RS, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of pentoxifylline from each solution.

$$\text{Amount (mg) of pentoxifylline} = \text{Amount (mg) of pentoxifylline RS} \times (A_T / A_S) \times 10$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 273 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of perchloric acid solution (1 in 1000), acetonitrile, tetrahydrofuran and methanol

(80 : 15 : 2.5 : 2).

Flow rate: 0.7 mL/min

System suitability

System performance: Proceed with 10 μL of the system suitability solution according to the above conditions; the resolution between the caffeine peak and the pentoxifylline peak is NLT 10.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions under the above operating conditions; the relative standard deviation of the peak areas of pentoxifylline is NMT 2.0%.

System suitability solution—Weigh accurately about 6 mg of caffeine and 12 mg of pentoxifylline RS, and dissolve in the mobile phase to make exactly 50 mL. Pipet 10 mL of this solution, add the mobile phase to make exactly 50 mL, and use this solution as the system suitability solution.

Each mL of 0.1 mol/L perchloric acid VS
= 27.831 mg of $C_{13}H_{18}N_4O_3$

Packaging and storage Preserve in tight containers.

Pentoxifylline Injection
펜톡시필린 주사액

Pentoxifylline Injection contains NLT 95.0% and NMT 105.0% of the labeled amount of pentoxifylline ($C_{13}H_{18}N_4O_3$: 278.31).

Method of preparation Prepare as directed under Injections, with Pentoxifylline.

Identification Perform the test as directed under the Thin Layer Chromatography with the test solution and the standard solution from the Assay. Spot 2 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform and ethanol(95) (8 : 2) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (principal wavelength: 254 nm); the R_f values of the spots from the test solution and the standard solution are the same.

pH Between 5.0 and 8.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 3 EU per mg of pentoxifylline

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Pentoxifylline Injection equivalent to 20 mg of pentoxifylline ($C_{13}H_{18}N_4O_3$), put in a separatory funnel, extract 3 times by shaking vigorously with about 10 mL of chloroform each, combine the extracts, and evaporate to dryness on a steam bath. Dissolve the residue in a small amount of methanol, transfer to a 100-mL volumetric flask, wash the container with methanol, and combine washings in the volumetric flask. Add methanol to make 100 mL. Pipet 10.0 mL of this solution, add methanol to make 200 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of pentoxifylline RS and dissolve in methanol to make 100 mL. Pipet 10.0 mL of this solution, add methanol to make 200 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at 274 nm as directed under the Ultraviolet-visible Spectroscopy, using methanol as the control solution.

$$\text{Amount (mg) of pentoxifylline } (C_{13}H_{18}N_4O_3) = Amount\ (mg)\ of \text{ pentoxifylline RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in light-resistant, hermetic containers.

Pentoxifylline Extended-Release Tablets
펜톡시필린 서방정

Pentoxifylline Extended-Release Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of pentoxifylline ($C_{13}H_{18}N_4O_3$: 278.31).

Method of preparation Prepare as directed under Tablets, with Pentoxifylline.

Identification The retention time of major peak and the ultraviolet absorption spectrum between 200 nm and 400 nm of the test solution and the standard solution for Assay are the same.

Purity ***Related substances***—Pipet 10 mL of the test stock solution from the Assay, add diluent to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately about 9.6 mg of pentoxifylline RS, add 0.8 mL of methanol, mix for 1 minute, and add diluent to make exactly 100 mL. Pipet 10 mL of this solution, add diluent to make exactly 50 mL, then pipet 5 mL of this solution, and add diluent to make exactly 100 mL. Use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak area, A_T, of the peak of each related substance ob-

tained from the test solution, and the peak area, A_S, of the pentoxifylline obtained from the standard solution; the amount of each related substance in the test solution is NMT 0.3%, and the total amount of related substances is NMT 1.0%.

$$\text{Content (\%) of related substance} = (A_T / A_S) \times (C_S / C_T) \times 100$$

C_S: Concentration (mg/mL) of pentoxifylline in the standard solution

C_T: Concentration (mg/mL) of pentoxifylline in the test solution

Operating conditions

Proceed as directed under the operating conditions under the Assay.

Time span of measurement: NLT 5 times the retention time of pentoxifylline

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above conditions; the relative standard deviation of the peak areas of pentoxifylline is NMT 5.0%.

Uniformity of dosage units Meets the requirements.

Dissolution Perform the test with 1 tablet of Pentoxifylline Extended-Release Tablets at 100 revolutions per minute according to Method 2, using 1000 mL of water as the dissolution medium. Take the medium 1 hour, 3 hours, and 6 hours after starting the test, add water of the same amount taken, then filter the medium, and use the filtrate as the test solution. Separately, weigh accurately about 20 mg of pentoxifylline RS, and dissolve in water to make 100 mL. Take 5.0 mL of this solution, add water to make 50 mL, and use this solution as the standard solution. The dissolution rates in 1 hour, 3 hours, and 6 hours are NMT 30%, 25% to 50%, and 50% to 75% respectively.

Assay Weigh accurately the mass of NLT 20 Pentoxifylline Extended-Release Tablets, and powder. Weigh accurately an amount equivalent to about 40 mg of pentoxifylline ($C_{13}H_{18}N_4O_3$), add 0.4 mL of methanol, mix for about 1 minute, and add 30 mL of diluent. Dissolve by sonicating for 60 minutes. To this solution, add 15 mL of diluent, cool, then add diluent to make exactly 50 mL, and use this solution as the test stock solution. Centrifuge this solution, pipet 3 mL of the clear supernatant, add diluent to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 40 mg of pentoxifylline RS, proceed in the same manner as the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of pentoxifylline in each solution.

$$\text{Amount (mg) of pentoxifylline} = \text{Amount (mg) of pentoxifylline RS} \times (A_T / A_S)$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 273 nm). However, a photo-diode array detector (200 nm to 400 nm) is used when Identification is performed.

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of perchloric acid solution (1 in 1000), acetonitrile, tetrahydrofuran and methanol (80 : 15 : 2.5 : 2).

Flow rate: 0.7 mL/min

System suitability

System performance: Proceed with 10 μL of the system suitability solution according to the above conditions; the resolution between the caffeine peak and the pentoxifylline peak is NLT 10.0.

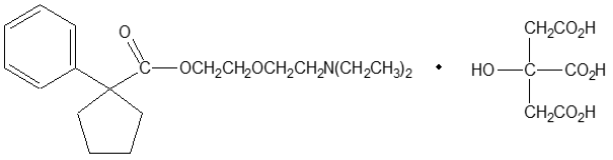
System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above conditions; the relative standard deviation of the peak areas of pentoxifylline is NMT 2.0%.

System suitability solution—Weigh accurately about 10 mg of caffeine and 20 mg of pentoxifylline RS, dissolve in the 0.2 mL of methanol, and add diluent to make exactly 25 mL. Pipet 3 mL of this solution, add diluent to make exactly 50 mL, and use this solution as the system suitability solution.

Diluent—A mixture of water and ethanol(95) (7 : 3).

Packaging and storage Preserve in tight containers.

Pentoxyverine Citrate
펜톡시베린시트르산염



$C_{20}H_{31}NO_3 \cdot C_6H_8O_7$: 525.59

2-[2-(Diethylamino)ethoxy]ethyl1-phenyl cyclopentane-1-carboxylate 2-hydroxypropane -1,2,3-tricarboxylate [*23142-01-0*]

Pentoxyverine Citrate, when dried, contains NLT 98.5% and NMT 101.0% of pentoxyverine citrate ($C_{20}H_{31}NO_3 \cdot C_6H_8O_7$).

Description Pentoxyverine Citrate occurs as a white crystalline powder.

It is very soluble in acetic acid(100), freely soluble in

water or ethanol(95), and practically insoluble in ether.

Identification (1) Dissolve 0.1 g of Pentoxyverine Citrate in 10 mL of water, and add 10 mL of Reinecke salt TS; a pale red precipitate is formed.

(2) Determine the infrared spectra of Pentoxyverine Citrate and pentoxyverine citrate RS, previously dried, as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Pentoxyverine Citrate (1 in 10) responds to the Qualitative Analysis (1) and (2) for citrate.

Melting point Between 92 and 95 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Pentoxyverine Citrate in 10 mL of water; the resulting solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 2.0 g of Pentoxyverine Citrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Pentoxyverine Citrate according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.20 g of Pentoxyverine Citrate in 10 mL of ethanol(95), and use this solution as the test solution. Pipet 1 mL of this solution, add ethanol(95) to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 15 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. After air-drying the plate, develop immediately the plate with a mixture of chloroform, methanol, ethyl acetate and ammonia water(28) (25 : 10 : 10 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Allow the plate to stand in iodine vapor for 10 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, phosphorus pentoxide, 60 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately 0.5 g of Pentoxyverine Citrate, previously dried, dissolve in 30 mL of acetic acid(100), add 30 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (indicator: 3 drops of methylrosaniline chloride TS) However, the endpoint of the titration is when the violet color of the solution changes from bluish green to green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 52.56 of $C_{20}H_{31}NO_3 \cdot C_6H_8O_7$

Packaging and storage Preserve in well-closed containers.

Saccharated Pepsin
함당펩신

Saccharated Pepsin is an enzyme preparation with proteolytic activities containing Lactose Hydrate mixed with pepsin obtained from the gastric mucous membrane of pigs or cattle and contains NLT 3800 units and NMT 6000 units per gram.

Description Saccharated Pepsin occurs as a white powder. It has a characteristic odor and has a slight sweet taste.
Saccharated Pepsin is slightly turbidly soluble in water and insoluble in ethanol(95) or ether.
It is sparingly hygroscopic.

Purity (1) ***Rancidity***—Saccharated Pepsin has no unpleasant or rancid odor.

(2) ***Acid***—Dissolve 0.5 g of Saccharated Pepsin in 50 mL of water, and add 0.50 mL of 0.1 mol/L sodium hydroxide TS and 2 drops of phenolphthalein TS; the resulting solution exhibits a red color.

Loss on drying NMT 1.0% (1 g, 80 ℃, 4 hours).

Residue on ignition NMT 0.5% (1 g).

Assay (1) ***Test solution***—Weigh accurately an amount equivalent to about 1250 units of Saccharated Pepsin, and dissolve in 0.01 mol/L hydrochloric acid TS, previously cooled with ice, to make exactly 50 mL.

(2) ***Standard solution***—Weigh accurately an appropriate amount of saccharated pepsin RS, and dissolve in 0.01 mol/L hydrochloric acid TS, previously cooled with ice, to make a solution containing about 25 units per mL.

(3) ***Substrate solution***—Use substrate solution 1 as directed under Protein digestive activity of Protein Digestion Test (2). However, adjust the pH to 2.0.

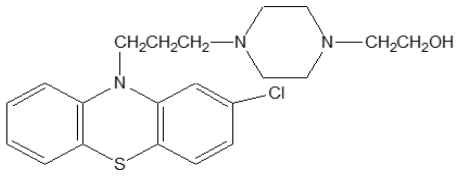
(4) ***Procedure***—Proceed as directed under Protein digestive activity of Protein Digestion Test (2), and determine A_T and A_{TB}. However, use trichloroacetic acid TS A as the precipitation TS. Separately, proceed with the standard solution in the same manner as the test solution, and determine A_S and A_{SB}. Unit per g of Saccharated Pepsin is calculated according to the following equation:

$$\text{Unit per g of Saccharated Pepsin} = U_S \times \frac{A_T - A_{TB}}{A_S - A_{SB}} \times \frac{1}{W}$$

U_S: Number of units per mL of the standard solution
W: Amount (g) of the sample per mL of the test solution

Packaging and storage Preserve in tight containers and store at below 30 ℃.

Perphenazine
페르페나진



$C_{21}H_{26}ClN_3OS$: 403.97

2-{4-[3-(2-Chloro-10*H*-phenothiazin-10-yl) propyl]piperazin-1-yl}ethan-1-ol [*58-39-9*]

Perphenazine, when dried, contains NLT 98.5% and NMT 101.0% of perphenazine ($C_{21}H_{26}ClN_3OS$).

Description Perphenazine occurs as white to pale yellow crystals or a crystalline powder. It is odorless and has a bitter taste.
It is freely soluble in methanol or ethanol(95), soluble in anhydrous ether, sparingly soluble in ether, and practically insoluble in water.
It dissolves in dilute hydrochloric acid.
It is gradually colored by light.

Identification Determine the infrared spectra of Perphenazine and perphenazine RS, previously dried, as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 95 and 100 ℃.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Perphenazine according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Perform the test using a light-resistant container in a stream of nitrogen gas. Dissolve 0.10 g of Perphenazine in 10 mL of ethanol(95), and use this solution as the test solution. Pipet 1 mL of this solution and add ethanol(95) to make exactly 10 mL. Pipet 1 mL of this solution, add ethanol(95) to make exactly 20 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of 1-butanone and 1 mol/L ammonia TS (5 : 1) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, phosphorus pentoxide, 65 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Perphenazine, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 3 drops of methylrosaniline chloride TS). The endpoint of the titration is when the violet color of this solution changes from bluish purple to bluish green. Perform a blank test in the same manner.

Each mL of 0.1 mol/L perchloric acid VS
= 20.198 mg of $C_{21}H_{26}ClN_3OS$

Packaging and storage Preserve in light-resistant, tight containers.

Perphenazine Tablets
페르페나진 정

Perphenazine Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of perphenazine ($C_{21}H_{26}ClN_3OS$: 403.98).

Method of preparation Prepare as directed under Tablets, with Perphenazine.

Identification The ultraviolet-visible absorption spectrum at 200 to 400 nm and the retention time of the major peak obtained from the test solution and the standard solution under the Assay are the same.

Dissolution Perform the test with 1 tablet of Perphenazine Tablets at 100 revolutions per minute according to Method 2, using 900 mL of diluted pH 6.8 phosphate buffer solution (1 in 2) as the dissolution medium. Take NLT 30 mL of the dissolved solution 90 minutes after starting the test, and filter through a membrane filter with a pore size of NMT 0.8 μm. Discard the first 10 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately about 10 mg perphenazine RS, previously dried in vacuum in a phosphorus pentoxide desiccator at 65 ℃ for 4 hours, dissolve in 5 mL of 0.1 mol/L hydrochloric acid TS, and add diluted pH 6.8 phosphate buffer solution (1 in 2) to make exactly 250 mL. Pipet 5 mL of this solution, add diluted pH 6.8 phosphate buffer solution (1 in 2) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy and determine the absorbances, A_T and A_S, at the wavelength of 255 nm.
It meets the requirements if the dissolution rate of Perphenazine Tablets in 90 minutes is NLT 70%.

Dissolution rate (%) of the labeled amount of perphenazine ($C_{21}H_{26}ClN_3OS$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 36$$

W_S: Amount (mg) of the reference standard

C: Labeled amount (mg) of perphenazine ($C_{21}H_{26}ClN_3OS$) in 1 tablet

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following procedure.

Disintegrate 1 Tablet of Perphenazine Tablets by shaking with 5 mL of water, shake well with 70 mL of methanol and add methanol to make exactly 100 mL. Centrifuge this solution, pipet χ mL of the clear supernatant, add methanol buffer solution to make V mL of a solution containing about 4 μg of perphenazine ($C_{21}H_{26}ClN_3OS$) per mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of perphenazine RS, previously dried in vacuum in a phosphorus pentoxide desiccator at 65 ℃ for 4 hours, and dissolve in methanol to make exactly 250 mL. Pipet 5 mL of this solution, add methanol to make exactly 50 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy and determine the absorbances, A_T and A_S, at the wavelength of 258 nm.

Amount (mg) perphenazine ($C_{21}H_{26}ClN_3OS$)

$$= \text{Amount (mg) of perphenazine RS} \times \frac{A_T}{A_S} \times \frac{V}{25} \times \frac{1}{x}$$

Assay Weigh accurately the mass of NLT 20 Perphenazine Tablets, and finely powder. Weigh accurately a portion of the powder, equivalent to about 5 mg of perphenazine ($C_{21}H_{26}ClN_3OS$) dissolve in methanol to make exactly 100 mL and filter. Discard the first 10 mL of the filtrate, pipet 10 mL of the subsequent filtrate and 5 mL of the internal standard solution, add methanol to make exactly 100 mL and use this solution as the test solution. Separately, weigh accurately about 25 mg of perphenazine RS, previously dried in vacuum in a phosphorus pentoxide desiccator at 65 ℃ for 4 hours, and dissolve in methanol to make exactly 100 mL. Pipet 2 mL of this solution and 5 mL of the internal standard solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of perphenazine to the peak area of the internal standard, respectively.

Amount (mg) perphenazine ($C_{21}H_{26}ClN_3OS$)

$$= \text{Amount (mg) of perphenazine RS} \times \frac{Q_T}{Q_S} \times \frac{1}{5}$$

Internal standard solution—Weigh 50 mg of anhydrous caffeine RS and dissolve in methanol to make 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm). However, a photo-diode array detector (200 nm to 400 nm) is used when the Identification is performed.

Column: A stainless steel column, about 4 mm in internal diameter and 15 cm to 30 cm in length, packed with nitrilized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

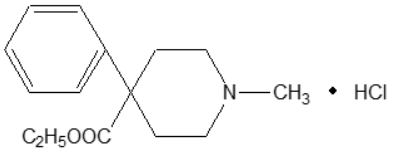
Mobile phase: Dissolve 0.65 g of ammonium acetate in 84 mL of water, and add 916 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of perphenazine is about 5.5 minutes.

Selection of column: Proceed with 20 μL of the standard solution according to the above conditions; the internal standard and perphenazine are eluted in this order with the resolution being NLT 3.0.

Packaging and storage Preserve in light-resistant, tight containers.

Pethidine Hydrochloride
페티딘염산염



Operidine $C_{15}H_{21}NO_2 \cdot HCl$: 283.79

Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride [*50-13-5*]

Pethidine Hydrochloride, when dried, contains NLT 98.0% and NMT 101.0% of pethidine hydrochloride ($C_{15}H_{21}NO_2 \cdot HCl$).

Method of preparation If there is any possibility of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine to be inserted as the potential impurities according to the manufacturing process of Pethidine Hydrochloride, take caution with starting material, manufacturing process, and intermediate material to minimize the residue of impurities in consideration of risk assessment results. If necessary, the manufacturing process may be verified by the test data proving that no quality risk exists in final drug substances.

Description Pethidine Hydrochloride occurs as a white crystalline powder.

It is freely soluble in water, acetic acid(100), or ethanol(95), sparingly soluble in acetic anhydride, and practically insoluble in ether.

Dissolve 1.0 g of Pethidine Hydrochloride in 20 mL of water; the pH of the solution is between 3.8 and 5.8.

Identification (1) Determine the absorption spectra of aqueous solutions of Pethidine Hydrochloride and pethidine hydrochloride RS (1 in 2000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Pethidine Hydrochloride, previously dried, and pethidine hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Pethidine Hydrochloride (1 in 50) responds to the Qualitative Analysis (2) for chloride.

Melting point Between 187 and 189 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Pethidine Hydrochloride in 10 mL of water; the resulting solution is clear and colorless.

(2) ***Sulfate***—Perform the test with 0.20 g of Pethidine Hydrochloride. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.240%).

(3) ***Related substances***—Dissolve 50 mg of Pethidine Hydrochloride in 20 mL of the mobile phase, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of each solution by the automatic integration method; the sum of peak areas other than the major peak from the test solution is not greater than the major peak area from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 257 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: Dissolve 2.0 g of sodium lauryl sulfate in 1000 mL of diluted phosphoric acid (1 in 1000), and add sodium hydroxide TS to adjust the pH to 3.0. To 550 mL of this solution, add 450 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of pethidine is about 7 minutes.

System suitability

Test for required detectability: Take exactly 2 mL of the standard solution, and add the mobile phase to make exactly 20 mL. Confirm that the peak area of pethidine obtained from 20 μL of this solution is equivalent to 5% to 15% of the peak area of pethidine obtained from the standard solution.

System performance: To 2 mL of the test solution and 2 mL of a solution of isoamyl p-hydroxybenzoate in the mobile phase (1 in 50000), add the mobile phase to make 10 mL. Proceed with 20 μL of this solution according to the above conditions; pethidine and isoamyl p-hydroxybenzoate are eluted in this order with the resolution between their peaks being NLT 2.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of pethidine is NMT 2.0%.

Time span of measurement: About 2 times the retention time of pethidine after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately 0.5 g of Pethidine Hydrochloride, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 28.379 mg of $C_{15}H_{21}NO_2 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Pethidine Hydrochloride Injection
페티딘염산염 주사액

Operidine Injection

Pethidine Hydrochloride Injection is an aqueous injection and contains NLT 95.0% and NMT 105.0% of the labeled amount of pethidine hydrochloride ($C_{15}H_{21}NO_2 \cdot HCl$: 283.79).

Method of preparation Prepare as directed under Injections, with Pethidine Hydrochloride.

Description Pethidine Hydrochloride Injection occurs as a clear, colorless liquid.
It is affected by light.

pH Between 4.0 and 6.0.

Identification Take an amount of Pethidine Hydrochloride Injection, equivalent to 0.1 g of Pethidine Hydrochloride according to the labeled amount, add water to make 200 mL, and determine the absorption spectra as directed under Ultraviolet-visible Spectroscopy; it exhibits maxima between 250 nm and 254 nm, between 599 nm and 259 nm, and between 261 nm and 265 nm.

Sterility Meets the requirements.

Bacterial endotoxins Less than 6.0 EU per mg of pethi-

dine hydrochloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Pethidine Hydrochloride Injection equivalent to about 0.1 g of pethidine hydrochloride ($C_{15}H_{21}NO_2$·HCl), add exactly 10 mL of the internal standard solution, and add the mobile phase to make 50 mL. Take 5 mL of this solution, add the mobile phase to make 20 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of Pethidine Hydrochloride RS, previously dried at 105 ℃ for 3 hours, add exactly 10 mL of the internal standard solution and add the mobile phase to make exactly 50 mL. Take 5 mL of this solution, add the mobile phase to make 20 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Calculate the ratios, QT and QS, of the peak area of pethidine to that of the internal standard for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of pethidine hydrochloride } (C_{15}H_{21}NO_2\cdot HCl) = \text{Amount (mg) of pethidine hydrochloride RS (mg)} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of isoamyl parahydroxybenzoate in the mobile phase (1 in 12500).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 257 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 2.0 g of sodium lauryl sulfate in 1000 mL of diluted phosphoric acid (1 in 1000), adjust the pH to 3.0 with sodium hydroxide TS and to 550 mL of this solution, add 450 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of pethidine is about 7 minutes.

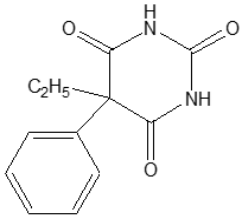
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above operating conditions; pethidine and the internal standard are eluted in this order with the resolution between their peaks being NLT 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio of pethidine to the internal standard is NMT 1%.

Packaging and storage Preserve in light-resistant, hermetic containers. Colored containers may be used for Pethidine Hydrochloride Injection.

Phenobarbital
페노바르비탈



$C_{12}H_{12}N_2O_3$: 232.24

5-Ethyl-5-phenyl-1,3-diazinane-2,4,6-trione [*50-06-6*]

Phenobarbital, when dried, contains NLT 99.0% and NMT 101.0% of phenobarbital ($C_{12}H_{12}N_2O_3$).

Description Phenobarbital occurs as white crystals or a crystalline powder. It is odorless and has a bitter taste.
It is very soluble in *N*,*N*-dimethylformamide, freely soluble in ethanol(95), acetone, or pyridine, soluble in ether, and very slightly soluble in water.
It is soluble in sodium hydroxide TS or ammonia TS.
The pH of the saturated solution of Phenobarbital is between 5.0 and 6.0.

Identification (1) Determine the absorption spectra of solutions of Phenobarbital and phenobarbital RS in boric acid-potassium chloride-sodium hydroxide buffer solution, pH 9.6 (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Phenobarbital and phenobarbital RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 175 and 179 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Phenobarbital in 5 mL of sodium hydroxide TS; the resulting solution is colorless and clear.

(2) ***Chloride***—Dissolve 0.30 g of Phenobarbital in 20 mL of acetone, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 20 mL of acetone, 6 mL of dilute nitric acid and water to 0.30 mL of 0.01 mol/L hydrochloric acid TS to make 50 mL (NMT 0.035%).

(3) ***Heavy metals***—Proceed with 1.0 g of Phenobar-

bital according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Phenylbarbituric acid***—Dissolve 1.0 g of Phenobarbital in 5 mL of ethanol(95) by boiling for 3 minutes; the resulting solution is clear.

(5) ***Related substances***—Dissolve about 0.10 g of Phenobarbital in 100 mL of acetonitrile, and use this solution as the test solution. Pipet 2 mL of the test solution, and add acetonitrile to make exactly 100 mL. Pipet 5 mL of this solution, add acetonitrile to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; each peak area of related substances other than the phenobarbital peak obtained from the test solution is not greater than the peak area of phenobarbital from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 150 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 45 ℃.

Mobile phase: A mixture of water and acetonitrile (11 : 9).

Flow rate: Adjust the flow rate so that the retention time of phenobarbital is about 5 minutes.

Time span of measurement: About 12 times the retention time of phenobarbital after the solvent peak.

System suitability

Test for required detectability: Weigh exactly 5 mL of the standard solution and add the acetonitrile to make exactly 20 mL. The peak area of phenobarbital obtained from 10 μL of this solution is equivalent to 20% to 30% of the peak area of phenobarbital from the standard solution.

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the number of theoretical plates is NLT 3000 with the symmetry factor being NMT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of phenobarbital is NMT 3.0%.

Loss on drying NMT 1.0% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Phenobarbital, previously dried, dissolve in 50 mL of *N*,*N*-dimethylformamide, and titrate the solution with 0.1 mol/L potassium hydroxide-ethanol (Indicator: 1 mL of alizarin yellow GG-thymolphthalein TS). However, the endpoint of the titration is when the color of the solution changes from yellow to yellowish green. Separately, perform a blank test with a solution prepared by adding 22 mL of ethanol(95) to 50 mL of *N*,*N*-Dimethylformamide in the same manner and make any necessary correction.

Each mL of 0.1 mol/L potassium hydroxide-ethanol VS
= 23.224 mg of $C_{12}H_{12}N_2O_3$

Packaging and storage Preserve in well-closed containers.

10% Phenobarbital Powder
페노바르비탈 10배산

10% Phenobarbital Powder contains NLT 9.3% and NMT 10.7% of phenobarbital ($C_{12}H_{12}N_2O_3$: 232.24).

Method of preparation

Phenobarbital	100 g
Starch, lactose hydrate or a mixture of these ingredients	A sufficient amount
Total amount	1000 g

Prepare as directed under Powders with the above.

Identification (1) Determine the absorption spectrum of the test solution obtained in the Assay as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 238 nm and 242 nm.

(2) Weigh 6 g of 10% Phenobarbital Powder, add 150 mL of ethanol, shake well to mix, then filter. Evaporate the filtrate on a steam bath until about 5 mL remains, add 50 mL of water to precipitate, then filter, and collect the crystals. Dry the crystals for 2 hours at 105 ℃ and measure as directed in the potassium bromide disk method under Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Dissolution Perform the test with about 0.3 g of 10% Phenobarbital Powder at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take the dissolved solution 30 minutes after starting the test, filter, then take NLT 20 mL of the filtrate, and filter using a membrane filter with a pore size of NMT 0.45 μm. Discard the first 10 mL of the filtrate, pipet 5 mL of the subsequent filtrate, add pH 9.6 boric acid-potassium chloride-sodium hydroxide buffer solution to make exactly 10 mL, and use this solution as the test solution. Separately weigh about 17 mg of phenobarbital RS, previously dried at 105℃ for 2 hours, and dissolve in water to make 100 mL. Pipet 5 mL of this solution and add water to make exactly 25 mL. Again, pipet 5 mL of this solution, add pH 9.6 boric acid-potassium chloride-sodium hydroxide

buffer solution to make exactly 10 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at 240 nm as directed under the Ultraviolet-visible Spectroscopy, using a mixture of pH 9.6 boric acid, potassium chloride, sodium hydroxide buffer solution and water (2 : 1) as the control solution. Meets the requirements if the dissolution rate of 10% Phenobarbital Powder in 30 minutes is NLT 80%.

Dissolution rate (%) with respect to the labeled amount of phenobarbital ($C_{12}H_{12}N_2O_3$)

$$= \frac{W_S}{W_T} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 180$$

W_S: Amount (mg) of phenobarbital RS

W_T: Amount (g) of 10% Phenobarbital Powder taken.

C: Labeled amount (mg) of phenobarbital ($C_{12}H_{12}N_2O_3$) per g

Particle size distribution estimation by analytical sieving Meets the requirements.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Weigh accurately about 0.2 g of 10% Phenobarbital Powder and dissolve in pH 9.6 boric acid-potassium chloride-sodium hydroxide buffer solution to make exactly 100 mL. Pipet 5.0 mL of this solution, add exactly 100 mL of pH 9.6 boric acid-potassium chloride-sodium hydroxide buffer solution, and use this solution as the test solution. Separately, weigh accurately about 20 mg of phenobarbital RS, previously dried for 2 hours at 105 ℃, and dissolve in pH 9.6 boric acid-potassium chloride-sodium hydroxide buffer solution to make exactly 100 mL. Pipet 5 mL of this solution, add pH 9.6 boric acid-potassium chloride-sodium hydroxide buffer solution to make 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S of the test solution and the standard solution, respectively, at 240 nm as directed under Ultraviolet-visible Spectroscopy, using pH 9.6 boric acid-potassium chloride-sodium hydroxide buffer solution as the control solution.

Amount (mg) of phenobarbital ($C_{12}H_{12}N_2O_3$)

$$= \text{Amount (mg) of phenobarbital RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in well-closed containers.

Phenobarbital Tablets
페노바르비탈 정

Phenobarbital Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of phenobarbital ($C_{12}H_{12}N_2O_3$: 232.24).

Method of preparation Prepare as directed under Tablets, with Phenobarbital.

Identification (1) Weigh an amount of Phenobarbital Tablets, previously powdered, equivalent to 60 mg of phenobarbital according to the labeled amount, add 50 mL of chloroform, shake well to mix, and then filter. Evaporate the filtrate to dryness, and dry at 105 ℃ for 2 hours. With this residue and phenobarbital RS, determine the infrared spectra as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers. If any difference appears in the absorption spectra, dissolve the residue and phenobarbital RS in chloroform, respectively, evaporate the solvent and repeat the test on the residues.

(2) The retention times of the major peaks obtained from the test solution and the standard solution in the Assay are the same.

Dissolution Perform the test with 1 tablet of Theophylline Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take the dissolved solution 45 minutes after starting the test, filter, dilute with pH 9.6 alkaline borate buffer solution to an appropriate concentration, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of phenobarbital RS, previously dried at 105 ℃ for 2 hours, dissolve in pH 9.6 alkaline borate buffer solution to make a solution having a certain concentration, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance at the absorbance maximum wavelength of about 240 nm.

It meets the requirements if the dissolution rate of Phenobarbital Tablets in 45 minutes is NLT 75%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Phenobarbital Tablets, and powdered. Weigh accurately an amount equivalent to about 20 mg of phenobarbital ($C_{12}H_{12}N_2O_3$), add 15.0 mL of the internal standard solution, sonicate, and shake to mix for 15 minutes. Filter, and use the filtrate as the test solution. Separately, weigh accurately about 20 mg of phenobarbital RS (previously dried at 105 ℃ for 2 hours), add 15.0 mL of the internal standard solution, and use this solution as the standard solution. If necessary, sonicate and shake to mix to dissolve. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of peak area of phenobarbital to the peak area of the internal standard, respectively.

Amount (mg) phenobarbital ($C_{12}H_{12}N_2O_3$)

= Amount (mg) of phenobarbital RS× $\frac{Q_T}{Q_S}$

Internal standard solution—Dissolve 12.5 mg of caffeine in 100 mL of a mixture of methanol and pH 4.5 buffer solution (1 : 1).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of pH 4.5 buffer solution and methanol (3 : 2).

Flow rate: 2.0 mL/min

System suitability

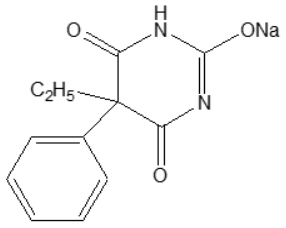
System performance: Proceed with 10 μL of the standard solution under the above conditions; the resolution between caffeine and phenobarbital is NLT 1.2, and the symmetry factor is NMT 2.0.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio is NMT 2.0%.

pH 4.5 buffer solution—Dissolve 6.6 g of sodium acetate trihydrate and 3.0 mL of acetic acid(100) in water to make 1000 mL. If necessary, add acetic acid(100) to adjust the pH to 4.5 ± 0.1.

Packaging and storage Preserve in well-closed containers.

Phenobarbital Sodium
페노바르비탈나트륨



$C_{12}H_{11}N_2NaO_3$: 254.22

Sodium 5-ethyl-4,6-dioxo-5-phenyl-1*H*-pyrimidin-2-olate [*57-30-7*]

Phenobarbital Sodium contains NLT 98.5% and NMT 101.0% of phenobarbital sodium ($C_{12}H_{11}N_2NaO_3$), calculated on the dried basis.

Description Phenobarbital Sodium occurs as white crystals or a crystalline powder. It is odorless and has a bitter taste.

It is very soluble in water, soluble in ethanol(95), and practically insoluble in ether or chloroform. It is hygroscopic and gradually decomposes if left in humid air.

Identification (1) Take 50 mg of Phenobarbital Sodium into a separatory funnel, dissolve in 15 mL of water, shake to mix by adding 2 mL of hydrochloric acid, and extract 4 times each with 25 mL of chloroform. Filter all chloroform extract solutions, take 50 mL of the filtrate, and evaporate on a steam bath in a stream of air. Add 10 mL of ether, evaporate again, and dry at 105 °C for 2 hours. With this residue and phenobarbital RS, determine the infrared spectra as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit maxima at the same wavenumbers.

(2) Ignite 0.2 g of Phenobarbital Sodium, and dissolve by adding 10 mL of water to the residue; the resulting solution turns red litmus paper into blue. Also, this solution responds to the Qualitative Analysis for sodium salt.

(3) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

pH Dissolve 1.0 g of Phenobarbital Sodium in 10 mL of freshly boiled and cooled water; the pH of this solution is between 9.2 and 10.2.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Phenobarbital Sodium in 10 mL of freshly boiled and cooled water; the resulting solution is clear and colorless after 1 minute.

(2) ***Heavy metals***—Dissolve 2.0 g of Phenobarbital Sodium in 52 mL of water, add 8 mL of 1 mol/L hydrochloric acid, shake vigorously to mix, and filter. Discard the first 5 mL of the filtrate, take 20 mL of the subsequent filtrate, and add water to make 25 mL. Use this solution as the test solution, proceed with the solution according to Method 1, and perform the test. Prepare the control solution with 1.5 mL of lead standard solution (NMT 30 ppm).

Loss on drying NMT 7.0% (1 g, 150 ℃, 4 hours).

Assay Weigh accurately about 22 mg of Phenobarbital Sodium, add 15.0 mL of internal standard solution, sonicate, and shake for 15 minutes to mix. Filter through a membrane filter with a pore size of NMT 0.5 μm, and use the filtrate as the test solution. Separately, weigh accurately about 20 mg of phenobarbital RS (previously dried at 105 ℃ for 2 hours), add 15.0 mL of internal standard solution, and use this solution as the standard solution. If necessary, dissolve it by sonication and shaking to mix. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios of the peak area, Q_T and Q_S, of phenobarbital to that of the internal standard.

Amount (mg) of phenobarbital sodium ($C_{12}H_{11}N_2NaO_3$)
= Amount (mg) of phenobarbital RS× $\frac{Q_T}{Q_S}$ ×1.095

Internal standard solution—Dissolve 12.5 mg of caffeine in 100 mL of a mixture of methanol and pH 4.5 buffer solution (1 : 1).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of pH 4.5 buffer solution and methanol (3 : 2).

Flow rate: 2 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the resolution between caffeine and phenobarbital is NLT 1.2, and the symmetry factor is NMT 2.0.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio is NMT 2.0%.

pH 4.5 buffer solution—Dissolve 6.6 g of sodium acetate trihydrate and 3.0 mL of acetic acid(100) in water to make 1000 mL. If necessary, add acetic acid(100) to adjust the pH to 4.5 ± 0.1.

Packaging and storage Preserve in tight containers.

Phenobarbital Sodium Tablets
페노바르비탈나트륨 정

Phenobarbital Sodium Tablets contain NLT 92.5% and NMT 107.5% of the labeled amount of phenobarbital sodium ($C_{12}H_{11}N_2NaO_3$: 254.22).

Method of preparation Prepare as directed under Tablets, with Phenobarbital Sodium.

Identification (1) To 0.2 g of the residue obtained from the Assay, add 15 mL of diluted ethanol (1 in 4), dissolve on a steam bath, and filter through a glass filter when hot. Then, cool. Wash with a small amount of diluted ethanol (1 in 4), evaporate the filtrate from the stoppered test tube, and then dry at 105 ℃ for 1 hour. With this residue and phenobarbital RS, determine the infrared spectra as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

(2) The powdered Phenobarbital Sodium Tablets responds to the Qualitative Analysis for sodium salt.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

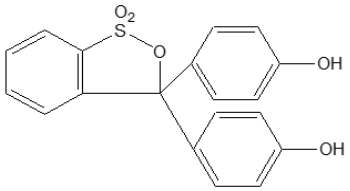
Assay Weigh accurately the mass of NLT 20 Phenobarbital Sodium Tablets, and powdered. Weigh accurately a portion of the powder, equivalent to 22 mg of phenobarbital sodium ($C_{12}H_{11}N_2NaO_3$), dissolve in 15 mL of internal standard solution, mix, and sonicate for 15 minutes. Filter, and use the filtrate as the test solution. Separately, weigh accurately about 20 mg of Phenobarbital RS (previously dried at 105 ºC for 2 hours), dissolve in 15 mL of internal standard solution, and use this solution as the standard solution. Perform the test as directed under the Assay of Phenobarbital Sodium.

$$\text{Amount (mg) of phenobarbital sodium } (C_{12}H_{11}N_2NaO_3) = \text{Amount (mg) of phenobarbital RS} \times \frac{Q_T}{Q_S} \times 1.095$$

Internal standard solution—Dissolve 12.5 mg of caffeine in 100 mL of a mixture of methanol and pH 4.5 buffer solution (1 : 1).

Packaging and storage Preserve in tight containers.

Phenolsulfonphthalein
페놀설폰프탈레인



$C_{19}H_{14}O_5S$: 354.38

4-[3-(4-Hydroxyphenyl)-1,1-dioxo-2,1λ6-benzoxathiol-3-yl]phenol [*143-74-8*]

Phenolsulfonphthalein, when dried, contains NLT 98.0% and NMT 101.0% of phenolsulfonphthalein ($C_{19}H_{14}O_5S$).

Description Phenolsulfonphthalein is a vivid red to dark red crystalline powder.
It is very slightly soluble in water or ethanol(95).
It is soluble in sodium hydroxide TS.

Identification (1) Dissolve 5 mg of Phenolsulfonphthalein in 2 to 3 drops of sodium hydroxide TS, add 2 mL of 0.05 mol/L bromine solution and 1 mL of dilute sulfuric acid, shake well to mix, and allow to stand for 5 minutes. Add sodium hydroxide TS to make the solution alkaline; the resulting solution exhibits a bluish purple color.

(2) Dissolve 10 mg of Phenolsulfonphthalein and phenolsulfonphthalein RS in diluted sodium carbonate TS (1 in 10) to make 200 mL. Take 5 mL of this solution, and add diluted sodium carbonate TS (1 in 10) to make 100 mL. Determine the absorption spectra of this solution as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the

same wavelengths.

Purity (1) ***Insoluble substances***—Weigh accurately about 1 g of Phenolsulfonphthalein, add 20 mL of sodium bicarbonate solution (1 in 40), shake to mix, and allow to stand for 1 hour. Add water to make 100 mL, and allow to stand for 24 hours. Filter and collect the insoluble substances using the previously weighed glass filter, wash 1 time with 25 mL of sodium bicarbonate solution (1 in 100) and 5 times with 5 mL each of water, and dry at 105 ℃ for 1 hour; the residue is NMT 0.2%.

(2) ***Related substances***—Dissolve 0.10 g of Phenolsulfonphthalein in 5 mL of dilute sodium hydroxide TS, and use this solution as the test solution. Pipet 0.5 mL of this solution, add dilute sodium hydroxide TS to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of *t*-amyl alcohol, acetic acid(100), and water (4 : 1 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. After allowing the plate to stand in ammonia vapor, examine under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 1.0% (1 g, silica gel, 4 hours).

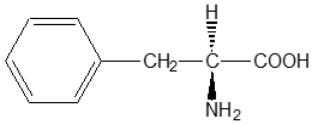
Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately 0.15 g of Phenolsulfonphthalein, previously dried, transfer to an iodine bottle, dissolve in 30 mL of sodium hydroxide solution (1 in 250), and add water to make 200 mL. Add exactly 50 mL of 0.05 mol/L bromine solution, rapidly add 10 mL of hydrochloric acid again, immediately close the stopper, and allow to stand for 5 minutes while occasionally shaking to mix. Add 7 mL of potassium iodide TS, immediately close the stopper again, shake gently for 1 minute to mix, and titrate free iodine with 0.1 mol/L sodium thiosulfate VS (indicator: 1 mL of starch TS). Perform a blank test in the same manner.

Each mL of 0.05 mol/L bromine VS
= 4.430 mg of $C_{19}H_{14}O_5S$

Packaging and storage Preserve in well-closed containers.

L-Phenylalanine
L-페닐알라닌



$C_9H_{11}NO_2$: 165.19
(2*S*)-2-Amino-3-phenylpropanoic acid [*63-91-2*]

L-Phenylalanine, when dried, contains NLT 98.5% and NMT 101.0% of L-phenylalanine ($C_9H_{11}NO_2$).

Description L-Phenylalanine occurs as white crystals or a crystalline powder. It is odorless or has a slight, characteristic odor and a slightly bitter taste.
It is freely soluble in formic acid, sparingly soluble in water, and practically insoluble in ethanol(95) or ether.
It dissolves in dilute hydrochloric acid.

Identification Determine the infrared spectra of L-Phenylalanine and L-phenylalanine RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -33.0° and -35.5° (0.5 g after drying, water, 25 mL, 100 mm).

pH Dissolve 0.20 g of L-Phenylalanine in 20 mL of water by warming, and cool; the pH of the solution is between 5.3 and 6.3.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of L-Phenylalanine in 10 mL of 1 mol/L hydrochloric acid TS; the resulting solution is clear and colorless.

(2) ***Chloride***—Perform the test with 0.5 g of L-Phenylalanine. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.021%).

(3) ***Sulfate***—Perform the test with 0.6 g of L-Phenylalanine. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid (NMT 0.028%).

(4) ***Ammonium***—Perform the test with 0.25 g of L-Phenylalanine. Prepare the control solution with 5.0 mL of ammonium standard solution (NMT 0.02%).

(5) ***Heavy metals***—Add 40 mL of water and 2 mL of dilute acetic acid to 1.0 g of L-Phenylalanine, and dissolve by warming. After cooling, add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 2 mL of dilute acetic acid and water to 2.0 mL of lead standard solution to make 50 mL (NMT 20 ppm).

(6) ***Iron***—Weigh accurately 0.333 g of L-Phenylalanine, dissolve in water to make 45 mL, add 2 mL of hydrochloric acid, and use this solution as the test solution. Add water to 1.0 mL of iron standard solution to make 45 mL, add 2 mL of hydrochloric acid, and use this solution as the standard solution. To the test solution and the standard solution, add 50 mg of ammonium peroxydisulfate and 3 mL of 30% ammonium thiocyanate solution, and mix; the color obtained from the test solution is not more intense than that from the standard solution (NMT 30 ppm).

(7) ***Arsenic***—Dissolve 1.0 g of L-Phenylalanine in 3 mL of 1 mol/L hydrochloric acid TS and 2 mL of water by warming and perform the test using this solution as the test solution (NMT 2 ppm).

(8) ***Related substances***—Dissolve 0.10 g of L-Phenylalanine in 25 mL of water, and use this solution as the test solution. Pipet 1 mL of this solution and add water to make exactly 50 mL. Pipet 5 mL of this solution, add water to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, water and acetic acid(100) (3 : 1 : 1) as the developing solvent to a distance of about 10 cm, and dry the plate at 80 ℃ for 30 minutes. Spray evenly a solution of ninhydrin in acetone (1 in 50) on the plate, and heat at 80 ℃ for 5 minutes; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.3% (1 g, 105 ℃, 3 hours).

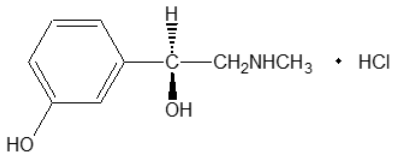
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.17 g of L-Phenylalanine, previously dried, dissolve in 3 mL of formic acid, add 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 16.519 mg of $C_9H_{11}NO_2$

Packaging and storage Preserve in tight containers.

Phenylephrine Hydrochloride
페닐레프린염산염



$C_9H_{13}NO_2 \cdot HCl$: 203.67
3-[(1*R*)-1-Hydroxy-2-(methylamino)ethyl]phenol hydrochloride [*61-76-7*]

Phenylephrine Hydrochloride, when dried, contains NLT 98.0% and NMT 102.0% of phenylephrine hydrochloride ($C_9H_{13}NO_2 \cdot HCl$).

Description Phenylephrine Hydrochloride occurs as white crystals or a crystalline powder, and is odorless and has a bitter taste.
It is very soluble in water, freely soluble in ethanol(95), and practically insoluble in ether.
Dissolve 1.0 g of Phenylephrine Hydrochloride in 100 mL of water; the pH of the solution is between 4.5 and 5.5.

Identification (1) To 1 mL of an aqueous solution of Phenylephrine Hydrochloride (1 in 100), add 1 drop of copper(II) sulfate TS, and add 1 mL of sodium hydroxide solution (1 in 5); the resulting solution exhibits a blue color. Add 1 mL of ether, and shake to mix; the ether layer does not exhibit a blue color.

(2) To 1 mL of an aqueous solution of Phenylephrine Hydrochloride (1 in 100), add 1 drop of iron(III) chloride TS; the resulting solution exhibits a violet color which persists.

(3) Dissolve 0.3 g of Phenylephrine Hydrochloride in 3 mL of water, add 1 mL of ammonia TS, and rub the inner wall of the test tube with a glass rod; a precipitate is formed. Filter and collect the precipitate, wash with a few drops of water cooled with ice, and dry at 105 ℃ for 2 hours; the melting point is between 170 and 177 ℃.

(4) An aqueous solution of Phenylephrine Hydrochloride (1 in 100) responds to the Qualitative Analysis (2) for chloride.

Optical rotation $[\alpha]_D^{20}$: Between -42.0° and -47.5° (0.5 g after drying, water, 10 mL, 100 mm).

Melting point Between 140 and 145 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Phenylephrine Hydrochloride in 10 mL of water; the resulting solution is colorless and clear.

(2) ***Sulfate***—Perform the test with 0.5 g of Phenylephrine Hydrochloride. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid (NMT 0.048%).

(3) ***Ketone***—Dissolve 0.20 g of Phenylephrine Hydrochloride in 1 mL of water, add 2 drops of sodium nitroprusside TS and 1 mL of sodium hydroxide TS, and add 0.6 mL of acetic acid(100); the color of the resulting solution is not more intense than the following control solution.

Control solution—Without using Phenylephrine Hydrochloride, proceed in the same manner as above.

(4) ***Related substances***—Weigh accurately 500 mg of Phenylephrine Hydrochloride, dissolve in methanol to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of phenylephrine hydrochloride RS, dissolve in methanol to make exactly 20 mL, and use this solution as the standard solution (1). Pipet 5 mL of the standard solution (1), add methanol to make exactly 10 mL, and use this solution as the standard solution (2). Pipet 1 mL of the standard solution (1), add methanol to make exactly 4 mL, and use this solution as the standard solution (3). Pipet 1 mL of the standard solution (1), add methanol to make exactly 10 mL, and use this solution as the standard solution (4).

Pipet 1 mL of the standard solution (1), add methanol to make exactly 20 mL, and use this solution as the standard solution (5). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution, the standard solution (2), the standard solution (3), the standard solution (4), and the standard solution (5) on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography, develop the plate with a mixture of 1-butanol, water and formic acid (7 : 2 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate with warm air. Spray anhydrous sodium carbonate solution (1 in 10), and spray saturated p-nitrobenzene diazonium fluoroborate solution. After drying the plate, examine the plate under ultraviolet light (main wavelength: 254 nm). The sum of spots other than the principal spot obtained from the test solution is not more intense than that of the standard solution (2) (NMT 1.0%), and individual related substances are not more intense than those in the standard solution (3) (NMT 0.5%).

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

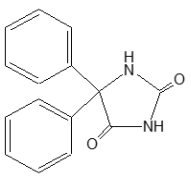
Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.1 g of Phenylephrine Hydrochloride, previously dried, transfer into the iodine bottle, dissolve in 40 mL of water, and add exactly 50 mL of 0.05 mol/L bromine VS. To this solution, add 5 mL of hydrochloric acid, immediately close the stopper, shake to mix, and allow to stand for 15 minutes. Carefully add 10 mL of potassium iodide TS, immediately close the stopper, shake well to mix, and allow to stand for 5 minutes. Titrate free iodine with 0.1 mol/L sodium thiosulfate VS (indicator: 1 mL of starch TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L bromine VS
= 3.3945 mg of $C_9H_{13}NO_2 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Phenytoin
페니토인



Diphenylhydantoin $C_{15}H_{12}N_2O_2$: 252.27
5,5-Diphenylimidazolidine-2,4-dione [*57-41-0*]

Phenytoin, when dried, contains NLT 99.0% and NMT 101.0% of phenytoin ($C_{15}H_{12}N_2O_2$).

Description Phenytoin occurs as a white crystalline powder or grain, and is odorless and tasteless. It is sparingly soluble in ethanol(95) or acetone, slightly soluble in ether, and practically insoluble in water.
It dissolves in sodium hydroxide TS.

Melting point—About 296 ℃ (with decomposition).

Identification (1) Dissolve 20 mg of Phenytoin in 2 mL of ammonia TS, and add 5 mL of silver nitrate TS; a white precipitate is formed.

(2) To 10 mg of Phenytoin, add 1 mL of ammonia TS and 1 mL of water, boil, and add dropwise 2 mL of a solution prepared by adding 10 mL of ammonia TS to 50 mL of copper sulfate solution (1 in 20); a red crystalline precipitate is formed.

(3) Mix 0.1 g of Phenytoin and 0.2 g of sodium hydroxide, and fuse by heating; the produced gas turns the moistened red litmus paper blue.

(4) To 0.1 g of Phenytoin, add 3 mL of chlorinated lime TS, shake for 5 minutes to mix, and dissolve the oily sediment in 15 mL of hot water. After cooling, add 1 mL of dilute hydrochloric acid, add 4 mL of water, filter the produced white precipitate, and take the precipitate. Wash with water, remove the moisture attached to the precipitate by pressing with a filter paper, dissolve the precipitate in 1 mL of chloroform, and add 5 mL of diluted ethanol (9 in 10). Scrape the inner wall of the test tube with a glass rod to form a white crystalline precipitate. Wash this precipitate with ethanol(95), and dry; the melting point is between 165 and 169 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 0.20 g of Phenytoin in 10 mL of 0.2 mol/L sodium hydroxide TS; the resulting solution is colorless and clear. Also, heat the solution; it does not become turbid. After cooling, mix with 5 mL of acetone; the resulting solution is colorless and clear.

(2) ***Acidity or alkalinity***—To 2.0 g of Phenytoin, add 40 mL of water, shake for 1 minute to mix, filter, and perform the test using the filtrate as the test solution.

(i) To 10 mL of the test solution, add 2 drops of phenolphthalein TS; the resulting solution is colorless. Also, add 0.15 mL of 0.01 mol/L sodium hydroxide TS; the resulting solution exhibits a red color.

(ii) To 10 mL of the test solution, add 0.30 mL of 0.01 mol/L hydrochloric acid and 5 drops of methyl red TS; the resulting solution exhibits a red to orange color.

(3) ***Chloride***—Dissolve 0.30 g of Phenytoin in 30 mL of acetone, and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 30 mL of acetone, 6 mL of dilute nitric acid, and water into 0.60 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.071%).

(4) ***Heavy metals***—Proceed with 1.0 g of Phenytoin according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(5) ***Related substances***—Weigh accurately about

0.1 g of Phenytoin, dissolve in methanol to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 mg of phenytoin RS, dissolve in methanol to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area by the automatic integration method, and calculate the amount of related substances according to the following equation; the total amount of related substances other than benzophenone is NMT 0.9%.

$$\text{Content (\%) of related substances} = 100 \times \frac{C_S}{C_T} \times \frac{A_i}{A_S}$$

C_S: Concentration (μg/mL) of phenytoin in the standard solution

C_{T1}: Concentration (μg/mL) of phenytoin in the test solution

A_i: Peak area of each related substance in the test solution

A_S: Peak area of phenytoin in the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of methanol and water (55:45).

Flow rate: About 1.5 mL/min.

System suitability

System performance: Weigh accurately 1 mg of benzoin, dissolve in 100 mL of methanol, take 10 mL of this solution, and dissolve 10 mg of phenytoin in the solution. Use this solution as the system suitability solution. Proceed with the system suitability solution according to the above conditions; the relative retention times of phenytoin and benzoin are 0.75 and 1.0, respectively, and the resolution is NLT 1.5.

(6) ***Benzophenone***—Weigh accurately about 0.1 g of Phenytoin, dissolve in methanol to make exactly 100 mL, and use this solution as the test solution. Separately, weigh 0.1 mg of benzophenone, add methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak areas, A_T and A_S, of benzophenone from the test solution and the standard solution, respectively. Calculate the amount of benzophenone according to the following equation; it is NMT 0.1%.

$$\text{Content (\%) of benzophenone} = 100 \times \frac{C_S}{C_T} \times \frac{A_T}{A_S}$$

C_S: Concentration (μg/mL) of benzophenone in the standard solution

C_T: Concentration (μg/mL) of phenytoin in the test solution

A_T: Peak area of benzophenone in the test solution

A_S: Peak area of benzophenone in the standard solution

Operating conditions

Perform the test according to the operating conditions under the Purity (5) Related substances.

System suitability

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above operating conditions; the relative standard deviation of the peak area of benzophenone is NMT 5.0%.

Loss on drying NMT 0.5% (2 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Phenytoin, previously dried, dissolve in 40 mL of ethanol(95) by warming, immediately add 0.5 mL of thymolphthalein TS, and titrate with 0.1 mol/L sodium hydroxide VS until the solution exhibits a pale blue color. Add 1 mL of pyridine, 5 drops of phenolphthalein TS, and 25 mL of silver nitrate TS, and titrate with 0.1 mol/L sodium hydroxide VS until the solution exhibits a 1 minute-persisting pale red color.

Each mL of 0.1 mol/L sodium hydroxide VS
= 25.227 mg of $C_{15}H_{12}N_2O_2$

Packaging and storage Preserve in well-closed containers.

Phenytoin Capsules
페니토인 캡슐

Phenytoin Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of phenytoin ($C_{15}H_{12}N_2O_2$: 252.27).

Method of preparation Prepare as directed under Capsules, with Phenytoin.

Identification The retention times of major peaks obtained from the test solution and standard solution under the Assay are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Take NLT 20 capsules of Phenytoin Capsules,

weigh accurately the mass of the contents and powder. Weigh accurately an amount equivalent to about 0.1 g of phenytoin ($C_{15}H_{12}N_2O_2$), dissolve in acetonitrile to make 100.0 mL, filter, and use the filtrate as the test solution. Separately, proceed in the same manner as in the preparation of the test solution with about 0.1 g of phenytoin RS, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak areas, A_T and A_S, of the test solution and the standard solution, respectively.

$$\text{Amount (mg) of phenytoin } (C_{15}H_{12}N_2O_2) = \text{Amount (mg) of phenytoin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and water (50 : 50).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Phenytoin Tablets
페니토인 정

Diphenylhydantoin Tablets

Phenytoin Tablets contain NMT 95.0% and NLT 105.0% of the labeled amount of phenytoin ($C_{15}H_{12}N_2O_2$: 252.27).

Method of preparation Prepare as directed under Tablets, with Phenytoin.

Identification Weigh an amount of Phenytoin Tablets, previously powdered, equivalent to 0.3 g of phenytoin according to the labeled amount, transfer into a separatory funnel, and add 1 mL of dilute hydrochloric acid and 10 mL of water. Extract 1 time with 100 mL of ether and 4 times each with 25 mL of ether while shaking well, combine the extracts, and filter. Evaporate the filtrate to dryness on a steam bath, and perform the test with the residue as directed under the Identification of Phenytoin.

Dissolution Perform the test with 1 tablet of Phenytoin Tablets at 100 revolutions per minute according to Method 2, using 900 mL of 0.05 mol/L tris buffer solution as the dissolution medium. Take the dissolved solution 120 minutes after starting the test, and filter. Discard the first 3 mL of the filtrate, pipet 10.0 mL of the subsequent filtrate, add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of phenytoin RS, dissolve in methanol to make a solution containing about 3.0 mg per mL, and then add the dissolution medium to make a solution containing about 0.06 mg per mL. Pipet an appropriate amount of this solution, add the mobile phase to make a solution containing the same concentration as the test solution, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of phenytoin in each solution. Meets the requirements if the dissolution rate of Phenytoin Tablets in 120 minutes is NLT 70% (Q).

$$\text{Dissolution rate (\%) of the labeled amount of phenytoin } (C_{15}H_{12}N_2O_2) = C_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 450000$$

A_T: Peak area of phenytoin in the test solution

A_S: Peak area of phenytoin in the standard solution

C_S: Concentration of the standard solution (mg/mL)

C: Labeled amount (mg) of phenytoin ($C_{15}H_{12}N_2O_2$) in 1 tablet

0.05 mol/L tris buffer solution—Dissolve 60.5 g of 2-amino-2-hydroxymethyl-1,3-propanediol in 6 L of water, add another water to make 10 L, and adjust the pH to 9.0 ± 0.05 with phosphoric acid. Take 6 L of this solution, dissolve 100 g of sodium lauryl sulfate, combine with the remaining solution, and mix well.

Triethylamine solution—To 1 mL of triethylamine, add water to make 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (1.5 to 10 μm in particle diameter).

Mobile phase: A mixture of water, methanol, acetonitrile, triethylamine solution and acetic acid(31) (500 : 270 : 230 : 5 : 1).

Flow rate: 1.5 mL/min

System suitability

System performance: Proceed with 25 μL of the standard solution according to the above conditions; the number of theoretical plates and the symmetry factor of the peak of phenytoin are NLT 6500 and NMT 1.5, respectively.

System repeatability: Repeat the test 5 times with 25 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of phenytoin is NMT 2.0%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Phenytoin Tablets, and powder. Weigh accurately an amount equivalent to about 25 mg of phenytoin ($C_{15}H_{12}N_2O_2$), add the mobile phase, shake for about 10 minutes to mix, and add the mobile phase again to make exactly 25 mL. Then filter. Discard the first 10 mL of the filtrate, take exactly 5 mL of the subsequent filtrate, add 10.0 mL of the internal standard solution, add the mobile phase to make exactly 50 mL and use this solution as the test solution. Separately, weigh accurately about 25 mg of Phenytoin RS (previously dry at 105 ºC for 2 hours and measure the loss on drying), dissolve in the internal standard solution to make exactly 25 mL. Pipet 5 mL of this solution, add 10.0 mL of the internal standard solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios of the peak area, Q_T and Q_S, of phenytoin to the peak area of the internal standard, respectively.

$$\text{Amount (mg) phenytoin } (C_{15}H_{12}N_2O_2) = \text{Amount (mg) of phenytoin RS, calculated on the dried basis} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of butyl p-hydroxybenzoate in methanol (1 in 10000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm to 30 cm in length, packed with octadecylsilanized silica gel (5 μm to 10 μm in particle diameter).

Column temperature: Ordinary temperature

Mobile phase: A mixture of 5 mol/L ammonium monohydrogen phosphate solution and methanol (50 : 50)

Flow rate: Adjust the flow rate so that the retention time of phenytoin is about 5 minutes.

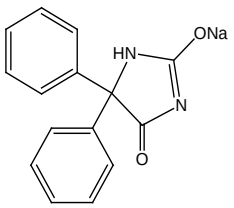
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; phenytoin and the internal standard are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the ratios of phenytoin peak area is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Phenytoin Sodium
페니토인나트륨



$C_{15}H_{11}N_2NaO_2$: 274.25

Sodium 5,5-diphenylimidazolidin-3-ide-2,4-dione [*630-93-3*]

Phenytoin Sodium contains NLT 98.0% and NMT 102.0% of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$), calculated on the dried basis.

Description Phenytoin Sodium occurs as white crystals or a crystalline powder and is odorless.

It is soluble in water or ethanol(95) and practically insoluble in ether or chloroform.

Dissolve 1.0 g of Phenytoin Sodium in 20 mL of water; the pH of this solution is about 12.

It is hygroscopic.

Allow to stand an aqueous solution of Phenytoin Sodium; the solution slowly absorbs carbon dioxide and precipitates crystals of phenytoin.

Identification (1) Transfer 0.3 g of Phenytoin Sodium into the separatory funnel, dissolve in 50 mL of water, add 10 mL of dilute hydrochloric acid, and extract with 100 mL of ether. Next, extract 4 times each with 25 mL of ether, combine the extracts, and filter. Evaporate the filtrate to dryness on a steam bath, and perform the test with the residue as directed under the Identification of Phenytoin.

(2) Ignite 0.5 g of Phenytoin Sodium. After cooling, dissolve the residue in 10 mL of water; the resulting solution turns red litmus paper blue. Phenytoin Sodium responds to the Qualitative Analysis (1) for sodium salt.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Phenytoin Sodium in 20 mL of freshly boiled and cooled water; the resulting solution is colorless and clear. Also, even if it is slightly turbid, add 4.0 mL of 0.1 mol/L sodium hydroxide TS; the resulting solution is colorless and clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Phenytoin Sodium according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Weigh accurately about 0.1 g of Phenytoin Sodium, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 μg of benzophenone, about 0.1 mg of phenytoin RS, about 0.9 mg of phenytoin related substance I {diphenylglycine} RS, and about 0.9 mg of phenytoin related substance II {diphenylhydantoin} RS, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following con-

ditions. Determine the peak area of each solution by the automatic integration method, and calculate the amount of related substances according to the following equation; the amount of phenytoin related substance I and phenytoin related substance II are NMT 0.9%, respectively, and the amount of benzophenone is NMT 0.1%.

$$\text{Content (\%) of related substances} = 100 \times \frac{C_S}{C_T} \times \frac{A_T}{A_S}$$

C_S: Concentration (μg/mL) of each related substance in the standard solution

C_T: Concentration (μg/mL) of Phenytoin Sodium in the test solution

A_S: Peak area of each related substance obtained from the standard solution

A_T: Peak area of each related substance obtained from the test solution

Also, calculate the amount of other individual related substances according to the following equation; the total amount of related substances other than benzophenone is NMT 0.9%.

$$\text{Content (\%) of individual related substances} = 100 \times \frac{274.25}{252.27} \times \frac{C}{D} \times \frac{A_i}{A_S}$$

274.25: Molecular weight of phenytoin sodium

252.27: Molecular weight of phenytoin

C: Concentration (μg/mL) of phenytoin in the standard solution

D: Concentration (μg/mL) of phenytoin sodium in the test solution

A_i: Peak area of related substances obtained from the test solution

A_S: Peak area of phenytoin obtained from the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: Ordinary temperature

Mobile phase: A mixture of 0.05 mol/L ammonium dihydrogen phosphate buffer solution, acetonitrile and methanol (45 : 35 : 20) with a pH level adjusted to 2.5 with phosphoric acid.

Flow rate: About 1.5 mL/min.

System suitability

System performance: Dissolve about 75 mg of benzoin in 10 mL of methanol, add a mixture of 0.05 mol/L ammonium dihydrogen phosphate buffer solution and acetonitrile (45 : 35) with a pH level adjusted to 2.5 with phosphoric acid to make 50 mL. Pipet 1.0 mL of this solution, transfer into a 10-mL volumetric flask, add a solution containing 10.0 mg of phenytoin RS dissolved in 100 mL of the mobile phase to make 10 mL, and use this solution as the system suitability solution. Proceed with the system suitability solution according to the above conditions; the relative retention time for phenytoin and benzoin are 1.0 and 1.3, respectively, with the resolution being NLT 1.5. The number of theoretical plates and symmetry factor of the phenytoin peak are NLT 9400 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation is NMT 5.0%.

Assay Weigh accurately about 25 mg of Phenytoin Sodium, and dissolve in mobile phase to make exactly 25 mL. Pipet 5 mL of this solution, add 10.0 mL of the internal standard solution, add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg of phenytoin RS, and dissolve in mobile phase to make exactly 25 mL. Pipet 5 mL of this solution, add 10.0 mL of the internal standard solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios of the peak area, Q_T and Q_S, of phenytoin to that of the internal standard.

$$\text{Amount (mg) of phenytoin sodium } (C_{15}H_{11}N_2NaO_2) = \text{Amount (mg) of phenytoin RS, calculated on the dried basis} \times \frac{Q_T}{Q_S} \times 1.087$$

Internal standard solution—A solution of butyl p-hydroxybenzoate in methanol (1 in 10000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of 0.005 mol/L ammonium monohydrogen phosphate VS and methanol (50 : 50).

Flow rate: Adjust the flow rate so that the retention time of phenytoin is about 5 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; phenytoin and internal standard are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the ratios of the peak area of phenytoin to that of the internal standard is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Phenytoin Sodium for Injection
주사용 페니토인나트륨

Diphenylhydantoin Sodium for Injection
$C_{15}H_{11}N_2NaO_2$: 274.25

Phenytoin Sodium for Injection, when dried, contains NLT 98.5% and NMT 101.0% of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$) and contains NLT 92.5% and NMT 107.5% of the labeled amount of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$).

Method of preparation Prepare as directed under Injections.

Description Phenytoin Sodium for Injection occurs as white crystals or a crystalline powder and is odorless.
It is soluble in water or ethanol(95) and practically insoluble in ether or chloroform.
Dissolve 1.0 g of Phenytoin Sodium in 20 mL of water; the pH of this solution is about 12.
It is hygroscopic.
When allowed to stand, an aqueous solution of Phenytoin Sodium for Injection slowly absorbs carbon dioxide and precipitates phenytoin crystals.

Identification (1) Transfer 0.3 g of Phenytoin Sodium into the separatory funnel, dissolve in 50 mL of water, add 10 mL of dilute hydrochloric acid, and extract with 100 mL of ether. Next, extract 4 times each with 25 mL of ether, combine the extracts, and filter. Evaporate the filtrate to dryness on a steam bath, and perform the test with the residue as directed under the Identification of Phenytoin.

(2) Ignite 0.5 g of Phenytoin Sodium. After cooling, dissolve the residue in 10 mL of water; the resulting solution turns red litmus paper blue. Phenytoin Sodium responds to the Qualitative Analysis (1) for sodium salt.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Phenytoin Sodium in 20 mL of freshly boiled and cooled water; the resulting solution is colorless and clear. Also, even if it is slightly turbid, add 4.0 mL of 0.1 mol/L sodium hydroxide TS; the resulting solution is colorless and clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Phenytoin Sodium according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Loss on drying NMT 2.5% (1 g, 105 ℃, 4 hours).

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Measure accurately the mass of the contents of about 10 units of phenytoin sodium for injection. Weigh accurately about 25 mg of Phenytoin Sodium for Injection and dissolve in the mobile phase to make exactly 25 mL. Pipet 5 mL of this solution, add 10.0 mL of the internal standard solution, then add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg of phenytoin RS, and dissolve in mobile phase to make exactly 25 mL. Pipet 5 mL of this solution, add 10.0 mL of the internal standard solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios the peak area, Q_T and Q_S of phenytoin to that of the internal standard.

Amount (mg) of phenytoin sodium ($C_{15}H_{11}N_2NaO_2$)
= Amount (mg) of phenytoin RS, calculated on the dried basis$\times \frac{Q_T}{Q_S} \times 1.087$

Internal standard solution—A solution of butyl p-hydroxybenzoate in methanol (1 in 10000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: Room temperature

Mobile phase: A mixture of 0.005 mol/L ammonium phosphate dibasic solution and methanol (50 : 50).

Flow rate: Adjust the flow rate so that the retention time of phenytoin is about 5 minutes.

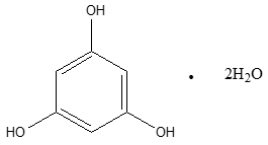
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; phenytoin and the internal standard are eluted in this order with resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio is NMT 2.0%.

Packaging and storage Preserve in hermetic containers.

Phloroglucinol Dihydrate
플로로글루시놀수화물



$C_6H_6O_3 \cdot 2H_2O$: 162.1

Benzene-1,3,5-triol dihydrate [*6099-90-7*]

Phloroglucinol Dihydrate, when dried, contains NLT 99.0% and NMT 101.0% of phloroglucinol dihydrate ($C_6H_6O_3$: 126.1).

Description Phloroglucinol Dihydrate occurs as a white powder.
It is freely soluble in ethanol(99.5) or ethanol(95), sparingly solution in water, and practically insoluble in dichloromethane.

Identification (1) Determine the infrared spectra of Phloroglucinol Dihydrate and phloroglucinol dihydrate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Weigh accurately about 200 mg of Phloroglucinol Dihydrate, dissolve in methanol to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately 200 mg of phloroglucinol dihydrate RS, dissolve in methanol to make exactly 10 mL, and use this solution as the standard solution. Spot each 10 μL of the test solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, hexane and anhydrous formic acid (125 : 75 : 4) to a distance of NLT 2/3 of the length of the plate and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f value, position and size of the principal spot obtained from the test solution corresponds to those of the principal spot from the standard solution.

pH Dissolve 2.5 g of Phloroglucinol Dihydrate in ethanol(95) to make 25 mL. To 10 mL of this solution, add carbon dioxide-free water to make 100 mL; the pH of the solution is between 4.0 and 6.0.

Purity (1) ***Clarity and color of solution*—**Dissolve about 2.5 g of Phloroglucinol Dihydrate in ethanol(95) to make 25 mL; the solution is clear and not more intense than the control solution.

Control solution—To a mixture of 1.0 mL of cobalt(II) chloride hexahydrate colorimetric stock solution, 2.4 mL of iron(III) chloride hexahydrate colorimetric stock solution and 0.4 mL of copper(II) sulfate pentahydrate colorimetric stock solution, add 10 g/L hydrochloric acid to make 10 mL. To 12.5 mL of this solution, add 10 g/L hydrochloric acid to make 100 mL.

(2) ***Chloride*—**Perform the test with 0.5 g of Phloroglucinol Dihydrate. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.02%).

(3) ***Sulfate***—Perform the test with 0.5 g of Phloroglucinol Dihydrate. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid (NMT 0.05%).

(4) ***Heavy metals*—**Proceed with 1.0g of Phloroglucinol Dihydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(5) ***Related substances*—**Weigh accurately about 50 mg of Phloroglucinol Dihydrate, add the diluent to make exactly 10 mL, and use this solution as the test solution. Pipet 1 mL of the test solution and add the diluent to make exactly 100 mL. Pipet 1 mL of this solution, add the diluent to make exactly 10 mL, and use this solution as the standard solution. Perform the test with each 20 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine all peak areas of each solution by the automatic integration method and calculate the amount of related substances in the test solution; phloroglucinol related substance I {pyrogallol}, phloroglucinol related substance II {phloroglucide}, benzene-1,2,4-triol, 2,6-dichlorophenol, phloroglucinol related substance III {4-chlororesorcinol} and 3,5-dichloroaniline are eluded at the relative retention time of about 0.9, about 1.3, about 0.7, about 1.8, about 1.5 and about 2.0 to phloroglucinol, respectively, and each peak area of those peaks are NMT 0.15%; any other individual related substance is NMT 0.1%, and the total amount of related substances is NMT 0.3%. Exclude any related substance the percent peak area of which is NMT 0.05%. Determine the peak areas of phloroglucinol related substance I, phloroglucinol related substance II, benzene-1,2,4-triol, 2,6-dichlorophenol, phloroglucinol related substance III and 3,5-dichloroaniline by multiplying the peak areas determined by the automatic integration method by their response factors, 0.6, 0.2, 0.7, 0.6, 0.6 and 0.4, respectively. Protect the test solution and standard solution from light after preparation and use immediately.

Diluent—A mixture of mobile phase A and mobile phase B (1 : 9).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 265 nm).

Column: A stainless steel column, about 4.0 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Adjust the mobile phase using a stepwise change or gradient elution by mixing mobile phase A and mobile phase B as directed under the following table.

Mobile phase A: Dissolve 1.36 g of potassium dihydrogen phosphate in 900 mL of water, adjust pH to 3.0 with phosphoric acid, and add water to make 1000 mL.

Mobile phase B: Acetonitrile

Time (minute)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 9	100	0
9 - 15	100 → 50	0 → 50
15 - 25	50 → 20	50 → 80
25 - 30	20	80

Flow rate: 1.0 mL/min (the retention time of phloroglucinol is about 12 minutes).

System suitability

System performance: Dissolve each 6 mg of phloroglucinol related substance I RS, resorcinol and phloroglucinol related substance II RS in the diluent to make 10 mL. To this solution, add 2 mL of the test solution and add the diluent to make 20 mL. Pipet 1 mL of this solution, add the diluent to make 50 mL, and use this solution as the system suitability solution. Proceed with 10 μL of the system suitability solution according to the above operating conditions; the resolution of the peaks of phloroglucinol related substance I and phloroglucinol related substance II is NLT 2.5, and the resolution of the peaks of phloroglucinol related substance II and resorcinol is NLT 4.0.

Loss on ignition Between 20.0% and 23.0%(1 g, 105 ℃).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.6 g of Phloroglucinol Dihydrate and dissolve in 50 mL of water. Titrate this solution with 1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry).

Each mL of 1 mol/L sodium hydroxide VS
= 63.05 mg of $C_6H_6O_3$

Packaging and storage Preserve in light-resistant, tight containers.

Phloroglucinol Tablets
플로로글루시놀 정

Phloroglucinol Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of phloroglucinol hydrate ($C_6H_6O_3 \cdot 2H_2O$: 162.14).

Method of preparation Prepare as directed under Tablets, with Phloroglucinol Hydrate.

Identification (1) Weigh the amount of Phloroglucinol Tablets, equivalent to 80 mg of phloroglucinol hydrate according to the labeled amount, dissolve in 8 mL of methanol, and use this solution as the test solution. Separately, dissolve about 80 mg of phloroglucinol RS in methanol to make 8 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Next, develop the plate with a mixture of toluene, ethyl acetate and acetic acid(100) (5 : 4 : 1) (as the developing solvent) to a distance of about 15 cm and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots from the test solution exhibits an R_f value corresponding to that of the standard solution.

(2) The absorbance maximum wavelength of the absorption spectra obtained from the test solution correspond to those of the standard solution, as obtained in the Assay.

Disintegration Perform the test with Phloroglucinol Tablets as directed under the Disintegration. (However, in the case of sublingual tablets, perform the test as directed under Disintegration in the section on soluble tablets of the British Pharmacopoeia.)

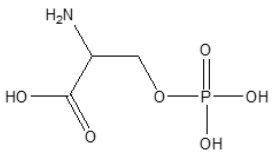
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Phloroglucinol Tablets, and powder. Weigh accurately an amount of the powder equivalent to about 20 mg of phloroglucinol hydrate ($C_6H_6O_3 \cdot 2H_2O$), add methanol to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of phloroglucinol RS, previously dried at 105 ℃ for 2 hours, proceed in the same manner as in the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 267 nm as directed under the Ultraviolet-visible Spectroscopy, using methanol as a control solution.

Amount (mg) phloroglucinol hydrate ($C_6H_6O_3 \cdot 2H_2O$)
= Amount (mg) phloroglucinol RS × A_T / A_S × 162.14/126.11

Packaging and storage Preserve in light-resistant, tight containers.

DL-Phosphoserine
DL-포스포세린



$C_3H_8NO_6P$: 185.07

2-Aino-3-phosphonooxypropanoicacid, [*17885-08-4*]

DL-Phosphoserine, when dried, contains NLT 97.0% and NMT 101.0% of DL-phosphoserine

($C_3H_8NO_6P$).

Description DL-Phosphoserine occurs as a white crystalline powder.
It is very soluble in water.

Identification (1) To 5 mL of an aqueous solution of DL-Phosphoserine (1 in 1000), add 1 mL of ninhydrin TS; the solution exhibits a bluish purple to violet color.

(2) An aqueous solution of DL-Phosphoserine responds to the Qualitative Analysis for phosphate.

Melting point—Between 166 and 167 ℃.

Purity ***Heavy metals***—Proceed with 1.0 g of DL-Phosphoserine according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

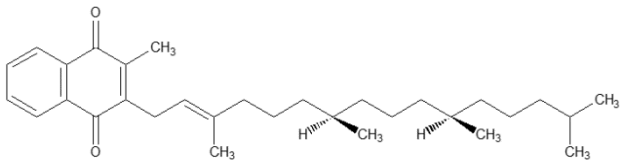
Residue on ignition NMT 0.1% (1 g)

Assay Weigh accurately an amount equivalent to 30 mg of DL-Phosphoserine, previously dried, transfer into a 100-mL Kjeldahl flask, add 8 mL of perchloric acid, and mix. Add 2 to 3 glass beads, and heat slowly on a hot plate until the white smoke disappears completely. After the complete decomposition, cool the decomposed solution, transfer into a 100-mL volumetric flask using a small amount of water, and wash the Kjeldahl flask with a small amount of water. Combine the washings with the content of the volumetric flask. Fill up to the gauge line with water, and mix evenly. Transfer 1.0 mL of this solution into a volumetric flask, add 2 drops of 0.1% alcoholic phenolphthalein TS, and slowly add 1 to 2 drops of 40% sodium hydroxide TS until the solution becomes red. Add 5 mL of a mixture of 5% ammonium molybdate solution and 10 mol/L sulfuric acid (1 : 1) TS and 0.5 mL of a solution prepared by dissolving 0.25 g of 1-amino-2-naphthol-4-sulfonic acid in a mixture of 97.5 mL of 18% potassium metabisulfite solution and 2.5 mL of 18.27% sodium metabisulfite, and add water to make 25.0 mL. Maintain the solution on a steam bath at 37 to 40 ℃ for 7 minutes, take it out, and use this solution as the test solution. Separately, weigh accurately about 30 mg of DL-phosphoserine RS, proceed in the same manner as the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy using the blank test solution as the control solution, and determine the absorbances, A_T and A_S, at 750 nm.

Amount (mg) of DL-phosphoserine ($C_3H_8NO_6P$)
= Amount (mg) of DL-phosphoserine RS$\times \frac{A_T}{A_S}$

Packaging and storage Preserve in tight containers.

Phytonadione
피토나디온



Vitamin K1
Phytomenadione $C_{31}H_{46}O_2$: 450.70
2-Methyl-3-((7*R*,11*R*,*E*)-3,7,11,15-tetramethylhexadec-2-en-1-yl)naphthalene-1,4-dione [*84-80-0*]

Phytonadione contains NLT 97.0% and NMT 102.0% of lactulose ($C_{31}H_{46}O_2$).

Description Phytonadione occurs as a pale yellow to orange clear viscous solution.
It is miscible with chloroform.
It is soluble in ethanol(99.5) and practically insoluble in water.
It is gradually decomposed, and exhibits to reddish brown by light.

Specific gravity—d_{20}^{20}: About 0.967.

Identification (1) Determine the absorption spectra of solutions of Phytonadione and phytonadione RS in isooctane (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.
Determine the ultraviolet-visible absorption spectrum of solutions of Phytonadione and phytonadione RS in isooctane (1 in 10000); both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Determine the infrared absorption spectrum of Phytonadione and phytonadione RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Refractive index n_D^{20}: Between 1.525 and 1.529.

Purity (1) ***the ratio of absorbance***—Perform the test with the solution of Phytonadione in isooctane (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbances A_1, A_2 and A_3 at the wavelengths of 248.5 nm, 253.5 nm and 269.5 nm; A_2/A_1 is between 0.69 and 0.73, and $A_2/A3$ is between 0.74 and 0.78. Determine the absorbances A_4 and A_5 at the wavelengths of 284.5 nm and 326 nm with the solution of Phytonadione in isooctane (1 in 100000); A_4/A_5 is between 0.28 and 0.34.

(*2*) ***Heavy metals***—Carbonize 1.0 g of Phytonadione by gentle ignition. After cooling, add 10 mL solution of magnesium nitrate in ethanol(95) (1 in 10) and ignite in ethanol to burn. After cooling, add 1 mL of sulfuric acid, proceed according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Menadione***—Dissolve 20 mg of Phytonadione in 0.5 mL of a mixture of ethanol(95) and water (1 : 1), add 1 drop of the solution of 3-methyl-phenyl-5-pyrazolone in ethanol(95) (1 in 20) and 1 drop of ammonia water(28), and allow to stand for 2 hours; the resulting solution does not exhibit a green to bluish purple color.

Isomer ratio Perform the test quickly away from sunlight. Dissolve 30 mg of Phytonadione in 50 mL of the mobile phase. To 4 mL of this solution, add the mobile phase to make 25 mL. Add the mobile phase to 10 mL of this solution to make 25 mL, and use this solution as the test solution. With 50 μL of the test solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of the Z-form A_{TZ} and E-form A_{TE}; $A_{TZ}/(A_{TZ} + A_{TE})$ is between 0.28 and 0.34.

Operating conditions

Proceed as directed under the operating conditions under the Assay.

System suitability

System performance: Proceed with 50 μL of the standard solution according to the above conditions; Z-form and E-form are eluted in this order with the resolution being NLT 1.5.

System repeatability: Repeat the test 6 times with 50 μL each of the standard solution according to the above conditions; the relative standard deviation of the sum of the peaks of Z-form and E-form is NMT 2.0%.

Assay Perform the test quickly away from sunlight. Weigh accurately about 30 mg each of Phytonadione and phytonadione RS, previously dried, and dissolve each in the mobile phase to make exactly 50 mL. Pipet 4 mL of each of these solutions, and add the mobile phase to each solution to make exactly 25 mL. Pipet10 mL of this solution, add 7 mL each of the internal standard solution, add the mobile phase to make exactly 25 mL, and use this solution as the test solution and the standard solution. Perform the test with 50 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak areas of E-form and Z-form, Q_T and Q_S, to that of the internal standard in each solution.

$$\text{Amount (mg) of phytonadione } (C_{31}H_{46}O_2) = \text{Amount (mg) of phytonadione RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of cholesterol benzoate in the mobile phase (1 in 400).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of hexane and n-amyl alcohol (4000 : 3).

Flow rate: Adjust the flow rate so that the retention time of the lately eluted peak of the 2 peaks of phytonadione is about 25 minutes.

System suitability

System performance: Proceed with 50 μL of the standard solution according to the above conditions; Z-form and E-form are eluted in this order with the resolution being NLT 1.5.

System repeatability: Repeat the test 6 times with 50 μL each of the standard solution according to the above conditions; the relative standard deviation of the sum of the ratio of the peak areas of Z-form and E-form to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers in a cold place.

Phytonadione Injection
피토나디온 주사액

Vitamin K1 Injection

Phytonadione Injection is an aqueous solution for injection. Phytonadione Injection contains NLT 90.0% and NMT 110.0% of the labeled amount of phytonadione (C31H46O2: 450.70).

Method of preparation Prepare as directed under Injections, with Phytonadione. A suitable solubilizing agent or suspending agent may be added to Phytonadione Injection.

Identification The retention times of the major peaks from the test solution and the standard solution obtained in the Assay are the same.

pH Between 3.5 and 7.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 14.0 EU/mg of phytonadione.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet Phytonadione Injection in the amount equivalent to about 10 mg of phytonadione ($C_{31}H_{46}O_2$)

according to the labeled amount, add the mobile phase to make exactly 10 mL, and mix. Pipet 1 mL of this solution, add the mobile phase to make exactly 10 mL, and use this solution as the test solution. And in case of Phytonadione Injection containing less than 10 mg of Phytonadione per mL, pipet a volume of Phytonadione Injection, equivalent to 1 mg of phytonadione ($C_{31}H_{46}O_2$), add the mobile phase to make exactly 10 mL. Separately, weigh accurately about 10 mg of phytonadione RS, and add the mobile phase to make exactly 10 mL. Take 1.0 mL of this solution, add the mobile phase to make exactly 10 mL, and use the resulting solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak areas, A_T and A_S, of phytonadione in the solutions, respectively.

$$\text{Amount (mg) of phytonadione } (C_{31}H_{46}O_2) = D \times \frac{C}{V} \times \frac{A_T}{A_S}$$

D: 100 (in case of Phytonadione Injection containing 10 mg or more of phytonadione per mL)

10 (for injection containing less than 10 mg of phytonadione per mL)

C: Concentration (mg/mL) of the standard solution.

V: Amount (mL) of sample

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of ethanol(99.5) and water (95 : 5).

Flow rate: 0.7 mL/min

System suitability

System repeatability: Repeat the test 6 times according to the above conditions with 10 μL each of the standard solution; the relative standard deviation of the peak area is NMT 1.5%.

Packaging and storage Preserve in light-resistant, hermetic containers.

Phytonadione Tablets
피토나디온 정

Vitamin K1 Tablets

Phytonadione Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of phytonadione ($C_{31}H_{46}O_2$: 450.70).

Method of preparation Prepare as directed under Tablets, with Phytonadione.

Identification (1) Reduce Phytonadione Tablets to powder, weigh an amount of the powder equivalent to about 10 mg of phytonadione according to the labeled amount, and dissolve in 750 mL of ethanol(99.5) with shaking. Add ethanol(99.5) to make 1000 mL, filter the resulting solution, and use the filtrate as the test solution. Separately, proceed with the phytonadione RS in the same manner as the test solution, and use this solution as the standard solution. Determine the absorption spectra of the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Disintegration Meets the requirements (disintegration time: 30 minutes).

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Pyrazinamide Tablets, and reduce to powder. Weigh accurately the amount of the powder equivalent to about 5 mg of phytonadione ($C_{31}H_{46}O_2$), add 20 mL of ethanol(99.5), shake vigorously to mix for 15 minutes to dissolve, and add ethanol(99.5) to make exactly 50 mL. Filter and use the filtrate as the test solution. Separately, weigh accurately 5 mg of phytonadione RS, dissolve in ethanol(99.5) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of phytonadione, A_T and A_S, in each solution.

$$\text{Amount (mg) of phytonadione } (C_{31}H_{46}O_2) = \text{Amount (mg) of phytonadione RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of ethanol (99.5)·and water (95 : 5).

Flow rate: 1.5 mL/min

System suitability

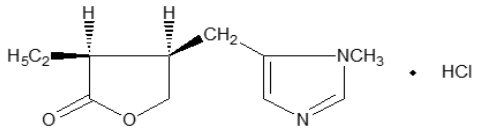
System performance: Proceed with 10 μL of the standard solution under the above operating conditions; the symmetry factor is NMT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas is NMT 2.0%

Packaging and storage Preserve in light-resistant, tight

containers.

Pilocarpine Hydrochloride
필로카르핀염산염



$C_{11}H_{16}N_2O_2 \cdot HCl$: 244.72

(3*S*,4*R*)-3-Ethyl-4-[(1-methyl-1*H*-imidazol-5-yl)methyl]dihydrofuran-2(3*H*)-one [*54-71-7*]

Pilocarpine Hydrochloride, when dried, contains NLT 99.0% and NMT 101.0% of pilocarpine hydrochloride ($C_{11}H_{16}N_2O_2 \cdot HCl$).

Description Pilocarpine Hydrochloride occurs as colorless crystals or a white powder. It is odorless and has a slightly bitter taste.
It is very soluble in acetic acid(100), freely soluble in water, methanol or ethanol(95), soluble in acetic anhydride, and practically insoluble in ether.
Dissolve 1.0 g of Pilocarpine Hydrochloride in 10 mL of water; the pH of the solution is between 3.5 and 4.5.
It is hygroscopic.
It is affected by light.

Identification (1) Dissolve 0.1 g of Pilocarpine Hydrochloride in 5 mL of water, add 1 drop of dilute nitric acid, 1 mL of hydrogen peroxide TS, 1 mL of chloroform, and 1 drop of potassium dichromate (1 in 300), and shake vigorously to mix; the chloroform layer exhibits a violet color, and the water layer becomes colorless to pale yellow.

(2) ***Chloride***—To 1 mL of an aqueous solution of Pilocarpine Hydrochloride (1 in 20), add 1 mL of dilute nitric acid and 2 to 3 drops of silver nitrate TS; a white precipitate or turbidity is formed.

Melting point Between 200 and 203 ℃.

Purity (1) ***Sulfate***—Dissolve 0.5 g of Pilocarpine Hydrochloride in 20 mL of water, and use this solution as the test solution. To 5.0 mL of the test solution, add 1 mL of dilute hydrochloric acid and 0.5 mL of barium chloride TS; the resulting solution is not turbid.

(2) ***Nitrate***—To 2.0 mL of the test solution from (1), add 2 mL of iron(II) sulfate TS, and superimpose on the 4 mL of sulfuric acid; the interface does not exhibit a dark brown color.

(3) ***Related substances***—Dissolve 0.3 g of Pilocarpine Hydrochloride in 10 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, methanol and ammonia water (85 : 14 : 2) to a distance of about 13 cm, and dry the plate at 105 ℃ for 10 minutes. After cooling, spray evenly bismuth potassium iodide TS; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

(4) ***Readily carbonizable substances***—Proceed with 0.25 g of Pilocarpine Hydrochloride and perform the test. The color of the solution is not more intense than that of the matching fluid for color B.

Loss on drying NMT 3.0% (1 g, 105 ℃, 2 hours).

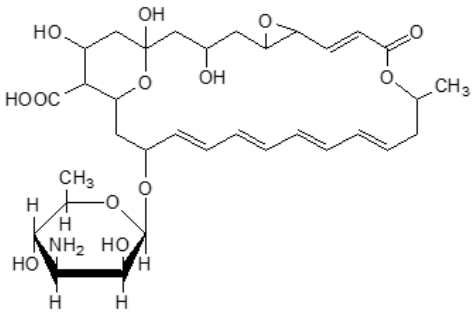
Residue on ignition NMT 0.5% (0.1 g).

Assay Take accurately 0.5 g of Pilocarpine Hydrochloride, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 24.472 mg of $C_{11}H_{16}N_2O_2 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Pimaricin
피마리신



$C_{33}H_{47}NO_{13}$: 665.73

(1*R*,3*S*,5*R*,7*R*,8*E*,12*R*,14*E*,16*E*,18*E*,20*E*,22*R*,24*S*,25*R*,26*S*)-22-[(3-Amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,26-trihydroxy-12-methyl-10-oxo--6,11,28-Trioxatricyclo[22.3.1.$0^{5,7}$]octacosa-8,14,16,18,20-pentaene-25-carboxylic acid [*7681-93-8*]

Pimaricin is a polyene marcrolide compound with antitumor activity obtained from the incubation of *Streptomyces parvulus*. Pimaricin contains NLT 900 μg (potency) and NMT 1020 μg (potency) of pimaricin ($C_{33}H_{47}NO_{13}$: 665.73) per mg, calculated on the anhydrous basis.

Description Pimaricin occurs as a white to yellowish white crystalline powder. It is slightly soluble in methanol or acetic acid(100) and practically insoluble in water or ethanol(99.5).

Identification (1) To 3 mg of Pimaricin, add 1 mL of hydrochloric acid and shake to mix; it exhibits a bluish purple color.

(2) Weigh 5 mg each of Pimaricin and pimaricin RS, and dissolve each in a solution of acetic acid(100) in methanol (1 in 100) to make 1000 mL. Determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Optical rotation $[\alpha]_D^{20}$: Between +243° and +259° (0.1 g, acetic acid(100), 25 mL, 100 mm).

pH Suspend 0.1 g (potency) of Pimaricin in 10 mL of water; the pH of the solution is between 4.0 and 7.0.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Pimaricin according to Method 4 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(2) ***Related substances***—Weigh 20 mg of Pimaricin, dissolve in methanol to make exactly 100 mL, and use this solution as the test solution. Proceed with 10 μL of the test solution as directed under the Liquid Chromatography according to the following conditions, and determine each peak area according to the automatic integration method. Determine the amount of substances other than pimaricin according to the percentage peak area method; the sum of the amounts is NMT 4.0%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 303 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 1.0 g of ammonium acetate in 1000 mL of a mixture of water, methanol and tetrahydrofuran (47 : 44 : 2).

Flow rate: Adjust the flow rate so that the retention time of pimaricin is about 10 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the test solution, add methanol to make exactly 100 mL, and use this solution as the system suitability solution. Pipet 1 mL of the system suitability test solution and add mobile to make exactly 10 mL. The peak area of pimaricin obtained from 10 μL of this solution is between 7% to 13% of that obtained from the system suitability solution.

System performance: Proceed with 10 μL of the system suitability solution according to the above conditions; the number of theoretical plates and the symmetry factor of the peak of pimaricin are NLT 1500 plates and NMT 2.0, respectively.

System repeatability: Repeat the test 6 times with 10 μL of the system suitability solution under the above operating conditions; the relative standard deviation of the peak area of pimaricin is NMT 2.0%.

Time span of measurement: About 3 times the retention time of pimaricin

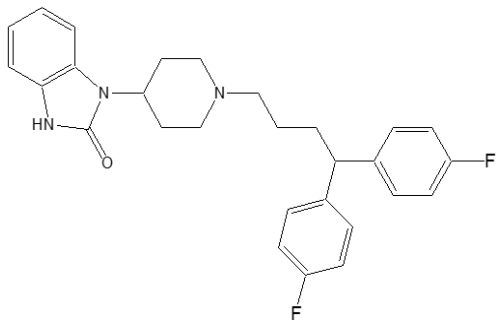
Water Between 6.0% and 9.0% (0.2 g, volumetric titration, direct titration).

Assay Weigh accurately about 25 mg (potency) each of Pimaricin and pimaricin RS, and dissolve each in methanol to make exactly 100 mL. Pipet 2 mL each of the dissolved solutions, add a solution of acetic acid(100) in methanol (1 in 100) to make exactly 100 mL, and use the resulting solutions as the test solution and the standard solution. With the test solution and the standard solution, determine the absorbances, A_{T1}, A_{S1}, A_{T2}, A_{S2}, A_{T3} and A_{S3}, at the wavelengths of 295.5 nm, 303 nm and 311 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Potency (μg) of pimaricin } (C_{33}H_{47}NO_{13}) = \text{Potency (μg) of pimaricin RS} \times \frac{A_{T2} - \frac{A_{T1} + A_{T3}}{2}}{A_{S2} - \frac{A_{S1} + A_{S3}}{2}}$$

Packaging and storage Preserve in light-resistant, tight containers.

Pimozide
피모지드



$C_{28}H_{29}F_2N_3O$: 461.55

1-{1-[4,4-Bis(4-fluorophenyl)butyl]piperidin-4-yl}-1*H*-benzo[d]imidazol-2(3*H*)-one [*2062-78-4*]

Pimozide contains NLT 98.0% and NMT 101.0% of pimozide ($C_{28}H_{29}F_2N_3O$), calculated on the dried basis.

Description Pimozide occurs as a white crystalline powder.

It is freely soluble in acetic acid(100), slightly soluble in methanol or ethanol(99.5), and practically insoluble in water.

Identification (1) Dissolve 35 mg each of Pimozide and pimozide RS in a solution of 0.1 mol/L hydrochloric acid in methanol (1 in 10) to make 100 mL. To 5.0 mL of this solution, add the solution of 0.1 mol/L hydrochloric acid in methanol (1 in 10) to make 50 mL, and determine the absorption spectra of the resulting solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Proceed with Pimozide and pimozide RS according as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 216 and 220 ℃.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Pimozide according to Method 2 under the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Pimozide according to Method 3 and perform the test (NMT 2 ppm).

(3) ***Related substances***—Weigh accurately about 0.10 g of Pimozide, dissolve exactly in 10 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 200 mL, and use it as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas of each solution according to the automatic integration method; the peak areas other than pimozide from the test solution are not larger than that of pimozide from the standard solution. The total area of the peaks other than pimozide from the test solution is not greater than 1.5 times the peak area of pimozide from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: Dissolve 2.5 g of ammonium acetate and 8.5 g of tetrabutylammonium hydrogen sulfate in water to make 1000 mL.

Mobile phase B: Acetonitrile

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 10	80 → 70	20 → 30
10 - 15	70	30

Flow rate: 2.0 mL/min

System suitability

Test for required detectability: Pipet 1 mL of the standard solution, and add methanol to make exactly 10 mL. Confirm that the peak area of pimozide obtained from 10 μL of this solution is equivalent to 8% - 12% of the peak area of pimozide obtained from the standard solution.

System performance: Dissolve 5 mg of Pimozide and 2 mg of mebendazole in methanol to make 100 mL. Proceed with 10 μL of this solution under the above operating conditions; mebendazole and pimozide are eluted in this order with the resolution between these peaks being NLT 5.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of pimozide is NMT 2.0%.

Time span of measurement: About 1.5 times the retention time of pimozide.

Loss on drying NMT 0.5% (1 g, in vacuum, 80 ℃, 4 hours).

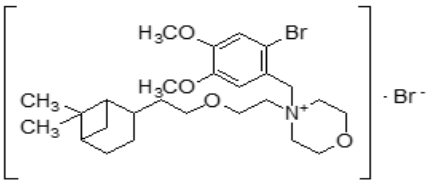
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Pimozide, dissolve in 40 mL of acetic acid(100), and titrate with 1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 46.155 mg of $C_{28}H_{29}F_2N_3O$

Packaging and storage Preserve in light-resistant, tight containers.

Pinaverium Bromide
피나베륨브롬화물



$C_{26}H_{41}Br_2NO_4$: 591.42

4-[(2-Bromo-4,5-dimethoxyphenyl) methyl]-4-[2-[2-(6,6-dimethylbicyclo [3.1.1]hept-2-yl)ethoxy]ethyl]morpholinium bromide, [*53251-94-8*]

Pinaverium Bromide, when dried, contains NLT 99.0% and NMT 101.0% of pinaverium bromide ($C_{26}H_{41}Br_2NO_4$).

Description Pinaverium Bromide is a fine crystalline powder, and has a bitter taste.
It is slightly soluble in water, freely soluble in ethanol(95), and practically insoluble in ether.

Melting point—Between 159 and 164 °C.

Identification (1) Dissolve 0.2 g of Pinaverium Bromide in 10 mL of chloroform and use this solution as the test solution. Weigh 0.2 g of pinaverium bromide RS, dissolve in 10 mL of chloroform, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 mL each of the test solution and the standard solution on the thin plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol, acetone and hydrochloric acid (45: 5 : 2), and air-dry the plate. Spray evenly Dragendorff's TS on the plate; the R_f value and the color of the spots obtained from the test solution are same as those from the standard solution.

(2) Dissolve 10 mg of Pinaverium Bromide in 100 mL of water. With this solution, determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima around 286 nm, 243 nm, and between 212 and 217 nm.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Pinaverium Bromide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 0.2 g of Pinaverium Bromide in 5 mL of ethanol(95) and use this solution as the test solution. With this solution, perform the test as directed under the Thin Layer Chromatography. Spot the test solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate using a mixture of ethanol(95) and ammonia water (99 : 1), dry the plate at 40 ℃. Expose the plate to ultraviolet light (main wavelength: 254 nm); a black spot (bromomethyl-1-bromo-2-demethoxy-3,4-benzene) does not appear at R_f value of 0.67. Spray evenly Dragendorff's TS; a yellow spot (dimethyl-6,6-norpyranyl ethoxyl-ethylmorpholine) does not appear at R_f value of 0.65.

Loss on drying NMT 1.0% (1 g, in vacuum, phosphorus pentoxide, 60 ℃, constant mass).

Residue on ignition NMT 1.0% (1.0 g).

Assay Weigh accurately 0.45 g of Pinaverium Bromide, previously dried, transfer to a beaker, add 2 mL of anhydrous formic acid, dissolve in 50 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 59.14 mg of $C_{26}H_{41}Br_2NO_4$

Packaging and storage Preserve in tight containers.

Pinaverium Bromide Tablets
피나베륨브롬화물 정

Pinaverium Bromide Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of pinaverium bromide ($C_{26}H_{41}Br_2NO_4$: 591.42).

Method of preparation Prepare as directed under Tablets, with Pinaverium Bromide.

Identification (1) Take 2 tablets of Pinaverium Bromide Tablets, add 10 mL of chloroform, filter, and use the filtrate as the test solution. Weigh 0.1 g of pinaverium bromide RS, add 10 mL of chloroform, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol, acetone and hydrochloric acid (45 : 5 : 2) as the developing solvent, and air-dry the plate. Spray evenly Dragendorff's TS on the plate; the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

(2) Take 1 tablet of Pinaverium Bromide Tablets, add 100 mL of water, and dissolve by warming on a steam bath. After cooling, filter and take 10 mL of the filtrate. Then add water to make 100 mL, and determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima at around the wavelengths of 286 nm, 243 nm and 212 nm to 217 nm.

Dissolution Perform the test with 1 tablet of Pinaverium Bromide Tablets at 50 revolutions per minute according to Method 2, using 900 mL of 0.05 mol/L acetic acid-sodium acetate buffer solution, pH 4.0, as the dissolution medium. Filter the dissolved solution 15 minutes after starting the dissolution test, and use this filtrate as the test solution. Separately, weigh accurately about 10 mg of pinaverium bromide RS, and add the dissolution medium to make exactly 100 mL. Take exactly 50 mL of this solution, add the dissolution medium to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of pinaverium bromide, A_T and A_S, in each solution. Meets the requirements if the dissolution rate of Pinaverium Bromide Tablets in 15 minutes is NLT 80%.

Dissolution rate (%) of the labeled amount of pinaverium bromide ($C_{26}H_{41}Br_2NO_4$)
$= W_S \times (A_T / A_S) \times (1 / C) \times 450$

Ws: Amount (mg) of pinaverium bromide RS

C: Labeled amount (mg) of pinaverium bromide ($C_{26}H_{41}Br_2NO_4$) per tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 243 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of acetonitrile and 0.01 mol/L potassium dihydrogen phosphate (3 : 1).

Flow rate: 0.8 mL/min

System suitability

System repeatability: Repeat the test 6 times with 20 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of pinaverium bromide is NMT 2.0%.

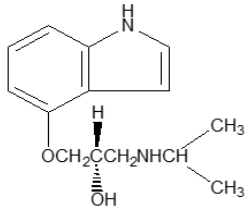
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Pinaverium Bromide Tablets, and powder them. Weigh accurately an amount of the powder, equivalent to about 50 mg of pinaverium bromide ($C_{26}H_{41}Br_2NO_4$), add 150 mL of water, dissolve on a steam bath by shaking occasionally to mix, add water to make exactly 200 mL, and filter. Discard the first 20 mL of the filtrate, pipet 5 mL of the subsequent filtrate, add water to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of pinaverium bromide RS, and add water to make exactly 200 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 243 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of pinaverium bromide ($C_{26}H_{41}Br_2NO_4$)
= Amount (mg) of pinaverium bromide RS × (A_T / A_S)

Packaging and storage Preserve in tight containers.

Pindolol
핀돌롤



and enantiomer

$C_{14}H_{20}N_2O_2$: 248.32

1-[(1*H*-indol-4-yl)oxy]-3-(isopropylamino)propan-2-ol [*13523-86-9*]

Pindolol, when dried, contains NLT 98.5% and NMT 101.0% of pindolol ($C_{14}H_{20}N_2O_2$).

Description Pindolol occurs as a white crystalline powder and has a slightly characteristic odor.
It is sparingly soluble in methanol, slightly soluble in ethanol(95), and practically insoluble in water or ether.
It dissolves in dilute sulfuric acid or acetic acid(100).

Identification (1) To 1 mL of a solution of Pindolol in methanol (1 in 10000), add 1 mL of a solution of hydrochloric acid in 1-(4-pyridyl)pyridinium chloride hydrochloride (1 in 1000) and 1 mL of sodium hydroxide TS, and add 1 mL of hydrochloric acid; the resulting solution exhibits a blue to bluish purple color and the color soon changes to purple.

(2) Dissolve 50 mg of Pindolol in 1 mL of dilute sulfuric acid, and add 1 mL of Reinecke salt TS; a pale red precipitate is formed.

(3) Determine the absorption spectra of solutions of Pindolol and pindolol RS in methanol (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared spectra of Pindolol and pindolol RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 169 and 173 ℃.

Absorbance $E_{1cm}^{1\%}$ (264 nm): Between 333 and 350 (10 mg, methanol, 500 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Pindolol in 10 mL of acetic acid(100), and examine immediately; the resulting solution is clear, and the color is not more intense than the following control solution.

Control solution—Pipet 4 mL of the matching fluid for color A, add exactly 6 mL of water, and mix.

(2) ***Heavy metals*—**Proceed with 1.0 g of Pindolol

according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Pindolol according to Method 3, and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.10 g of Pindolol in 10 mL of methanol, and use this solution as the test solution. Pipet 2 mL of this solution and add methanol to make exactly 100 mL. Pipet 5 mL of this solution, add methanol to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, acetone and isopropylamine (5 : 4 : 1) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Spray evenly a sulfuric acid solution (3 in 5) and a sodium nitrite solution (1 in 50) on the plate; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

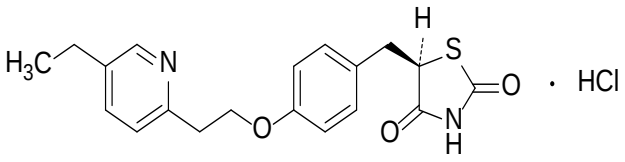
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Pindolol, previously dried, dissolve in 80 mL of methanol, and titrate with 0.1 mol/L hydrochloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L hydrochloric acid VS
= 24.832 mg of $C_{14}H_{20}N_2O_2$

Packaging and storage Preserve in light-resistant, tight containers.

Pioglitazone Hydrochloride
피오글리타존염산염



and enantiomer

$C_{19}H_{20}N_2O_3S \cdot HCl$: 392.90

(5*RS*)-5-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione monohydrochloride [*112529-15-4*]

Pioglitazone Hydrochloride contain NLT 99.0% and NMT 101.0% of the labeled amount of Pioglitazone Hydrochloride ($C_{19}H_{20}N_2O_3S \cdot HCl$: 392.90), calculated on the anhydrous basis.

Description Pioglitazone Hydrochloride occurs as a white crystalline powder.

It is soluble in dimethylformamide and methanol, slightly soluble in ethanol(99.5) and practically insoluble in water.

It dissolves in 0.1 mol/L hydrochloric acid TS.

A solution of Pioglitazone Hydrochloride in *N*,*N*-dimethylformamide (1 in 20) shows no optical rotation.

Identification (1) Determine the absorption spectra of solutions of Pioglitazone Hydrochloride and pioglitazone hydrochloride RS in 0.1 mol/L hydrochloric acid TS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Pioglitazone Hydrochloride and pioglitazone hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 50 mg of Pioglitazone Hydrochloride in 1 mL of nitric acid, and add 4 ml of dilute nitric acid; the resulting solution responds to the Chemical identification reaction (2) for chloride.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Pioglitazone Hydrochloride according to Method 4 and perform the test. After incinerating, use 3 mL of hydrobromic acid instead of 3 mL of hydrochloric acid. However, prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Weigh 20 mg of Pioglitazone Hydrochloride, dissolve in 20 mL of methanol, add the mobile phase to make 100 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to it make exactly 200 mL, and use this solution as the standard solution. Perform the test with 40 μL each of the test solution and standard solution as directed under the Liquid Chromatography under the following conditions. Determine the peak area of each solution by the automatic integration method; the peak area with a relative retention time to pioglitazone of about 0.7, 1.4 and 3.0 from the test solution is not greater than 3/10 of the peak area of pioglitazone from the standard solution (NMT 0.15%); the peak area of pioglitazone and the above peak from the test solution is not greater than 1/5 of the peak area of pioglitazone from the standard solution (NMT 0.10%). The sum of peak areas other than pioglitazone from the test solution is not greater than that of pioglitazone from the standard solution (NMT 0.5%).

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

Time span of measurement: About 4 times the retention time of pioglitazone after the solvent peak.

System suitability

Test for required detectability: Take exactly 1 mL of the standard solution, and add the mobile phase to

make exactly 10 mL. Confirm that the peak area of pioglitazone obtained from 40 μL of this solution is equivalent to 7 to 13% of the peak area of pioglitazone obtained from the standard solution.

System performance: Dissolve 50 mg of Pioglitazone Hydrochloride in a solution of benzophenone in methanol (1 in 750), and add methanol to make 100 mL. Pipet 1 mL of this solution, and add the mobile phase to make 20 mL. Proceed with 40 μL of this solution under the above operating conditions; pioglitazone and benzophenone are eluted in this order with the resolution being NLT 10.

System repeatability: Repeat the test 6 times with 40 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of pioglitazone is NMT 2.0%.

Water NMT 0.2% (0.5 g, coulometric titration). However, use anolyte for water determination A for anolyte for water determination.

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg of Pioglitazone Hydrochloride and pioglitazone hydrochloride RS (previously determine the content of water), add exactly 10 mL each of the internal standard solution, and add methanol to make 100 mL. Pipet 2 mL each of this solution, add the mobile phase to make exactly 20 mL, and use these solutions as the test solution and the standard solution, respectively. Take 20 μL each of the test solution and the standard solution, perform the test according to the Liquid Chromatography under the following conditions, and calculate the peak area ratios Q_T and Q_S of pioglitazone to that of the internal standard, respectively.

$$\text{Amount (mg) of pioglitazone hydrochloride } (C_{19}H_{20}N_2O_3S\cdot HCl) = W_S \times Q_T / Q_S$$

W_{Sb}: Amount (mg) of pioglitazone hydrochloride RS, calculated on the anhydrous basis

Internal standard solution—A solution of benzophenone in methanol (1 in 750).

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 269 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: A mixture of ammonium acetate solution (77 in 10000), acetonitrile and acetic acid(100) (25 : 25 : 1).

Flow rate: Adjust the flow rate so that the retention time of pioglitazone is about 7 minutes.

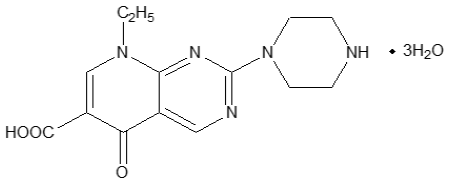
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above operating conditions; pioglitazone and the internal standard are eluted in this order with the resolution being NLT 10.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio of pioglitazone to the peak area of the internal standard is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Pipemidic Acid Hydrate
피페미드산수화물



Pipemidic Acid

Pipemidic Acid Trihydrate $C_{14}H_{17}N_5O_3\cdot 3H_2O$: 357.36

8-Ethyl-5-oxo-2-(piperazin-1-yl)-5,8-dihydropyrido[2,3-d]pyrimidine-6-carboxylic acid [*72571-82-5*]

Pipemidic Acid Hydrate contains NLT 98.5% and NMT 101.0% of pipemidic acid ($C_{14}H_{17}N_5O_3$: 303.32), calculated on the anhydrous basis.

Description Pipemidic Acid Hydrate occurs as a pale yellow crystalline powder.

It is freely soluble in acetic acid(100), soluble, very slightly soluble in water or ethanol(99.5), and practically insoluble in methanol.

It dissolves in sodium hydroxide TS.

It is gradually colored by light.

Melting point—About 250 ℃ (with decomposition).

Identification (1) Dissolve 0.1 g of Pipemidic Acid Hydrate in 20 mL of sodium hydroxide TS, heat on a steam bath for 1 hour under the reflux condenser, and cool. Take 2 mL of this solution, add 1 drop of phenolphthalein TS, add dilute acetic acid to neutralize, and add another 1 mL of dilute acetic acid. Add 4 mL of a solution of *p*-benzoquinone in methanol (1 in 1000) and boil with mild heat; the resulting solution exhibits an orange color.

(2) Dissolve 0.1 g each of Pipemidic Acid Hydrate and pipemidic acid hydrate RS in 20 mL of sodium hydroxide TS, and add water to make 200 mL. Take 1 mL each of these solutions, and add water to make 100 mL. Determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Pipemidic Ac-

id Hydrate and pipemidic acid hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Chloride*—**Dissolve 1.0 g of Pipemidic Acid Hydrate in 35 mL of water and 10 mL of sodium hydroxide TS, add 15 mL of dilute nitric acid, shake well to mix, and filter with the glass filter. Pipet 30 mL of the filtrate and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 5 mL of sodium hydroxide TS, 13.5 mL of dilute nitric acid, and water to 0.30 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.021%).

(2) ***Sulfate*—**Dissolve 1.0 g of Pipemidic Acid Hydrate in 35 mL of water and 10 mL of sodium hydroxide TS, add 15 mL of dilute hydrochloric acid, shake well to mix, and filter with the glass filter. Take 30 mL of the filtrate and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 5 mL of sodium hydroxide TS, 7.5 mL of dilute hydrochloric acid, and water to 0.50 mL of 0.005 mol/L sulfuric acid to make 50 mL (NMT 0.048%).

(3) ***Heavy metals*—**Proceed with 2.0 g of Pipemidic Acid Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic*—**Proceed with 1.0 g of Pipemidic Acid Hydrate according to Method 3 and perform the test (NMT 2 ppm).

(5) ***Related substances*—**Dissolve 0.10 g of Pipemidic Acid Hydrate in 10 mL of diluted acetic acid(100) (1 in 20), and use this solution as the test solution. Pipet 1 mL of this solution, add diluted acetic acid(100) (1 in 20) to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform, methanol, formic acid, and triethylamine (25 : 15 : 5 :1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Water Between 14.5% and 16.0% (20 mg, volumetric titration).

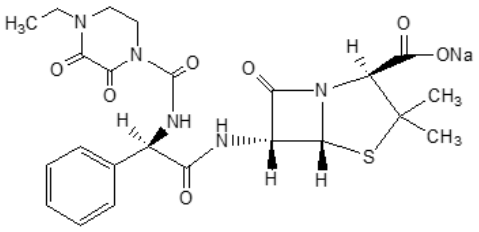
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.35 g of Pipemidic Acid Hydrate, dissolve in 40 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 30.33 mg of $C_{14}H_{17}N_5O_3$

Packaging and storage Preserve in light-resistant, well-closed containers.

Piperacillin Sodium
피페라실린나트륨



$C_{23}H_{26}N_5NaO_7S$: 539.54

Sodium (2*S*,5*R*,6*R*)-6-{[(2*R*)-2-[(4-ethyl-2,3-dioxopiperazine-1-carbonyl)amino]-2-phenyl-acetyl]amino}-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate [*59703-84-3*]

Piperacillin Sodium contains NLT 863 μg (potency) of piperacillin ($C25H_{23}N9O_{27}S$: 517.55) per mg, calculated on the anhydrous basis.

Description Piperacillin Sodium occurs as a white powder or a mass.
It is very soluble in water, freely soluble in methanol or ethanol(95) and practically insoluble in acetonitrile.

Identification (1) Determine the infrared spectra of Piperacillin Sodium and piperacillin sodium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Piperacillin Sodium responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between +175° and +190° (0.8 g, calculated on the anhydrous basis, water, 20 mL, 100 mm).

pH Dissolve 1.0 g of Piperacillin Sodium in 4 mL of water; the pH is between 5.0 and 7.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Piperacillin Sodium in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 2.0 g of Piperacillin Sodium according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Proceed with 2.0 g of Piperacillin Sodium according to the Method 4, and perform the test (NMT 1 ppm).

(4) ***Related substances***—Weigh accurately about

0.1 g of Piperacillin Sodium, dissolve in the mobile phase A to make exactly 50 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase A to make exactly 100 mL, and use this solution as the standard solution. Pipet 20 μL each of the test solution and the standard solution, perform the test with these solutions as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas from each solution by calculating each peak area from each solution with the automatic integration method; the peak area with the retention time of about 7 minutes from the test solution is not greater than 1/2 of the peak area of piperacillin from the standard solution; the sum of the peak areas of the related substances I with the retention time of about 17 minutes and 21 minutes is not more than twice the peak area of piperacillin from the standard solution; the peak area of the related substances II with the retention time of about 56 minutes is not greater than the peak area of piperacillin from the standard solution. In addition, the sum of peak areas other than piperacillin in the test solution is not greater than 5 times the peak area of piperacillin from the standard solution. However, the peak areas of ampicillin, related substances I and related substances II are determined by multiplying the measured areas by their respective correction factors of 1.39, 1.32 and 1.11.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: A mixture of water, acetonitrile and 0.2 mol/L potassium dihydrogen phosphate TS (45 : 4 : 1).

Mobile phase B: A mixture of acetonitrile and 0.2 mol/L potassium dihydrogen phosphate TS (25 : 24 : 1).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 7	100	0
7 - 13	100 → 83	0 → 17
13 - 41	83	17
14 - 56	83 → 20	17 → 80
56 - 60	20	80

Flow rate: 1.0 mL/minute. Under this condition, the retention time of piperacillin is about 33 minutes.

Time span of measurement: About 1.8 times the retention time of piperacillin after the solvent peak

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the number of theoretical plates and the symmetry factor of the peak of piperacillin are NLT 15000 and NMT 1.5, respectively.

System repeatability: Repeat the test 3 times with 20 μL each of the standard solutions according to the above operating conditions; the relative standard deviation of the peak area of piperacillin is NMT 2.0%.

(5) ***Dimethylaniline***—Weigh accurately about 1.0 g of Piperacillin Sodium, add 5 mL of 1 mol/L sodium hydroxide TS and 1 mL of the internal standard solution, centrifuge, if necessary, and use the supernatant as the test solution. Separately, weigh accurately about 50 mg of dimethylaniline, add 2.0 mL of hydrochloric acid, and add water to make 50 mL. Pipet 5.0 mL of this solution, and add water to make exactly 250 mL. Pipet 1.0 mL of this solution, add 5.0 mL of 1 mol/L sodium hydroxide TS, add 1.0 mL of the internal standard solution, centrifuge, if necessary, and use the supernatant as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the peak area ratio, Q_T and Q_S, of dimethylaniline to that of the internal standard, respectively (NMT 20 ppm).

$$\text{Content (ppm) of dimethylaniline} = \text{Amount (mg) of dimethylaniline taken} \times \frac{Q_T}{Q_S} \times \frac{Purity\ (\%)\ of\ dimethylaniline}{Amount\ (mg)\ of\ Piperacillin\ Sodium\ taken} \times 4$$

Internal standard solution—Dissolve 50.0 mg of naphthalene in cyclohexane to make 50 mL. Take 5.0 mL of this solution, add cyclohexane to make 100 mL, and use this solution as the internal standard solution.

Operating conditions

Detector: A flame ionization detector

Column: A column about 2 mm in internal diameter and about 2 m in length, packed with diatomaceous earth for gas chromatography coated with 50% phenyl-50% methyl polysiloxane for gas chromatography equivalent to 3% of the mass.

Column temperature: 120 °C

Temperatures of the sample injection port and the detector: 150 °C

Carrier gas: Nitrogen

Flow rate: 30 mL/min

Water NMT 1.0% (3 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, the manufacturing process of sterile preparations which include the terminal sterile process is exceptional.

Bacterial endotoxins Less than 0.07 EU per mg (potency) of piperacillin when used in the manufacturing of sterile preparations.

Assay Weigh accurately about 0.1 g (potency) of Piperacillin Sodium, and dissolve in water to make exactly 100 mL. Pipet 5.0 mL of this solution, add exactly 5 mL of the internal standard solution, and use this solution as the test solution. Separately, weigh accurately an amount equivalent to about 0.1 mg (potency) of piperacillin RS, and dissolve in the mobile phase to make exactly 100 mL. Pipet 5 mL of this solution, add exactly 5 mL of the internal standard solution, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under Liquid Chromatography according to the following conditions and calculate the ratios of the peak height, Q_T and Q_S, of piperacillin to that of the internal standard for the test solution and the standard solution, respectively.

$$\text{Potency (μg) of piperacillin } (C_{23}H_{26}N_5O_7S) = \text{Potency (μg) of piperacillin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of acetanilide in the mobile phase (1 in 5000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 150 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Weigh 60.1 g of acetic acid(100), 101.0 g of triethylamine and water to make exactly 1000 mL. To 25 mL of this solution, add 25 mL of dilute acetic acid, 210 mL of acetonitrile and water to make exactly 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of piperacillin is about 5 minutes.

System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; the internal standard and piperacillin are eluted in this order with the resolution being NLT 3.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solutions under the above operating conditions; the relative standard deviation of the peak height ratio of piperacillin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in hermetic containers.

Piperacillin Sodium for Injection
주사용 피페라실린나트륨

Piperacillin Sodium for Injection is a preparation for injection which is dissolved before use, and contains NLT 93.0% and NMT 107.0% of the labeled amount of piperacillin ($C_{23}H_{27}N_5O_7S$: 517.55).

Method of preparation Prepare as directed under Injections, with Piperacillin Sodium.

Description Piperacillin Sodium occurs as a white powder or a mass.

Identification Perform the test as directed under the Identification (1) and (2) under Piperacillin Sodium.

pH Take Piperacillin Sodium for Injection in the amount equivalent to 1.0 g (potency) as piperacillin sodium according to the labeled amount and dissolve it in 4 mL of water; the pH of the solution is 5.0 to 7.0.

Purity (1) ***Clarity and color of solution***—Take Piperacillin Sodium for Injection in the amount equivalent to 4.0 g (potency) as piperacillin sodium according to the labeled amount, and dissolve in 17 mL of water; the solution is colorless and clear.

(2) ***Related substances***—Proceed as directed under the Purity (4) under Piperacillin Sodium.

Water NMT 1.0% (3 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.04 EU per mg (potency) of piperacillin.

Uniformity of dosage units Meets the requirements of the mass variation test.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Assay Take NLT 10 containers of Piperacillin Sodium Injection, weigh accurately the amount equivalent to about 20 mg (potency) as piperacillin sodium according to the labeled amount, and dissolve in water to make exactly 20 mL. Pipet 5 mL of this solution, add exactly 5 mL of the internal standard solution, and use the resulting solution as the test solution. Separately, weigh accurately about 20 mg (potency) of piperacillin RS, and dissolve in the mobile phase to make exactly 20 mL. Pipet 5 mL of this solution, add exactly 5 mL of the internal standard solution, and use the resulting solution as the standard solution. Perform the test as directed under the Operating conditions of the Assay under Piperacillin Sodium.

$$\text{Potency (μg) of piperacillin } (C_{23}H_{26}N_5O_7S) = \text{Potency (μg) of piperacillin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of acetanilide in the mobile phase (1 in 5000).

Packaging and storage Preserve in hermetic containers. Plastic containers for aqueous injections may be used.

Piperacillin Sodium·Tazobactam Sodium
피페라실린나트륨·타조박탐나트륨

Piperacillin Sodium·Tazobactam Sodium contains NLT 837 μg (potency) and NMT 980 μg (potency) of piperacillin ($C_{23}H_{27}N_5O_7S$: 517.56) per mg and NLT 103 μg and NMT 120 μg of tazobactam ($C_{10}H_{12}N_4O_5S$: 300.29) per mg.

Description Piperacillin Sodium·Tazobactam Sodium occurs as a white or milky white powder consisting of freeze-dried mixture of piperacillin sodium and tazobactam sodium, or piperacillin, tazobactam, and sodium bicarbonate dissolved in water for injection.
It is freely soluble in water or methanol, sparingly soluble in ethanol, and practically insoluble in acetone, chloroform, or ethyl acetate.

Identification (1) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

(2) Dissolve 0.5 g of Piperacillin Sodium·Tazobactam Sodium in a mixture of acetone and water (1 : 1) to make 25 mL. Separately, weigh about 0.4 g (potency) of piperacillin RS and about 50 mg of tazobactam RS, dissolve each in 2 mL of 1 mol/L sodium bicarbonate VS, and add a mixture of acetone and water (1 : 1) to make 25 mL. Use these solutions as the piperacillin standard solution and the tazobactam standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography, develop the plate using a mixture of toluene, acetone, and acetic acid(100) (5 : 2 : 2) as the developing solvent, air-dry the plate, and examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values and colors of the spots obtained from the test solution and piperacillin standard solution are the same. Again, spray evenly 4-dimethylaminobenzaldehyde-methanol TS on the plate, and dry; the R_f values of the red spots obtained from the test solution and tazobactam standard solution are the same.

pH Dissolve Piperacillin Sodium·Tazobactam Sodium in water to make 0.2g (potency)/mL solution; the pH of the solution is between 4.5 and 6.8.

Purity ***Related substances***—Perform the test as directed under the Assay and determine the ratio of the peak area of each related substance to the total peak area of peaks other than the solvent peak in the test solution. However, weigh accurately 20 mg of related substance I RS [(2R,4S)-2-{(1R)-Carboxy[2-(4-ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]methyl}-5,5-dimethylthiazolidine-4-carboxylic acid], dissolve in the mobile phase to make exactly 250 mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 25 mL, and use this solution as the related substance I standard solution (this solution is stable for about 1 hour at room temperature). The amount of related substance I is NMT 5.0%, and the total amount of related substances other than related substance I is NMT 5.0%.

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins Meet the requirement when Piperacillin Sodium·Tazobactam Sodium is used in sterile preparations. However, Piperacillin Sodium·Tazobactam Sodium is NMT 0.07 EU per mg (potency) as piperacillin.

Water NMT 2.0% (0.5 g, volumetric titration, direct titration)

Assay Weigh accurately about 0.5 g of Piperacillin Sodium·Tazobactam Sodium, and dissolve in the mobile phase to make exactly 50 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg (potency) of piperacillin RS and about 15 mg of tazobactam RS, dissolve each in the mobile phase to make exactly 25 mL, and use these solutions as the piperacillin standard stock solution and tazobactam standard stock solution. Mix 5.0 mL of piperacillin standard stock solution and 1.0 mL of tazobactam standard stock solution, add the mobile phase to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of piperacillin and tazobactam, A_{T1}, A_{T2}, A_{S1}, and A_{S2}, for each solution.

$$\text{Potency (μg) piperacillin } (C_{23}H_{27}N_5O_7S) = Potency\ (\mu g)\ of\ piperacillin\ RS \times \frac{A_{T1}}{A_{S1}} \times 20$$

A_{T1}: Peak area of piperacillin in the test solution
A_{S1}: Peak area of piperacillin in the standard solution

$$\text{Content (μg) tazobactam } (C_{10}H_{12}N_4O_5S) = Content\ (\mu g)\ of\ tazobactam\ RS \times \frac{A_{T2}}{A_{S2}} \times 4$$

A_{T2}: Peak area of tazobactam in the test solution
A_{S1}: Peak area of tazobactam in the standard solution

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 210 nm).

Column: A stainless steel column between 3.9 mm and 4.5 mm in internal diameter and about 15 cm in length, packed with methylphenylpropylsilanized silica gel for liquid chromatography (4 μm to 5 μm in particle diameter).

Mobile phase: Mix 775 mL of 0.005 mol/L tetrabutylammonium hydroxide TS and 225 mL of acetonitrile, and adjust the pH to between 3.5 and 3.7 with 20% phosphoric acid solution.

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Piperacillin Sodium·Tazobactam Sodium for Injection
주사용 피페라실린나트륨·타조박탐나트륨

Piperacillin Sodium·Tazobactam Sodium for Injection is an injection which is dissolved before use and contains NLT 90.0% and NMT 120.0% of the labeled amount of piperacillin ($C_{23}H_{27}N_5O_7S$: 517.56) and tazobactam ($C_{10}H_{12}N_4O_5S$: 300.29).

Description Piperacillin Sodium·Tazobactam Sodium for Injection occurs as a white to milky white powder or a mass.

Method of preparation Prepare as directed under Injections, with Piperacillin Sodium·Tazobactam Sodium.

Identification Perform the test as directed under the Identification (1) and (2) under Piperacillin Sodium·Tazobactam Sodium.

pH Dissolve Piperacillin Sodium·Tazobactam Sodium for Injection in water to make 0.2 g (potency)/mL of piperacillin; the pH of the solution is 4.5 to 6.8.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.07 EU per mg (potency) of piperacillin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

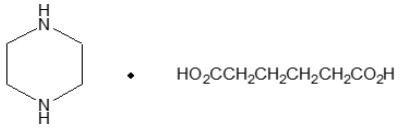
Uniformity of dosage units Meets the requirements.

Water NMT 2.0% (0.5 g, volumetric titration, direct titration)

Assay Perform the test as directed under the Assay under Piperacillin Sodium·Tazobactam Sodium. Prepare the test solution by weighing accurately Piperacillin Sodium·Tazobactam Sodium for Injection in the amount equivalent to about 2 g (potency) as piperacillin according to the labeled potency and adding the mobile phase to make a solution having a concentration of 0.2 mg (potency) as piperacillin per mL.

Packaging and storage Preserve in hermetic containers.

Piperazine Adipate
피페라진아디프산염



$C_4H_{10}N_2 \cdot C_6H_{10}O_4$: 232.28

Piperazine hexanedioate [*142-88-1*]

Piperazine Adipate, when dried, contains NLT 98.5% and NMT 101.0% of piperazine adipate ($C_4H_{10}N_2 \cdot C_6H_{10}O_4$).

Description Piperazine Adipate occurs as a white crystalline powder. It is odorless and has a slightly sour taste. It is soluble in water or acetic acid(100) and practically insoluble in ethanol(95), acetone or ether.

Melting point—About 250 ℃ (with decomposition).

Identification (1) Dissolve 0.5 g of Piperazine Adipate in 10 mL of water, add 1 mL of hydrochloric acid, and extract 2 times each with 20 mL of ether. Combine the ether extracts, evaporate the residue to dryness on a steam bath, and dry the residue at 105 ℃ for 1 hour; the melting point is between 152 and 155 ℃.

(2) To 3 mL of an aqueous solution (1 in 100) of Piperazine Adipate, add 3 drops of Reinecke salt TS; a pale red precipitate is formed.

(3) Determine the infrared spectra of Piperazine Adipate and piperazine adipate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

pH Dissolve 1 g of Piperazine Adipate in 20 mL of water; the pH of this solution is between 5.0 and 6.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Piperazine Adipate in 30 mL of water; the resulting solution is clear and colorless.

(2) ***Heavy metals*—**Proceed with 2.0 g of Piperazine Adipate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Weigh accurately 1 g of Piperazine Adipate, dissolve in the diluent to make exact-

ly 10 mL, and use this solution as the test solution (1). Pipet 1.0 mL of the test solution (1), dissolve in the diluent to make exactly 10 mL, and use this solution as the test solution (2). Separately, weigh accurately 0.1 g of piperazine adipate RS, dissolve in the diluent to make exactly 10 mL, and use this solution as the standard solution (1). Weigh accurately 25 mg of ethylenediamine, dissolve in the diluent to make exactly 100 mL, and use this solution as the standard solution (2). Weigh accurately 25 mg of triethylenediamine, dissolve in the diluent to make exactly 100 mL, and use this solution as the standard solution (3). Weigh accurately 25 mg of triethylenediamine and 1 g of piperazine adipate RS, dissolve in the diluent to make exactly 100 mL, and use this solution as the standard solution (4). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solutions (1) and (2) and the standard solutions (1), (2), (3), and (4) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of acetone and 13.5 mol/L ammonia water (80 : 20) as the developing solvent to a distance of about 15 cm, and dry the plate at 105 ℃. Spray a solution of 0.3% ninhydrin in a mixture of 1-butanol and acetic acid(100) (100 : 3) on the plate, spray a 0.15% ninhydrin-anhydrous alcohol solution additionally, dry the plate at 105 ℃ for 10 minutes, and examine the plate; the spots other than the principal spot obtained from the test solution (1) are not more intense than the principal spot from the standard solution (2) (NMT 0.25%). Spray iodine TS on the plate, allow to stand for 10 minutes, and examine the plate. The spot corresponding to triethylenediamine obtained from the test solution (1) is not more intense than the principal spot from the standard solution (3) (NMT 0.25%). This test is valid when the principal spot obtained from the standard solution (4) and the spot corresponding to triethylenediamine are clearly separated.

Diluent—A mixture of 13.5 mol/L ammonia water and anhydrous alcohol (3 : 2).

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

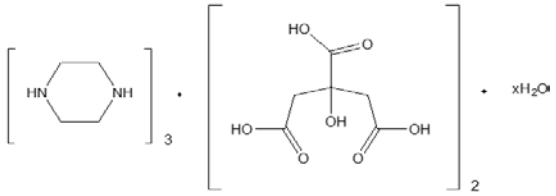
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Piperazine Adipate, previously dried, dissolve in 20 mL of acetic acid(100) and 40 mL of acetone for non-aqueous titration, and titrate with 0.1 mol/L perchloric acid VS (indicator: 6 drops of bromocresol green-methylrosaniline chloride TS). However, the endpoint of the titration is when the color of the solution changes from purple to bluish purple. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 11.614 mg of $C_4H_{10}N_2 \cdot C_6H_{10}O_4$

Packaging and storage Preserve in well-closed containers.

Piperazine Citrate Hydrate
피페라진시트르산염수화물



Piperazine Citrate $(C_4H_{10}N_2)_3 \cdot 2C_6H_8O_7 \cdot xH_2O$
Piperazine 2-2-hydroxypropane-1,2,3-tricarboxylate hexahydrate [*41372-10-5*]

Piperazine Citrate Hydrate contains NLT 98.0% and NMT 100.5% of piperazine citrate [$(C_4H_{10}N_2)_3 \cdot 2C_6H_8O_7$: 642.65], calculated on the anhydrous basis.

Description Piperazine Citrate Hydrate occurs as a white crystalline powder and has a slight odor.
It is soluble in water and practically insoluble in ethanol(95) or ether.
The pH of an aqueous solution of Piperazine Citrate Hydrate (1 in 10) is about 5.

Identification (1) Dissolve 0.2 g of Piperazine Citrate Hydrate in 5 mL of 3 mol/L hydrochloric acid, add 1 mL of sodium nitrite solution (1 in 2) while shaking to mix. Next, immerse in ice for 15 minutes, shake to mix if necessary, precipitate the crystals, and filter the precipitate using a glass filter. Wash with 10 mL of cold water, and dry at 105 ℃. The melting point of the obtained *N*,*N'*-dinitrosopiperazine is between 156 and 160 ℃.

(2) Piperazine Citrate Hydrate responds to the Qualitative Analysis for citrate.

Purity (1) ***Primary amine and ammonia***—Dissolve 0.5 g of Piperazine Citrate Hydrate in 10 mL of water, add 1 mL of 2.5 mol/L sodium hydroxide, 1 mL of acetone and 1 mL of sodium nitroprusside TS, shake to mix, and allow to stand for 10 minutes. Determine the absorbance A_1 and A_2 at wavelengths of 520 nm and 600 nm; the ratio A_2/A_1 is NMT 0.5. Prepare the blank test solution by using the same amount of the same test solution, and using water instead of sodium hydroxide solution (NMT 0.7% of primary amine and ammonia).

(2) ***Heavy metals***—Dissolve 1.25 g of Piperazine Citrate Hydrate in water to make 25 mL. Use this solution as the test solution and perform the test. Separately, to 3 mL of lead standard solution, add water to make 30 mL. To 10 mL of this solution, add 2 mL of the test solution, and use this solution as the control solution. Also, to 10 mL of water, add 2 mL of the test solution, and use this solution as the blank test solution. To 12 mL each of the test solution, the control solution, and the blank test solution, add 2 mL of pH 3.5 acetate buffer solution, mix, add 1.2 mL of thioacetamide TS, and mix immediately. Allow them to stand for 2 minutes; the color of the test

solution is not more intense than that of the control solution (NMT 20 ppm).

System suitability—The control solution exhibits a faint brown color compared to the blank test solution.

(3) ***Related substances***—Weigh accurately 1 g of Piperazine Citrate Hydrate, dissolve in the diluent to make exactly 10 mL, and use this solution as the test solution (1). Pipet 1.0 mL of the test solution (1), add diluent to make exactly 10 mL, and use this solution as the test solution (2). Separately, weigh accurately 0.1 g of piperazine citrate RS, dissolve in the diluent to make exactly 10 mL, and use this solution as the standard solution (1). Weigh accurately 25 mg of ethylenediamine, dissolve in diluent to make exactly 100 mL, and use this solution as the standard solution (2). Weigh accurately 25 mg of triethylenediamine, dissolve in diluent to make exactly 100 mL, and use this solution as the standard solution (3). Weigh accurately 25 mg of triethylenediamine and 1.0 g of piperazine citrate RS, dissolve in diluent to make exactly 100 mL, and use this solution as the standard solution (4). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solutions (1) and (2) and the standard solutions (1), (2), (3), and (4) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of acetone and 13.5 mol/L ammonia water (80 : 20) as the developing solvent to a distance of about 15 cm, and dry the plate at 105 ℃. Spray evenly a solution of 0.3% ninhydrin in a mixture of 1-butanol and acetic acid(100) (100 : 3) on the plate, spray a 0.15% ninhydrin-anhydrous alcohol solution additionally, dry the plate at 105 ℃ for 10 minutes, and examine the plate. The spots other than the principal spot obtained from the test solution (1) are not more intense than the principal spot from the standard solution (2) (NMT 0.25%). Spray iodine TS on the plate, allow to stand for 10 minutes, and examine the plate; the spot corresponding to triethylenediamine obtained from the test solution (1) is not more intense than the spot obtained from the standard solution (3) (NMT 0.25%). This test is valid when the principal spot obtained from the standard solution (4) and the spot corresponding to triethylenediamine are clearly separated.

Diluent—A mixture of 13.5 mol/L ammonia water and anhydrous alcohol (3 : 2).

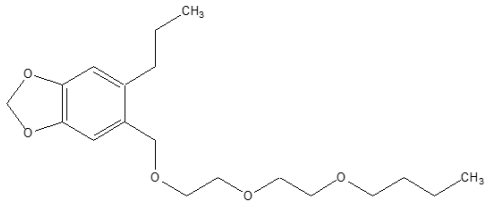
Water NMT 12.0% (0.3 g, direct titration).

Assay Weigh accurately about 0.2 g of Piperazine Citrate Hydrate, and dissolve in 100 mL of acetic acid(100). Dissolve by heating if necessary, and titrate with 0.1 mol/L perchloric acid VS (indicator: 3 drops of methylrosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 10.711 mg $(C_4H_{10}N_2)_3 \cdot 2C_6H_8O_7$

Packaging and storage Preserve in well-closed containers.

Piperonyl Butoxide
피페로닐부톡시드



$C_{19}H_{30}O_5$: 338.43
5-[[2-(2-Butoxyethoxy)ethoxy]methyl]-6-propyl-1,3-benzodioxole, [*51-03-6*]

Piperonyl Butoxide contains NLT 80.0% of piperonyl butoxide ($C_{19}H_{30}O_5$).

Description Piperonyl Butoxide occurs as a pale yellow to pale brown transparent oily liquid that is odorless or has a slight odor.
It is miscible with methanol, acetone, or hexane.
It is practically insoluble in water.
Refractive index n_D^{20}: Between 1.497 and 1.512.

Identification (1) To 0.5 mL of a solution of Piperonyl Butoxide in methanol (1 in 1000), add 20 mL of tannic acid-acetic acid TS and heat while occasionally shaking to mix; the resulting solution exhibits a blue color.

(2) Determine the absorption spectrum of a solution of Piperonyl Butoxide in diluted methanol (9 in 10) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima at a wavelength of between 236 nm and 240 nm and between 288 nm and 292 nm, and when the absorbance values obtained at each maximum wavelength are A_1 and A_2, A_1/A_2 is between 1.13 and 1.33.

Specific gravity d_{20}^{20}: Between 1.050 and 1.070.

Purity (1) ***Color***—The color of Piperonyl Butoxide is not more intense than the color of a mixture of 1.4 mL of cobalt chloride colorimetric stock solution, 0.3 mL of copper sulfate colorimetric stock solution, and 4.3 mL of ferric chloride colorimetric stock solution.

(2) ***Heavy metals***—Proceed with 1.0 g of Piperonyl Butoxide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Piperonyl Butoxide according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Take each 0.1 μL to 0.2 μL of Piperonyl Butoxide, perform the test as directed under the Gas Chromatography according to the following conditions, and determine A_1, the sum of the peak

areas of peaks other than the major peak which appears in the ratio of retention time to the major peak ranging from 0.02 to 2.0, and A_2, the total peak area including all peaks; A_1/A_2 is NMT 0.12.

Operating conditions

Detector: A flame ionization detector

Column: A glass column, about 2 mm to 3 mm in internal diameter and 1 m to 2 m in length, packed with diatomaceous earth for gas chromatography coated with phenylmethylsilicone polymer of 177 μm and 250 μm at a rate of 10%.

Column temperature: A constant temperature of about 250 ℃.

Carrier gas: Nitrogen

Flow rate: Adjust the flow rate so that the major peak shows after 15 to 20 minutes.

Assay Weigh accurately an amount of Piperonyl Butoxide equivalent to 20 mg of piperonyl butoxide ($C_{19}H_{30}O_5$), transfer into a 100-mL volumetric flask, add a mixture of methanol and water (80 : 20), and shake to mix and dissolve. Add a mixture of methanol and water (80 : 20) to make 100 mL, and use this solution as the test solution. Separately, weigh accurately 20 mg of piperonyl butoxide RS, transfer into a 100-mL volumetric flask, dissolve in a mixture of methanol and water (80 : 20), and add another mixture of methanol and water (80 : 20) to make 100 mL. Use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas of piperonyl butoxide, A_T and A_S, of each solution.

Amount (mg) of piperonyl butoxide ($C_{19}H_{30}O_5$)
= Amount (mg) of piperonyl butoxide RS× $\frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 254 nm).

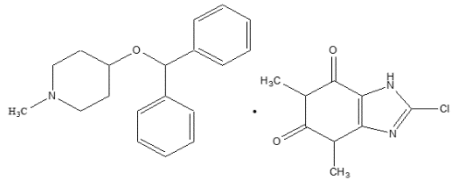
Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Mixture of methanol and water (80 : 20).

Flow rate: 1 mL/min

Packaging and storage Preserve in tight containers.

Piprinhydrinate
피프린히드리네이트



$C_{26}H_{30}ClN_5O_3$: 496.00

4-(Diphenylmethoxy)-1-methylpiperidine 8-chloro theophyllinate, [*606-90-6*]

Piprinhydrinate, when dried, contains NLT 98.0% and NMT 101.0% of piprinhydrinate ($C_{26}H_{30}ClN_5O_3$).

Description Piprinhydrinate occurs as a white crystalline powder. It is odorless and has a bitter taste.
It causes localized anesthesia on the tongue when tasted with the tongue.
It is freely soluble in ethanol and sparingly soluble in water.

Identification Add 10 mg of Piprinhydrinate to 2 mL of sulfuric acid and the solution exhibits an orange red. Add water to this solution and the solution changes to white.

Melting point Between 170 and 175 ℃.

Purity (1) ***Heavy metals***—Proceed with 1 g of Piprinhydrinate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Mix 0.2 g of Piprinhydrinate with 0.3 g of potassium nitrate and 0.5 g of anhydrous sodium carbonate, transfer into a platinum crucible, and heat until the ignition is complete. Next, cool this crucible, boil the residue with 10 mL of dilute sulfuric acid for 5 minutes, filter, and wash the undissolved residue with 10 mL of water. Combine the washings and the filtrate, and evaporate until the white smoke forms. Dissolve this residue in 5 mL of water and perform the test (NMT 10 ppm).

Loss on drying NMT 1.0% (1.0 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.15% (1.0 g)

Assay Weigh accurately about 0.5 g of Piprinhydrinate, previously dried, dissolve in 60 mL of acetic acid(100) for non-aqueous titration, and titrate with 0.05 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L perchloric acid VS
= 24.800 mg of $C_{26}H_{30}ClN_5O_3$

Packaging and storage Preserve in tight containers.

Piprinhydrinate Injection
피프린히드리네이트 주사액

Piprinhydrinate Injection contains NLT 95.0% and NMT 105.0% of the labeled amount of piprinhydrinate (C26H30ClN5O3 : 496.00).

Method of preparation Prepare as directed under Injections, with Piprinhydrinate.

Identification (1) Take Piprinhydrinate Injection in the amount equivalent to 10 mg of piprinhydrinate according to the labeled amount, evaporate to dryness on a steam bath, and add sulfuric acid to the residue; it exhibits a yellowish red color. Add water to it; it turns to a white color.

(2) Take Piprinhydrinate Injection in a suitable quantity according to the labeled amount, and add water to make a solution having a concentration of 15 μg to 20 μg per mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy, using water as a control solution; it exhibits a maximum at about 280 nm.

pH Between 6.0 and 8.0.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

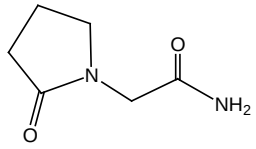
Extractable volume of injections Meets the requirements.

Assay Pipet Piprinhydrinate Injection in the amount equivalent to about 1.5 mg of piprinhydrinate (C26H30ClN5O3), add water to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 15 mg of piprinhydrinate RS, and dissolve in water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and use the resulting solution as the standard solution. Determine the absorbances, AT and AS, of the test solution and the standard solution, respectively, using water as a control solution, at the wavelength of 278 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of piprinhydrinate ($C_{26}H_{30}ClN_5O_3$)
= Amount (mg) of piprinhydrinate RS × (A_T / A_S) × 0.1

Packaging and storage Preserve in hermetic containers.

Piracetam
피라세탐



$C_6H_{10}N_2O_2$: 142.16
2-(2-Oxopyrrolidin-1-yl)acetamide [*72496-41-4*]

Piracetam contains NLT 98.0% and NMT 102.0% of piracetam ($C_6H_{10}N_2O_2$), calculated on the dried basis.

Description Piracetam occurs as a white powder.
It is freely soluble in water and soluble in ethanol(95).
It shows polymorphism.

Identification Determine the infrared spectra of Piracetam and piracetam RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the spectra, dissolve Piracetam and piracetam RS in ethanol(95), respectively, evaporate to dryness in water baths, and perform the test again with the residues.

Purity (1) ***Clarity and color of solution***—Dissolve 2.0 g of Piracetam in water to make 10 mL; the resulting solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 2.0 g of Piracetam according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 50.0 mg of Piracetam in a mixture of acetonitrile and water (10 : 90) to make exactly 100 mL, and use this solution as the test solution. Separately, dissolve 5 mg of Piracetam and 10 mg of piracetam related substance I (2-pyrrolidone) in a mixture of water and acetonitrile (90 : 10) to make exactly 100 mL, and use this solution as the standard solution (1). To 1.0 mL of the test solution, add a mixture of water and acetonitrile (90 : 10) to make exactly 100 mL. To 5.0 ml of this solution, add a mixture of water and acetonitrile (90 : 10) to make exactly 50 mL, and use this solution as the standard solution (2). Perform the test with 20 μL each of the test solution and the standard solution (2) as directed under the Liquid Chromatography according to the following conditions. The peak areas other than the major peak obtained from the test solution are not larger than the major peak obtained from the standard solution (2), and the sum of the peak areas other than the major peak obtained from the test solution is not larger than 3 times the area of the major peak obtained from the standard solution (2). However, exclude any peak having an area smaller than 0.5 times the area of the major peak from the standard solution (2).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of phosphate buffer solution and acetonitrile (90 : 10).

Flow rate: 1.0 mL/min

System suitability

Proceed with the standard solution (1) under the above conditions; the resolution between piracetam and piracetam related substance I is NLT 3.0, and the symmetry factor of piracetam peak is NMT 2.0.

Time span of measurement: About 8 times the retention time of piracetam.

Phosphate buffer solution (pH 6.0)—Dissolve 1.0 g of potassium dihydrogen phosphate in water to make 1000 mL and adjust its pH to 6.0 with phosphoric acid.

Loss on drying NMT 1.0% (1.0 g, 105 ℃, constant mass).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.75 g of Piracetam, dissolve it in 50 mL of water, add 20.0 mL of 1 mol/L sodium hydroxide, and heat to boiling for 15 minutes. After cooling, put 25.0 mL of 1 mol/L hydrochloric acid, and heat to boiling for 2 hours. After cool, titrate with 1 mol/L sodium hydroxide VS (indicator: 2 drops of phenolphthalein TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mL of 1 mol/L sodium hydroxide VS
= 142.15 mg of $C_6H_{10}N_2O_2$

Packaging and storage Preserve in light-resistant, well-closed containers.

Piracetam Capsules
피라세탐 캡슐

Piracetam Capsules contain NMT 95.0% and NLT 105.0% of the labeled amount of piracetam ($C_6H_{10}N_2O_2$: 142.16).

Method of preparation Prepare as directed under Capsules, with Piracetam.

Identification (1) Weigh 0.5 g of the content of Piracetam Capsules, dissolve in 15 mL of water, add 3 mL of 50% sodium hydroxide solution and heat the solution; the gas evolved (ammonia gas) turns a red litmus paper to blue.

(2) The retention times of the major peaks of the test solution and the standard solution obtained under the Assay are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the contents of NLT 20 capsules of Piracetam Capsules. Weigh accurately an amount equivalent to about 50 mg of piracetam ($C_6H_{10}N_2O_2$), dissolve in water to make exactly 50 mL, and filter. Take 2.0 mL of the filtrate, add water to make exactly 50 mL, and use this solution as the test solution. Separately, proceed in the same manner as in the preparation of the test solution with about 50 mg of piracetam RS, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of piracetam in each solution.

Amount (mg) of piracetam ($C_6H_{10}N_2O_2$)
$= \text{Amount (mg) of piracetam RS} \times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A solution obtained by adjusting the pH of 10% methanol to 6.5 with 0.001 mol/L ammonium monohydrogen phosphate solution.

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Piracetam Injection
피라세탐 주사액

Piracetam Injection contains NLT 95.0% and NMT 105.0% of the labeled amount of piracetam ($C_6H_{10}N_2O_2$: 142.16).

Method of preparation Prepare as directed under Injections, with Piracetam.

Identification (1) Weigh an amount of Piracetam Injection equivalent to 0.5 g of piracetam according to the labeled amount, dissolve in 15 mL of water, add 3 mL of 50% sodium hydroxide and heat; the gas produced (ammonia gas) turns red litmus paper to blue.

(2) The retention times of the major peaks from the test solution and the standard solution obtained under the Assay are the same.

pH Between 5.0 and 7.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.3 EU per mg of piracetam.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Piracetam Injection equivalent to 50 mg of piracetam ($C_6H_{10}N_2O_2$) according to the labeled amount, add water to make 50 mL, and filter. Take 2.0 mL of the filtrate, add water to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of piracetam RS, and proceed in the same manner as for the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of piracetam in each solution.

$$\text{Amount (mg) of piracetam } (C_6H_{10}N_2O_2) = \text{Amount (mg) of piracetam RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Mobile phase: A solution of 10% methanol, adjusted the pH to 6.5 with 0.001 mol/L ammonium monohydrogen phosphate.

Flow rate: 1.0 mL/min

Packaging and storage Preserve in light-resistant, hermetic containers.

Piracetam Tablets
피라세탐 정

Piracetam Tablets contain NMT 95.0% and NLT 105.0% of the labeled amount of piracetam ($C_6H_{10}N_2O_2$: 142.16).

Method of preparation Prepare as directed under Tablets, with Piracetam.

Identification (1) Weigh accurately the amount of Piracetam Tablets, equivalent to about 0.5 g of piracetam according to the labeled amount, dissolve in 15 mL of water, add 3 mL of 50% sodium hydroxide, and heat; the generated gas (ammonia gas) changes the red litmus paper to blue.

(2) The major peaks of the test solution and the standard solution obtained under the Assay are the same in the retention time.

Dissolution Take 1 tablet of Piracetam Tablets, and perform the test according to Method 2 under the Dissolution at 50 revolutions per minute, using 900 mL of water as the dissolution medium. Take the dissolved solution after 30 minutes from the start of the test and filter. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add water to make exactly *V'* mL of a solution containing about 50 μg of piracetam per mL according to the labeled amount. Separately, weigh accurately about 20 mg of piracetam RS, and dissolve in water to make 100 mL. Pipet 25 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and measure the peak areas, A_T and A_S, of piracetam ($C_6H_{10}N_2O_2$) in each solution. Meets the requirements if the dissolution rate of Piracetam Tablets in 30 minutes is NLT 80%.

$$\text{The dissolution rate (\%) of the labeled amount of piracetam } (C_6H_{10}N_2O_2) = W_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 225$$

W_S: Amount of piracetam RS (mg)

C: Labeled amount (mg) of piracetam ($C_6H_{10}N_2O_2$) in 1 tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A solution of 10% methanol, adjusted the pH to 6.5 with 0.001 mol/L ammonium monohydrogen phosphate.

Flow rate: 0.8 mL/min

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tables of Piracetam Tablets, and powder them. Weigh accurately the amount of the powder, equivalent to about 50 mg of piracetam ($C_6H_{10}N_2O_2$), dissolve in water to make exactly 50 mL, and filter. Take 2.0 mL of the filtrate, add water to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of

piracetam RS, proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of piracetam in each solution.

$$\text{Amount (mg) of piracetam } (C_6H_{10}N_2O_2) = Amount\ (mg)\ of\ piracetam\ RS \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

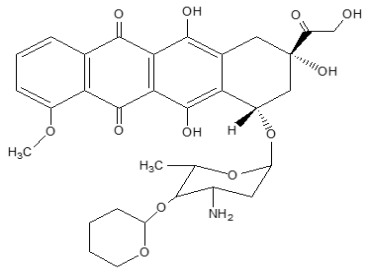
Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A solution of 10% methanol, adjusted the pH to 6.5 with 0.001 mol/L ammonium monohydrogen phosphate.

Flow rate: 1.0 mL/min

Packaging and storage Preserve in light-resistant, tight containers.

Pirarubicin
피라루비신



$C_{32}H_{37}NO_{12}$: 627.64

(8*S*,10*S*)-10-{[(2*R*,4*S*,5*S*,6*S*)-4-Amino-6-methyl-5-{[(*S*)-tetrahydro-2*H*-pyran-2-yl]oxy}tetrahydro-2*H*-pyran-2-yl]oxy}-6,8,11-trihydroxy-8-(2-hydroxy-acetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione [*72496-41-4*]

Pirarubicin is a derivative of daunorubicin. Pirarubicin contains NLT 950 μg (potency) of pirarubicin ($C_{32}H_{37}NO_{12}$) per mg, calculated on the anhydrous basis.

Description Pirarubicin is a reddish brown crystalline powder. It is soluble in chloroform, very slightly soluble in acetonitrile, methanol or ethanol(99.5), and practically insoluble in water.

Identification (1) Dissolve 10 mg of Pirarubicin in 80 mL of methanol and 6 mL of diluted hydrochloric acid (1 in 5000), and add water to make exactly 100 mL. Pipet 10 mL of the resulting solution, add diluted methanol (4 in 5) to make 100 mL, and determine the absorption spectra of this solution and pirarubicin RS as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Dissolve 5 mg each of Pirarubicin and pirarubicin RS in 5 mL of chloroform and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform and methanol (5 : 1) as the developing solution to a distance of 10 cm, and air-dry the plate; the principal spot obtained from the test solution and the spot obtained from the standard solution are reddish brown and their R_f values are the same.

Optical rotation $[\alpha]_D^{20}$: Between +195° and +215° (10 mg, chloroform, 10 mL, 100 mm).

Absorbance $E_{1cm}^{1\%}$ (495 nm): Between 195 and 220. Weigh accurately about 10 mg (potency) of Pirarubicin, dissolve in 80 mL of methanol and 6 mL of diluted hydrochloric acid (1 in 5000), and add water to make exactly 100 mL. Pipet 10 mL of this solution, add an aqueous solution of methanol (4 in 5) to make exactly 50 mL, and determine the absorbance as directed under the Ultraviolet-visible Spectroscopy at 495 nm.

Purity (1) ***Clarity and color of solution***—Dissolve 10 mg of Pirarubicin in 10 mL of 0.01 mol/L hydrochloric acid TS; the resulting solution is clear and red.

(2) ***Heavy metals***—Proceed with 1.0 g of Pirarubicin according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve 10 mg of Pirarubicin in 20 mL of the mobile phase, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine each peak area of the solutions by the automatic integration method; the areas of the doxorubicin peak with the relative retention times of about 0.45 and the peak with the relative retention time of about 1.2, compared to the peak of pirarubicin, are not larger than the peak area of pirarubicin from the standard solution and the sum of peak areas with the relative retention times of about 0.1.9 and about 2.0, respectively, compared to the peak area of pirarubicin is not larger than 5 times the peak area of pirarubicin from the standard solution. However, determine the peak area of doxorubicin by multiplying the correction factor of 0.94, and the peak areas with the relative retention time of about 1.9 and about 2.0 by multiplying the correction factor of 1.09.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed the test according to the operating conditions under the Assay.

System suitability

System performance and system repeatability: Proceed the test as directed under the system suitability under the Assay.

Test for required detectability: Pipet 2 mL of the standard solution and add the mobile phase to make exactly 10 mL. Confirm that the peak area of pirarubicin obtained from 20 μL of the resulting solution is equivalent to 14% to 26% of the peak area of pirarubicin from the standard solution.

Time span of measurement: About 4 times the retention time of pirarubicin.

Water NMT 2.0% (0.1 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in the manufacturing of a sterile preparation.

Bacterial endotoxins It is less than 2.50 EU per mg (potency) of pirarubicin when used in the manufacturing of sterile preparations.

Histamine It meets the requirements when used in a sterile preparation. Weigh an appreciated amount of Pirarubicin, and dissolve it in diluted hydrochloric acid (1 in 3800) to make a solution containing 2.0 mg (potency) per mL. Pipet an appreciated amount of the resulting solution, and dilute it 100 times with water, and use the solution as the test solution. Use 0.5 mL of the solution for the test.

Assay Weigh accurately about 10 mg (potency) each of Pirarubicin and pirarubicin RS and dissolve each in the mobile phase to make exactly 10 mL, respectively. Pipet 5.0 mL each of these solutions, add exactly 5 mL each of the internal standard solutions and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of the peak area of pirarubicin to that of the internal standard solution from each solution.

$$\text{Potency (μg) of pirarubicin } (C_{32}H_{37}NO_{12}) = \text{Potency (μg) of pirarubicin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of 2-naphthol in acetone (1 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of 0.05 mol/L ammonium formate buffer solution (pH 4.0) and acetonitrile (3: 2).

Flow rate: Adjust the flow rate so that the retention time of pirarubicin is about 7 minutes.

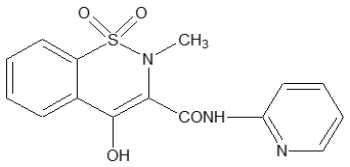
System suitability

System performance: Proceed with 20 μL of the standard solution under the above conditions; pirarubicin and the internal standard are eluted in this order with the resolution between these peaks being NLT 9.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of pirarubicin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in hermetic containers.

Piroxicam
피록시캄



$C_{15}H_{13}N_3O_4S$: 331.35

(3*E*)-3[Hydroxy-(pyridin-2-ylamino)methylidene]-2-methyl-1,1-dioxo-3,4-dihydro-1*H*-[1,2]benzo-thiazin-4-one [*36322-90-4*]

Piroxicam contains NLT 97.0% and NMT 103.0% of piroxicam ($C_{15}H_{13}N_3O_4S$), calculated on the anhydrous basis.

Description Piroxicam is a grayish white to pale brown or pale yellow powder and it is odorless.
It is sparingly soluble in acetic anhydride, slightly soluble in acetonitrile, methanol or ethanol(99.5), very slightly soluble in acetic acid(100), and practically insoluble in water.

Identification Determine the infrared spectra of Piroxicam and piroxicam RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. When the any difference appears between two spectra, dissolve each with methylene chloride, evaporate to dryness, and perform the test with the residue in the same manner.

Purity ***Heavy metals***—Weigh 1.0 g of Piroxicam according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Water NMT 0.5% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.3% (1 g).

Assay Weigh accurately about 50 mg of Piroxicam, dissolve with 0.01 mol/L methanolic hydrochloric acid TS to make exactly 100 mL. Place 10.0 mL of this solution in a 100-mL volumetric flask, add 50 mL of 0.01 mol/L methanolic hydrochloric acid TS and 20.0 mL of water, fill 0.01 mol/L methanolic hydrochloric acid TS to the gauge line line, mix, and use this solution as the test solution. Separately, weigh accurately about 50 mg of piroxicam RS, and dissolve with 0.01 mol/L methanolic hydrochloric TS to make exactly100 mL. Place 10.0 mL of this solution in a 100-mL volumetric flask, add 50 mL of 0.01 mol/L methanolic hydrochloric acid TS and 20.0 mL of water, fill 0.01 mol/L methanolic hydrochloric acid TS to the gauge line, mix, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of piroxicam, A_T and A_S, from each solution.

$$\text{Amount (mg) of piroxicam } (C_{15}H_{13}N_3O_4S) = \text{Amount (mg) of piroxicam RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column, about 3.9 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm - 10 μm in particle diameter).

Mobile phase: A mixture of buffer solution and methanol (55 : 45).

System suitability

System performance: Proceed with 25 μL of the standard solution according to the above conditions; the symmetry factor is NMT 1.5.

System repeatability: Repeat the test 6 times with 25 μL of the standard solution according to the above conditions; the relative standard deviation of the peak is NMT 2.0%.

Buffer solution—Dissolve 7.72 g of anhydrous citric acid in 400 mL of water and separately dissolve 5.35 g of sodium monohydrogen phosphate in 100 mL of water. Combine the phosphate solution and the citric acid solution, and add water to make 1000 mL.

Packaging and storage Preserve in light-resistant, tight containers.

Piroxicam Capsules
피록시캄 캡슐

Piroxicam Capsules contain NLT 92.5% and NMT 107.5% of the labeled amount of piroxicam ($C_{15}H_{13}N_3O_4S$: 331.35).

Method of preparation Prepare as directed under Capsules, with Piroxicam.

Identification The retention time of the major peaks obtained from the test solution and the standard solution from the Assay and the ultraviolet absorption spectra between 200 and 400 nm are the same.

Water NMT 8.0%. (0.3 g. volumetric titration, direct titration).

Dissolution Perform the test with 1 capsule of Piroxicam Capsules at 50 revolutions per minute according to Method 1, using 900 mL of the 1st fluid for the Disintegration as the dissolution medium. Take the dissolved solution 45 minutes after starting the test, filter, and if necessary, dilute suitably with the dissolution medium, and use this solution as the test solution. Separately, weigh accurately a suitable amount of piroxicam RS, dissolve in methanol to obtain a solution having known concentration of about 0.5 mg of piroxicam per mL, and use this solution as the standard stock solution. Take a suitable amount of the standard stock solution, dilute exactly with the dissolution medium to obtain a solution of a certain concentration, and use this solution as the standard solution. Determine the absorbances of the test solution and the standard solution at the absorbance maximum wavelength around 333 nm.

It meets the requirements if the dissolution rate of Piroxicam Capsules in 45 minutes is NLT 75%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the contents of NLT 20 capsules of Piroxicam Capsules, completely transfer to a suitable container where possible, and determine the average weight of 1 capsule. Mix the contents well, weigh accurately the amount equivalent to about 50 mg of piroxicam ($C_{15}H_{13}N_3O_4S$) according to the labeled amount, and place into a 100-mL volumetric flask. Add 70 mL of 0.01 mol/L methanolic hydrochloric acid TS and shake to mix for 30 minutes using a mechanical shaker. Add 0.01 mol/L methanolic hydrochloric acid TS to dilute to 100 mL and mix the solution. Centrifuge this solution to obtain the clear supernatant. Transfer 10.0 mL of this solution to 100-mL volumetric flask, add about 50 mL of 0.01 mol/L methanolic hydrochloric acid and 20.0 mL of water, fill the flask up to the gauge line with 0.01 mol/L methanolic hydrochloric acid, and mix. Use this solution as the test solution. Perform the test as directed under the Assay of Piroxicam. However, use the following detector among the operating conditions.

Detector—An ultraviolet absorption photometer (wavelength: 254 nm) with a photo-diode array detector (200 nm to 400 nm).

$$\text{Amount (mg) of piroxicam } (C_{15}H_{13}N_3O_4S) = \text{Amount (mg) of piroxicam RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in light-resistant, tight containers.

Piroxicam Injection
피록시캄 주사액

Piroxicam Injection contains NLT 90.0% and NMT 110.0% of the labeled amount of piroxicam ($C_{15}H_{13}N_3O_4S$: 331.35).

Method of preparation Prepare as directed under Injections, with Piroxicam.

Identification The retention times of the major peaks from the test solution and standard solution obtained under the Assay are the same.

pH Between 7.7 and 8.3.

Sterility Meets the requirements.

Bacterial endotoxins Less than 15 EU per mg of piroxicam.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Piroxicam Injection equivalent to 40 mg of piroxicam ($C_{15}H_{13}N_3O_4S$) according to the labeled amount, and add 0.01 mol/L methanolic hydrochloric acid TS to make exactly 50 mL. Take 5 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 40 mg of piroxicam RS, add 0.01 mol/L methanolic hydrochloric acid TS to make exactly 50 mL, then proceed in the same manner as for the test solution, and use this solution as the standard solution. Pipet 20 μL each of the test solution and the standard solution, and perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S of piroxicam of each solution.

$$\text{Amount (mg) of piroxicam } (C_{15}H_{13}N_3O_4S) = \text{Amount (mg) of piroxicam RS} \times (A_T / A_S)$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Mobile phase: A mixture of buffer solution, methanol and acetonitrile (41 : 41 : 18).

Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area for piroxicam is NMT 2.0%.

Buffer solution—Dissolve 7.72 g of anhydrous citric acid in 400 mL of water, and separately dissolve 5.36 g of dibasic sodium phosphate dihydrate in 100 mL of water. Combine the dibasic sodium phosphate dihydrate solution and citric acid solution, add water to make 1000 mL and mix.

Packaging and storage Preserve in light-resistant, hermetic containers.

Piroxicam Tablets
피록시캄 정

Piroxicam Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of piroxicam ($C_{15}H_{13}N_3O_4S$: 331.35).

Method of preparation Prepare as directed under Tablets, with Piroxicam.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Water NMT 6.0% (0.2 g, volumetric titration, direct titration)

Dissolution Perform the test with 1 tablet of Piroxicam Tablets at 90 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of the Solution 1 for dissolution test as the dissolution medium. Take the medium 15 minutes after starting the test, filter the solution, dilute with fresh medium, if necessary, and use the filtrate as the test solution. Separately, weigh accurately an appropriate amount of piroxicam RS, dissolve in methanol to make a solution containing 0.5 mg per mL, and use this solution as the standard stock solution. Dilute this standard stock solution with the dissolution medium to obtain the same concentration as the test solution, and use as the standard solution. Determine the absorbances

of the test solution and the standard solution at the wavelength of 333 nm as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as a control solution. Meets the requirements if the dissolution rate of Piroxicam Tablets in 15 minutes is NLT 70%.

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following procedure.
Perform the test with 1 tablet of Piroxicam Tablets as directed under the Assay.

Assay Weigh accurately the mass of NLT 20 tables of Piroxicam Tablets, and powder them. Weigh accurately the amount of the powder, equivalent to about 50 mg of piroxicam ($C_{15}H_{13}N_4O_4S$), add 70 mL of 0.01 mol/L methanolic hydrochloride TS, shake and mix with a mechanical shaker for 30 minutes, and add 0.01 mol/L methanolic hydrochloride TS to make 100 mL. Centrifuge the resulting solution, pipet 10.0 mL, add about 50 mL of 0.01 mol/L methanolic hydrochloride TS and 20 mL of water, add again 0.01 mol/L methanolic hydrochloride TS to make 100 mL, and use this solution as the test solution. Separately, proceed with about 50 mg of piroxicam RS in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of piroxicam, A_T and A_S, in each solution.

$$\text{Amount (mg) of piroxicam } (C_{15}H_{13}N_3O_4S) = \textit{Amount (mg) of piroxicam RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of buffer solution and methanol (55 : 45).

System suitability

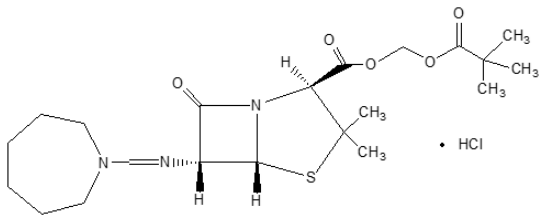
System performance: Proceed with 25 μL of the standard solution under the above operating conditions; the symmetry factor is NMT 1.5.

System repeatability: Repeat the test 6 times with 25 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peaks is NMT 2.0%.

Buffer solution—Dissolve 7.72 g of citric acid in 400 mL of water, and dissolve, separately, 5.35 g of sodium monohydrogen phosphate in 100 mL of water. Combine the phosphate solution and the citric acid solution, and add water to make 1000 mL.

Packaging and storage Preserve in light-resistant, tight containers.

Pivmecillinam Hydrochloride
피브메실리남염산염



$C_{21}H_{33}N_3O_5S \cdot HCl$: 476.03

2,2-Dimethylpropanoyloxymethyl (2*S*,5*R*,6*R*)-6[(azepan-1-ylmethylidene)amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate hydrochloride [*32887-03-9*]

Pivmecillinam Hydrochloride contains NLT 630 μg and NMT 710 μg (potency) of mecillinam ($C_{15}H_{23}N_3O_3S$: 325.43) per mg, calculated on the anhydrous basis.

Description Pivmecillinam Hydrochloride occurs as a white to yellowish white crystalline powder.
It is very soluble in methanol or acetic acid(100), freely soluble in water or ethanol(99.5) and soluble in acetonitrile.

Identification (1) Determine the infrared spectra of Pivmecillinam Hydrochloride and pivmecillinam hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve 0.5 g of Pivmecillinam Hydrochloride in 10 mL of water, and add 1 mL of dilute nitric acid and 1 drop of silver nitrate TS; a white precipitate forms.

Optical rotation $[\alpha]_D^{20}$: Between +200° and +220° (1 g, calculated on the anhydrous basis, water, 100 mL, 100 mm).

pH Dissolve 0.5 g of Pivmecillinam Hydrochloride in 10 mL of water; the pH of this solution is between 3.0 and 4.5.

Purity (1) ***Heavy metals***—Weigh 1.0 g of Pivmecillinam Hydrochloride, add 10 mL of a solution of magnesium nitrate hexahydrate and ethanol(95) (1 in 10), ignite the ethanol to burn, and carbonize by gradual heating. If a carbonized substance remains, moisten it with a small amount of nitric acid, and incinerate by ignition. After cooling, add 3 mL of hydrochloric acid to the residue, warm on a steam bath to dissolve, and then heat to evaporate to dryness. Add 10 mL of water to the residue, warm on a steam bath to dissolve, cool, and adjust the pH to 3

to 4 with ammonia TS added dropwise. Then add 2 mL of dilute acetic acid, filtrate, if necessary, wash with 10 mL of water, transfer the filtrate and the solution used for washing into a colorimetric tube, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 2.0 mL of lead standard solution in the same manner as in the preparation of the test solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Pivmecillinam Hydrochloride according to Method 4, and perform the test (NMT 2 ppm).

(3) ***Related substances***—Weigh accurately 50 mg of Pivmecillinam Hydrochloride, dissolve in 4.0 mL of a mixture of acetonitrile and acetic acid(100) (97 : 3), and use this solution as the test solution. Separately, weigh accurately 2.0 mg of pivmecillinam hydrochloride RS, dissolve in 4.0 mL of water, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the standard solutions on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, allow to stand for 30 minutes, spot 2 μL of the test solution, and develop the plate with a mixture of acetone, water and acetic acid(100) (10 : 1 : 1) as the developing solvent to a distance of about 12 cm. After air-drying the plate, allow it to stand for 10 minutes in iodine steam; the spots obtained from the test solution are not larger or not more intense than the spots from the standard solution. No spots other than the location of the spot from the standard solution are observed in the test solution.

(4) ***Dimethylaniline***—Weigh accurately about 1.0 g of Pivmecillinam Hydrochloride, add 5 mL of 1 mol/L sodium hydroxide TS and 1 mL of the internal standard solution, centrifuge, if necessary, and use the clear supernatant as the test solution. Separately, weigh accurately about 50 mg of dimethylaniline, add 2.0 mL of hydrochloric acid, and add water to make 50 mL. Pipet 5.0 mL of this solution, and add water to make exactly 250 mL. Pipet 1.0 mL of this solution, add 5.0 mL of 1 mol/L sodium hydroxide TS and 1.0 mL of the internal standard solution, centrifuge, if necessary, and use the clear supernatant as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the peak area ratio, Q_T and Q_S, of dimethylaniline to the internal standard from the test solution and the standard solution, respectively (NMT 20 ppm).

$$\text{Content (ppm) of dimethylaniline} = \text{Amount (mg) of dimethylaniline taken} \times \frac{Q_T}{Q_S} \times \frac{Purity\ (\%)\ of\ dimethylaniline}{Amount\ (mg)\ of\ \text{Pivmecillinam Hydrochloride taken}} \times 4$$

Internal standard solution—Dissolve 50.0 mg of naphthalene in cyclohexane to make 50 mL. Take 5.0 mL of this solution, add cyclohexane to make 100 mL, and use this solution as the internal standard solution.

Operating conditions

Detector: A flame ionization detector

Column: A column about 2 mm in internal diameter and about 2 m in length, packed with diatomaceous earth for gas chromatography coated with 50% phenyl-50% methyl polysiloxane for gas chromatography equivalent to 3% of the mass.

Column temperature: 120 °C

Temperatures of the sample injection port and the detector: 150 °C

Carrier gas: Nitrogen

Flow rate: 30 mL/min

Water NMT 1.0% (0.25 g, coulometric titration).

Assay Weigh accurately an amount equivalent to about 20 mg (potency) of Pivmecillinam Hydrochloride and pivmecillinam hydrochloride RS, dissolve in an appropriate amount of the mobile phase, add exactly 10 mL of the internal standard solution to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of pivmecillinam to that of internal standard from each solution.

$$\text{Potency (μg) of mecillinam } (C_{15}H_{23}N_3O_3S) = \text{Potency (μg) of pivmecillinam hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of diphenyl in the mobile phase (1 in 12500).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 0.771 g of ammonium acetate in about 900 mL of water, add acetic acid(100) to adjust the pH to 3.5, and again add water to make 1000 mL. To 400 mL of this solution, add 600 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of pivmecillinam is about 6.5 minutes.

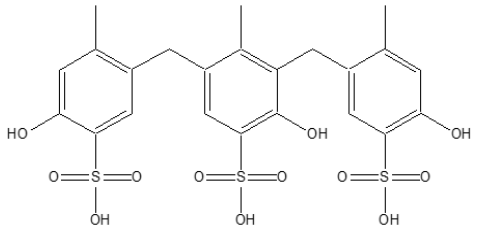
System suitability

System performance: Proceed with 10 μL of the standard solution under the above conditions; pivmecillinam and the internal standard are eluted in this order with the resolution being NLT 4.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak area ratios of pivmecillinam to the peak area of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Policresulen
폴리크레줄렌



$C_{23}H_{24}O_{12}S_3$: 588.61

2-Hydroxy-3,5-bis[(4-hydroxy-2-methyl-5-sulfophenyl)methyl]-4-methylbenzenesulfonic acid, [*101418-00-2*]

Policresulen contains NLT 90.0% and NMT 110.0% of the labeled amount of the condensation product of metacresolsulfonic acid and formaldehyde.

Description Policresulen occurs as a clear reddish-brown solution and has almost no odor.
It is miscible with water, ethanol(95) and acetone.
The color of Policresulen becomes brighter with the addition of alkali hydroxide.

Identification (1) Add 1 drop of Policresulen to 10 mL of water, shake and add a drop of 2.5% iron(III) chloride TS; the resulting solution exhibits a violet color.

(2) Add 10 mL of 10% acetic acid and 1 mL of 10% barium chloride to 1 mL of Policresulen; a white precipitate is formed.

(3) Dissolve 1 mL of Policresulen in 10 mL of water, 1 g of gelatin, and 1 g of sodium chloride, add water to make 100 mL, and add a few drops of 1% aqueous gelatin solution adjusted to pH 4.7; solidified precipitates of gelatin are formed.

(4) To 1 mL of Policresulen, add 5 mL of water and an appropriate amount of *N*-dimethyl-*p*-phenylenediamine hydrochloride and mix, add sodium hydroxide TS until it becomes alkaline, and then add 1 to 2 drops of 5% potassium ferricyanide TS; the solution immediately exhibits a blue color.

(5) Take about 0.4 mL of Policresulen, and add water to make 1000 mL. Take 10 mL of this solution and add water to make 100 mL. Use this solution as the test solution. Determine the absorbance as directed under the Ultraviolet-visible Spectroscopy using water as the control; it exhibits the maximum absorption at about 283 nm.

Specific gravity d_{20}^{20}: Between 1.206 and 1.226.

Purity (1) Add 10 mL of 20% hydrochloric acid and 10% barium chloride solution to 1.0 mL of Policresulen; no turbidity is produced within 5 minutes.

(2) Add 20 mL of 10% hydrochloric acid and 1 mL of 10% sulfuric acid to 1.0 mL of Policresulen; no turbidity is produced within 5 minutes.

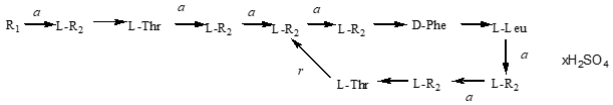
(3) Weigh accurately about 0.4 g of Policresulen and add water to make exactly 100 mL. Again, pipet 10 mL of this solution, and add water to make 100 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy using water as the control; it exhibits the maximum absorption at a wavelength of about 281 nm, and the specific absorbance is between 70.0 and 82.0.

Assay Pipet about 1 mL of Policresulen, add water to make 50 mL, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: methyl orange TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 20.0 mg of condensation product of metacresolsulfonic acid and formaldehyde

Packaging and storage Preserve in tight containers.

Polymyxin B Sulfate
폴리믹신B황산염



Polymyxin B_1 R_1 = 6-methyloctanoic acid
R_2 = L-α-γ-diaminobutyric acid
Polymyxin B_2 R_1 = 6-methylheptanoic acid
R_2 = L-α-γ-diaminobutyric acid

Thr: Threonine Phe: Phenylalanine
Leu: Leucine

Polymyxin B Sulfate
N-{(2*S*)-4-Amino-1-{{(2*S*,3*R*)-1-{{(2*S*)-4-amino-1-oxo-1-{{(3*S*,6*S*,9*S*,12*S*,15*R*,18*R*,21*S*)-6,9,18-*tris*(2-aminoethyl)-15-benzyl-3-[(1*R*)-1-hydroxyethyl]-12-(2-methylpropyl)-2,5,8,11,14,17,20-heptaoxo-1,4,7,10,13,16,19-heptazacyclotricos-21-yl}amino}butan-2-yl}amino}-3-hydroxy-1-oxobutan-2-yl}amino}-1-oxobutan-2-yl}-6-methyloctanamide sulfate [*1405-20-5*]

Polymyxin B Sulfate is the sulfate of a mixture of peptide-based compounds having antibacterial activity and obtained from *Bacillus polymyxa* culture.

Polymyxin B Sulfate contains NLT 6500 units (potency) of polymyxin B ($C_{55\sim56}H_{96\sim98}N_{16}O_{13}$) per mg, calculated on the dried basis. 1 unit corresponds to 0.129 μg of polymyxin B sulfate ($C_{55\sim56}H_{96\sim98}N_{16}O_{13}\cdot1\sim2H_2SO_4$).

Description Polymyxin B Sulfate occurs as a white to yellowish brown powder.

It is freely soluble in water and practically insoluble in ethanol(99.5).

Identification (1) To 5 mL of an aqueous solution of Polymyxin B Sulfate (1 in 10), add 5 mL of sodium hydroxide solution (1 in 10), and add 5 drops of copper(II) sulfate pentahydrate (1 in 100) while shaking to mix; the resulting solution exhibits a violet color.

(2) Transfer 5 mg each of Polymyxin B Sulfate and polymyxin B sulfate RS to stoppered test tubes, dissolve each in 1 mL of diluted hydrochloric acid (1 in 2), close the stoppers, and heat in 135 ℃ for 5 hours. Evaporate on a steam bath to dryness, and heat continuously until there is no hydrochloric acid odor. Dissolve the residues in 0.5 mL of water, and use these solutions as the test solution and the standard solution (1). Separately, dissolve 20 mg each of L-leucine, L-threonine, phenylalanine and L-serine in 10 mL of water, and use these solutions as the standard solution (2), the standard solution (3), the standard solution (4) and the standard solution (5). Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 3 μL each of the test solution and the standard solutions (1), (2), (3), (4) and (5) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. After passing the vapor of the saturated developing solvent through the plate for 15 hours, develop the plate with a mixture of phenol and water (3 : 1) as the developing solvent while protected from light to a distance of about 13 cm. Dry the plate at 110 ℃ for 5 minutes, spray evenly ninhydrin-acetic acid TS on the plate, and heat at 110 ℃ for 5 minutes; the R_f values of each spot obtained from the test solution are the same as the R_f values of each spot from the standard solution (1). Also, the spots obtained from the test solution are visible at positions corresponding to the spots obtained from the standard solutions (2), (3) and (4), and not visible at the position corresponding to the spot obtained from the standard solution (5).

(3) An aqueous solution of Polymyxin B Sulfate (1 in 20) responds to the Qualitative Analysis for sulfate.

Optical rotation $[\alpha]_D^{20}$: Between -78° and -90° (0.5 g calculated on the dried basis, water, 25 mL, 100 mm).

pH Dissolve 1.0 g of Polymyxin B Sulfate in 50 mL of water; the pH of this solution is between 5.0 and 7.0.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Polymyxin B Sulfate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Phenylalanine***—Weigh accurately 0.375 g of Polymyxin B Sulfate, and dissolve in 0.1 mol/L hydrochloric acid TS to make exactly 100 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbances, A_1, A_2, A_3, A_4, and A_5, at wavelengths of 252 nm, 258 nm, 264 nm, 280 nm and 300 nm. Calculate the amount of phenylalanine according to the following equation; it is between 9.0% and 12.0%.

$$\text{Content (\%) of phenylalanine} = \frac{A_2 - 0.5A_1 + 0.5A_3 - 1.8A_4\_0.8A_5}{W_T} \times 9.4787$$

W_T: Amount (g) of Polymyxin B Sulfate taken, calculated on the dried basis

Loss on drying NMT 6.0% (1 g, in vacuum, 60 ℃, 3 hours).

Residue on ignition NMT 0.75% (1 g).

Sterility It meets the requirements when used in the manufacturing of a sterile preparation. However, it is excluded in cases where there is a final sterilization process in the manufacturing of a sterile preparation.

Pyrogen It meets the requirements when used in the manufacturing of a sterile preparation. However, weigh an appropriate amount of Polymyxin B Sulfate, dissolve in isotonic sodium chloride injection to make a solution containing 20000 units (potency) per mL, and use this solution as the test solution. However, inject the test solution into a rabbit by 1.0 mL per kg of the rabbit weight.

Assay ***Cylinder plate method***—(1) Medium Agar medium for seed and base layer

Peptone	10.0 g
Meat extract	3.0 g
Sodium chloride	30.0 g
Agar	20.0 g

Dissolve in 1000 mL of water, and sterile. However, the pH after the sterilization is between 6.5 and 6.6.

(2) Test organism Use *Escherichia coli* NIHJ or NCCP 14134 as the test organism.

(3) Weigh accurately an amount of Polymyxin B Sulfate, equivalent to about 200000 units (potency), and dissolve in phosphate buffer solution, pH 6.0, to make exactly 20 mL. Take exactly an appropriate amount of this solution, dilute with phosphate buffer solution, pH 6.0, to make solutions containing 4000 units (potency) and 1000 units (potency) per mL, and use these solutions as the high-concentration test solution and low-concentration test solution, respectively. Separately, weigh accurately 200000 units (potency) of polymyxin B sulfate RS, dissolve in phosphate buffer solution, pH 6.0, to make exactly 20 mL, and use this solution as the standard stock solution. Store the standard stock solution at NMT 5 °C and use it within 14 days. Pipet an appropriate amount of the standard stock solution, dilute with phosphate buffer solution, pH 6.0, to make solutions containing 4000 units (potency) and 1000 units (potency) per mL, and use these solutions as the high-concentration standard solution and the low-concentration standard solution, respectively. Perform the test with these solutions as directed under the Microbial Assays for Antibiotics (A) (8).

Packaging and storage Preserve in light-resistant, tight

containers.

Polypase 1000
폴리파제1000

Polypase 1000 contains NLT 187 FIP lipase units per gram when tested as directed under the Digestive Power.

Description Polypase 1000 occurs as a grayish brown powder.

Identification Polypase 1000 shows positive when tested as directed under the Lipase potency test.

pH Between 5.0 and 7.0 (5% aqueous solution).

Loss on drying NMT 8.0% (2 g, 105 ℃, 1 hours).

Residue on ignition NMT 20% (1.0 g)

Particle size distribution estimation by analytical sieving Weigh 20 g of Polypase 1000 and pass it through a No. 4.7 sieve; no particles remain on the sieve.

Digestive power Weigh accurately about 70 to 90 mg of Polypase 1000, put it in a mortar, add 8 to 10 mL of water at 5℃, and grind well for 10 minutes. Then, put it in a 200-mL volumetric flask, and add cold water to make 200 mL. Each mL of this solution contains about 12 FIP fat digestion activity units. Mix well for several minutes and store at 4°C. Make this test solution before use in each test. When used in the test, the test solution is at 20 ℃. Put 10 mL of olive oil emulsion in a glass container of about 50 mL, buffer it with 8 mL of tris buffer solution and 2 mL of 8 w/v% sodium taurocholate solution, and then dilute with water to make the total amount (30 - X) mL. Allow the temperature to reach 37 ± 0.1 ℃. Adjust the pH to 9.05 using 0.05 to 0.1 mol/L sodium hydroxide solution: manually adjust using a micro buret to pH 9.0, and then automatically adjust it to pH 9.05. To the solution with the accurately adjusted pH of 9.05, add exactly X mL of test solution (containing 8 to 16 FIP lipase units), and titrate with 0.1 mol/L sodium hydroxide, maintaining the pH at 9.0 using an automatic micro buret. Measure the number of mL of 0.1 mol/L sodium hydroxide consumed per minute. Titrate, while stirring with a stirrer at a constant speed, under the nitrogen gas flow or in a well-closed container. Titrate 4 to 5 times, discard the first result, and use the average value of the remaining ones. After completing the preliminary test, adjust the amount of test solution so that the consumption of 0.1 mol/L sodium hydroxide per minute reaches 0.08 mL to 0.16 mL. Then, proceed again as above.

$$\text{Lipase potency per gram of Polypase 1000 (FIP unit)} = \frac{b \times 100000}{a} \times \frac{200}{X} \times F \times 100$$

a: Amount (mg) of sample taken
b: Number of mL of 0.1 mol/L sodium hydroxide consumed per minute
X: Number of mL of test solution taken
F: $\frac{\text{theoretical potency of standard}}{\text{test value potency of standard}}$
100000: 0.1 × 1000 × 1000
200: Dilution factor

Definition of potency—The amount of enzyme that releases 1 μmol of fatty acid per minute under the conditions of 37 ℃ and pH 9.0 is defined as 1 FIP unit of fat digestion activity.

Packaging and storage Preserve in tight containers.

Polysaccharide Iron Complex
폴리사카리드철착염

Polysaccharide Iron Complex is produced through a complex salt reaction between ferric hydroxide and a low-molecular-polysaccharide obtained by partial hydrolysis of starch. Polysaccharide Iron Complex, when dried, contains NLT 44.5% and NMT 47.5% of iron (Fe: 55.85).

Description Polysaccharide Iron Complex is a black-brown crystalline granule or brown powder. It has no odor or a slight caramel odor.
It is slowly soluble in water, and insoluble in ethanol, acetone, ether, and chloroform.

Identification (1) Dissolve 1 g of Polysaccharide Iron Complex in 25 mL of water, and add a small amount of dilute hydrochloric acid; a brown precipitate is formed. To this precipitate, add dilute sodium hydroxide TS; it dissolves again. When an excessive amount of dilute sodium hydroxide TS is added, no precipitate is formed.

(2) Put a small amount of Polysaccharide Iron Complex in a ceramic crucible and ignite it. Add hydrochloric acid to the residue, and dissolve it by heating until it turns into a yellow solution. This solution responds to the Qualitative Analysis for ferric salt.

(3) Determine the infrared spectra of Polysaccharide Iron Complex and polysaccharide iron complex RS, previously powdered, as directed under the ART method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Acidity or alkalinity***—Dissolve 1.125 g of Polysaccharide Iron Complex in 25 mL of water; the pH of this solution is between 9.0 and 11.0.

(2) ***Free alkali***—Weigh accurately 0.2 g of Polysaccharide Iron Complex, add 20 mL of water, shake well to dissolve, and then add 2 mL of 0.05 mol/L sulfuric acid; the pH of the mixture is NMT 7.5.

(3) ***Sodium chloride***—Weigh accurately 5.0 g of Polysaccharide Iron Complex, put it in a 150 mL stoppered Erlenmeyer flask, add 100 mL of water, and shake well for 1 hour to dissolve. Filter this solution with filter paper, discard the first 20 mL of the filtrate, take 60.0 mL of the next filtrate, and add it to a 400-mL beaker. Add 200 mL of nitric acid, and dissolve it completely by heating on a steam bath. After cooling, add water to make 325 mL. Add 20.0 mL of 0.1 mol/L silver nitrate TS, add 20 mL of ammonium iron(III) sulfate TS, and titrate with 0.1 mol/L potassium thiocyanate VS. Perform a blank test in the same manner and make any necessary correction (NMT 3.5%).

Each mL of 0.1 mol/L silver nitrate VS
= 5.844 mg of NaCl

(4) ***Free iron ions (Fe^{3+})***—Weigh accurately 1.0 g of Polysaccharide Iron Complex, dissolve in 50 mL of water, add 10 mL of 1 mol/L sodium hydroxide solution, and shake well to mix. Filter the precipitate by suction through a quantitative filter paper, and wash the filter paper and funnel well with water. Dissolve the residue on the filter paper by adding 4.2 mL of hydrochloric acid, wash the filter paper with water, and combine the washings with the filtrate. Then, transfer the filtrate to the flask with a volume of 50 mL, add water to make 50 mL, and use this solution as the test solution (20 mg/mL). Separately, weigh accurately 0.074 g of iron(III) nitrate nonahydrate ($Fe(NO_3)_3 \cdot 9H_2O$), dissolve in 1 mol/L hydrochloric acid to make 100 mL, and use this solution as the standard solution (Fe 0.1 mg/mL). Take 5 mL each of the test solution and the standard solution in a test tube, add 0.02 mL of newly prepared potassium ferrocyanide TS to each test tube, and observe immediately; the color of the test solution is not more intense than that of the standard solution (NMT 0.5%).

Assay Weigh accurately about 0.23 g of Polysaccharide Iron Complex, put it in a glass-stoppered flask, add 30 mL of water, and shake well to dissolve. Add 10 mL of hydrochloric acid to this solution and heat on a steam bath, shaking occasionally, until completely dissolved. After cooling, add 3 g of potassium iodide, stopper, shake well until dissolved, allow to stand for 15 minutes, and titrate with 0.1 mol/L sodium thiosulfate VS using starch TS as an indicator. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium thiosulfate VS
= 5.585 mg of Fe

Packaging and storage Preserve in well-closed containers.

Polysaccharide Iron Complex Capsules
폴리사카리드철착염 캡슐

Polysaccharide Iron Complex Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of polysaccharide iron complex (Fe : 55.85).

Method of preparation Prepare as directed under Capsules, with Polysaccharide Iron Complex.

Identification (1) Weigh an amount of Polysaccharide Iron Complex Capsules equivalent to 0.2 g as polysaccharide iron complex, add 2 mL of dilute nitric acid and 10 mL of water, shake to mix, and filter to extract. The filtrate responds to the Qualitative Analysis for ferric salt.

(2) Weigh an amount of Polysaccharide Iron Complex Capsules equivalent to 0.2 g as polysaccharide iron complex, add 20 mL of water, and filter to extract by warming. Evaporate the filtrate to concentrate to about 10 mL, transfer to a test tube, and add 2 to 3 drops of 5% α-Naphthol-methanol solution. Slowly add 1 mL of sulfuric acid through the wall of the test tube; the solution exhibits a violet color on the interface after 2 to 3 minutes.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the contents of NLT 20 capsules of Polysaccharide Iron Complex Capsules. Then, weigh accurately an amount equivalent to about 0.1 g as iron (Fe), add 50 mL of water, shake to mix, extract and filter. Transfer the filtrate and the washings to an iodine flask, add 10 mL of hydrochloric acid, and heat on a steam bath with occasional shaking. After cooling this solution, add 3 g of potassium iodide, place a stopper and shake well to mix. Allow to stand for 15 minutes in the dark and titrate with 0.1 mol/L sodium thiosulfate VS. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium thiosulfate VS
= 5.585 mg of Fe

Packaging and storage Preserve in tight containers.

Polysaccharide Iron Complex Tablets
폴리사카리드철착염 정

Polysaccharide Iron Complex Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of iron (Fe: 55.85).

Method of preparation Prepare as directed under Tablets, with Polysaccharide Iron Complex.

Identification (1) Weigh accurately an amount of Polysaccharide Iron Complex Tablets, equivalent to 0.2 g of polysaccharide iron complex, add 2 mL of dilute nitric acid and 10 mL of water, shake to mix, extract, and filter. The filtrate responds to the Qualitative Analy-

sis for ferric salt.

(2) Weigh an amount of Polysaccharide Iron Complex Tablets, equivalent to about 0.2 g of polysaccharide iron complex, add 20 mL of water, extract by warming, and filter. Evaporate the filtrate to concentrate to make about 10 mL, transfer to a test tube, add 2 to 3 drops of 5% α-Naphthol-methanol solution, and slowly add 1 mL of sulfuric acid through the test tube wall; the interface exhibits a purple color after 2 to 3 minutes.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Polysaccharide Iron Complex Tablets. Then weigh accurately an amount, equivalent to about 0.1 g of iron (Fe), add 50 mL of water, and shake to mix, extract, and filter. Transfer the filtrate and the washings to an iodine flask, add 10 mL of hydrochloric acid, and warm on a steam bath with occasional shaking. After cooling this solution, add 3 g of potassium iodide, seal tightly, shake well to mix, and allow to stand in the dark for 15 minutes. Then, titrate with 0.1 mol/L sodium thiosulfate VS using starch TS as an indicator. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium thiosulfate VS
= 5.585 mg of Fe

Packaging and storage Preserve in tight containers.

Potassium Bromide
브롬화칼륨

KBr : 119.00

Potassium bromide [*7758-02-3*]

Potassium Bromide, when dried, contains NLT 99.0% and not more 101.0% of potassium bromide (KBr).

Description Potassium Bromide occurs as a colorless or white crystal, grain or crystalline powder. It is odorless.
It is freely soluble in water or glycerin, soluble in hot ethanol, and slightly soluble in ethanol(95).

Identification An aqueous solution of Potassium Bromide (1 in 10) responds to the Qualitative Analysis for potassium salt and bromide.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Potassium Bromide in 3 mL of water; the resulting solution is clear and colorless.

(2) ***Alkalinity***—Dissolve 1.0 g of Potassium Bromide in 10 mL of water, add 0.10 mL of 0.05 mol/L sulfuric acid and 1 drop of phenolphthalein TS, heat to boiling, and cool it down; the resulting solution is colorless.

(3) ***Chloride***—Perform the test as directed under the Assay; the amount of 0.1 mol/L silver nitrate solution equivalent to 1 g of Potassium Bromide is NMT 84.5 mL.

(4) ***Sulfate***—Perform the test with 2.0 g of Potassium Bromide. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.024%).

(5) ***Iodide***—Dissolve 0.5 g of Potassium Bromide in 10 mL of water, add between 2 and 3 drops of iron(III) chloride TS and 1 mL of chloroform, and shake well to mix; the chloroform layer does not exhibit a purple to violet color.

(6) ***Bromate***—Dissolve 1.0 g of Potassium Bromide in 10 mL of newly boiled and cooled water, add 0.1 mL of potassium iodide TS, 1 mL of starch TS and 3 drops of dilute sulfuric acid, shake gently to mix, and allow to stand for 5 minutes; the resulting solution does not exhibit a blue color.

(7) ***Heavy metals***—Proceed with 2.0 g of Potassium Bromide according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(8) ***Magnesium and alkaline earth metals***—To 200 mL of water, add 0.1 g of hydroxylamine hydrochloride, 10 mL of ammonium chloride buffer solution, pH 10, 1 mL of 0.1 mol/L zinc sulfate solution and 0.2 g of eryochrome black T-sodium chloride indicator, and warm at 40°C. To this solution, drop 0.01 mol/L ethylenediaminetetraacetic acid disodium salt until the purple color of the solution changes to bluish purple. To this solution, add a solution of 10.0 g of Potassium Bromide dissolved in 100 mL of water. If the color of the solution changes to purple, titrate with 0.01 mol/L ethylenediaminetetraacetic acid disodium salt until the color of the solution exhibits a bluish purple color; the color; the consumed volume is NMT 5.0 mL (NMT 0.02%, calculated as calcium).

(9) ***Barium***—Dissolve 0.5 g of Potassium Bromide in 10 mL of water, add 0.5 mL of dilute hydrochloric acid and 1 mL of potassium sulfate TS, and allow to stand for 10 minutes; the resulting solution is not turbid.

(10) ***Iron***—Dissolve 0.5 g of Potassium Bromide in water to make 10 mL and use this solution as the test solution. To 1 mL of the iron standard solution, add water to make 10 mL, and use this solution as the standard solution. To the test solution and the standard solution, add 2.0 mL of citric acid (1 in 5) and 0.1 mL of thioglycolic acid, add ammonia water(28) until this solution makes the litmus paper alkaline, and add water to make 20 mL. The color obtained from the test solution after 5 minutes is not more intense than the color from the standard solution (NMT 20 ppm).

(11) ***Arsenic***—Proceed with 1.0 g of Potassium Bromide according to Method 1 and perform the test (NMT 2 ppm).

Loss on drying NMT 1.0% (1 g, 110 °C, 4 hours).

Assay Weigh accurately about 0.4 g of Potassium Bromide, previously dried, dissolve in 50 mL of water, add 10 mL of dilute nitric acid, add exactly 50 mL of 0.1 mol/L silver nitrate solution, and titrate the excess silver nitrate with 0.1 mol/L ammonium thiocyanate VS (indi-

cator: 2 mL of ammonium iron(III) sulfate TS). Perform a blank test in the same manner.

Each mL of 0.1 mol/L silver nitrate VS
= 11.900 mg of KBr

Packaging and storage Preserve in tight containers.

Potassium Chloride
염화칼륨

KCl : 74.55

Potassium Chloride [*7447-40-7*]

Potassium Chloride, when dried, contains NLT 99.0% and NMT 101.0% of potassium chloride (KCl).

Description Potassium Chloride occurs as colorless or white crystals or a crystalline powder, which is odorless and has a salty taste.
It is freely soluble in water and practically insoluble in ethanol(95) or ether.
An aqueous solution of Potassium Chloride (1 in 10) is neutral.

Identification An aqueous solution of Potassium Chloride (1 in 50) responds to the Qualitative Analysis for potassium salt and chloride.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Potassium Chloride in 5 mL of water; the solution is clear and colorless.

(2) ***Acid or alkalinity***—Dissolve exactly 50 mL of freshly boiled and cooled water in 5.0 g of Potassium Chloride, and add 3 drops of phenolphthalein TS; the solution does not exhibit a red color. Add 0.50 mL of 0.01 mol/L sodium hydroxide to this solution; the solution exhibits a red color.

(3) ***Bromide***—Dissolve 1.0 g of Potassium Chloride in water to make 100 mL. To 5 mL of this solution, add 3 drops of dilute hydrochloric acid and 1 mL of chloroform, and add 3 drops of chloramine TS dropwise while shaking to mix; the chloroform layer does not exhibit a yellow to yellowish red color.

(4) ***Iodide***—Dissolve 0.5 g of Potassium Chloride in 10 mL of water, add 3 drops of iron(III) chloride TS and 1 mL of chloroform, shake to mix, and allow to stand for 30 minutes. When shaking again to mix, the chloroform layer does not exhibit a purple to violet color.

(5) ***Heavy metals***—Proceed with 4.0 g of Potassium Chloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 5 ppm).

(6) ***Sodium***—Dissolve 1.0 g of Potassium Chloride in 20 mL of water, and perform the Flame Coloration (1); the solution does not exhibit a persistent yellow color.

(7) ***Aluminum***—Perform the test when used in the manufacturing of hemodialysis preparations. Weigh accurately 2.0 g of Potassium Chloride, add 50 mL of water, and sonicate for 30 minutes. To this solution, add 4 mL of nitric acid and then water to make 100 mL, and use this solution as the test solution. To an appropriate amount of aluminum, add 6 mol/L hydrochloric acid, and heat at 80 ℃ for several minutes. Weigh accurately 100 mg of this aluminum, dissolve it in a mixture of 10 mL of hydrochloric acid and 2 mL of nitric acid, and heat at 80 ℃ for 30 minutes. Continue heating until the volume of the solution is reduced to about 4 mL, and cool it to room temperature. To this solution, add 4 mL of water, heat again until the volume of the solution is reduced to 2 mL. After cooling, add water to make 100 mL. Pipet 10.0 mL of this solution and add water to make 100 mL. Take exactly 1.0 mL of the solution, add water again to make 100 mL to make a concentration of 1.0 μg/mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solutions as directed under the Atomic Absorption Spectroscopy according to the following conditions, and obtain the content of aluminum in the test solution using the calibration curve derived from the absorbance of the standard solution; the result is NMT 1 ppm.

Lamp: Aluminum hollow cathode lamp
Wavelength: 309.3 nm
Blank test solution: Dilute 40 mL of nitric acid with water to make 1000 mL of fluid.

(8) ***Calcium and magnesium***—Dissolve 0.20 g of Potassium Chloride in 20 mL of water, add 2 mL of ammonia TS, 2 mL of ammonium oxalate TS and 2 mL of sodium monohydrogen phosphate TS, and allow to stand for 5 minutes; the solution does not become turbid.

(9) ***Arsenic***—Proceed with 1.0 g of Potassium Chloride according to Method 1 and perform the test (NMT 2 ppm).

Loss on drying NMT 0.5% (1 g, 130 ℃, 2 hours).

Assay Weigh accurately about 0.2 g of Potassium Chloride, previously dried, dissolve in 50 mL of water, shake vigorously to mix, and titrate with 0.1 mol/L silver nitrate VS (indicator: 3 drops of fluorescein sodium TS).

Each mL of 0.1 mol/L silver nitrate VS
= 7.455 mg of KCl

Packaging and storage Preserve in tight containers.

Potassium Chloride Injection
염화칼륨 주사액

Potassium Chloride Injection is an aqueous injection and contains NLT 95.0% and NMT 105.0% of the labeled amount of potassium chloride (KCl : 74.55).

Method of preparation Prepare as directed under Injections, with Potassium Chloride.

Description Potassium Chloride Injection occurs as a clear, colorless liquid.

Identification Potassium Chloride Injection responds to the Qualitative Analysis for potassium salt and chloride.

pH Between 4.0 and 8.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.16 EU per mg of potassium chloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Potassium Chloride Injection equivalent to about 0.6 g of potassium chloride (KCl) and add water to make 500 mL. Take 5.0 mL of this solution and add water to make 100 mL. Take 5.0 mL of the resulting solution, add 2.0 mL of sodium chloride solution (1 in 5) and 1.0 mL of hydrochloric acid, then add water to make 100 mL and use this solution as the test solution. Separately, weigh accurately about 190.7 mg of potassium chloride, dried previously at 105 ℃ for 2 hours, add water to make 1000 mL, take 100.0 mL of this solution, and add water to make 1000 mL. Pipet 10.0 mL, 15.0 mL and 20.0 mL of the resulting solution, add 2.0 mL of sodium chloride solution (1 in 5) and 1.0 mL of hydrochloric acid, and then add water to make 100 mL. Use these solutions as the standard solutions. Perform the test with the test solution and the standard solutions as directed under the Atomic Absorption Spectroscopy, using water as a control solution.

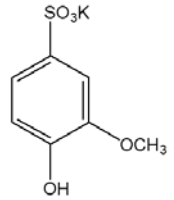
$$\text{Amount (mg) of potassium chloride (KCl)} = 200 \times C \times 1.907$$

C: Concentration (μg/mL) of potassium in the test solution from the calibration curve

Gas: Air–acetylen
Lamp: Potassium hollow cathode lamp
Wavelength: 766.5 nm

Packaging and storage Preserve in hermetic containers.

Potassium Guaiacolsulfonate
구아야콜설폰산칼륨



Sulfogaiacol $C_7H_7KO_5S$: 242.29
Potassium 4-hydroxy-3-methoxybenzenesulfonate [*1321-14-8*]

Potassium Guaiacolsulfonate contains NLT 98.5% and NMT 101.0% of potassium guaiacolsulfonate ($C_7H_7KO_5S$), calculated on the anhydrous basis.

Description Potassium Guaiacolsulfonate occurs as crystals or a crystalline powder. It is odorless or has a slight, characteristic odor and a slightly bitter taste.
It is freely soluble in water or formic acid, sparingly soluble in methanol and practically insoluble in ethanol(95), acetic anhydride, or ether.

Identification (1) Take 10 mL of potassium guaiacolsulfonate VS (1 in 100), and add 2 drops of iron(III) chloride TS; a bluish purple color develops.

(2) Dissolve Potassium Guaiacolsulfonate and 0.25 g of potassium guaiacolsulfonate RS in water to make 500 mL. Take 10 mL of these solutions respectively, and add phosphate buffer solution, pH 7.0 to make 100 mL each. Determine the absorption spectra of this solution as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) An aqueous solution of Potassium Guaiacolsulfonate (1 in 10) responds to the Qualitative Analysis for potassium salt.

pH Dissolve 1.0 g of Potassium Guaiacolsulfonate in 20 mL water. The pH of the solution is between 4.0 and 5.5.

Purity (1) ***Solubilized state***—Dissolve 1.0 g of Potassium Guaiacolsulfonate in 20 mL of water; the solution is clear and colorless.

(2) ***Sulfate***—Proceed with 0.8 g of Potassium Guaiacolsulfonate and perform the test. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid (NMT 0.030%).

(3) ***Heavy metals***—Proceed with 1.0 g of Potassium Guaiacolsulfonate according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic***—Proceed with 1.0 g of Potassium Guaiacolsulfonate according to Method 1 and perform the test (NMT 2 ppm).

(5) ***Selenium***—Weigh about 0.2 g of Potassium Guaiacolsulfonate and combust as directed under the Oxygen Flask Combustion with 25 mL of diluted nitric acid

(1 in 30) as an absorbent. Use a combustion flask with a volume of 1000 mL, combust, wash the stopper and the inner wall of the flask with 10 mL of water, and use 20 mL of water to move the solution in the combustion flask into a 150-mL beaker. Heat lightly until it boils, boil for 10 minutes, allow it to cool down at room temperature, and use this solution as the test solution. Separately, pipet 6 mL of standard selenium stock solution, add 25 mL of diluted nitric acid (1 in 30) and 25 mL of water, and use this solution as the standard solution. Add diluted ammonia (28) VS (1 in 2) to each of the test and standard solutions, adjust the pH to 2.0 ± 0.2, add water to dilute exactly to 60 mL, and add 10 mL of water to move to a separatory funnel. Then, wash the separatory funnel with 10 mL of water. Add 0.2 g of hydroxylamine, dissolve by mixing, add 5 mL of 2,3-diaminonaphthalene TS, and put stopper. Mix by stirring and allow to stand at room temperature for 100 minutes. Add 5.0 mL of cyclohexane, shake well, and allow to stand. If the layer is separated, remove the water layer, centrifuge cyclohexane extract, remove water, and take the cyclohexane layer. With these solutions and a control solution prepared with water added to 25 mL of diluted nitric acid (1 in 30) in the same way, perform the test as directed under the Ultraviolet-visible Spectroscopy. Determine the absorption at absorption maximum wavelength around 380 nm; the absorption of the solution from the test solution is not larger than the absorption from the standard solution (NMT 30 ppm).

(6) ***Related Substances***—Dissolve 0.20 g of Potassium Guaiacolsulfonate in 200 mL of mobile phase and use this solution as the test solution. Pipet 1.0 mL of the test solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test and standard solutions as directed under the Liquid Chromatography according to the following conditions. Determine each peak area obtained from the test solution and the standard solution by the automatic integration method; the total area of peaks other than the peak of Potassium Guaiacolsulfonate from the test solution is not larger than that of Potassium Guaiacolsulfonate from the standard solution.

Operating Conditions

Detector: An ultraviolet absorption photometer (wavelength: 279 nm).

Column: A stainless steel column, about 4 mm in internal diameter and 20 cm to 25 cm in length, with dimethylaminopropylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of 0.05 mol/L potassium dihydrogen phosphate VS and methanol (20 : 1).

Flow rate: Adjust the flow rate so that the retention time of Potassium Guaiacolsulfonate is about 10 minutes.

System suitability

Detection sensitivity: Adjust the sensitivity so that the peak height of Potassium Guaiacolsulfonate from 5 μL of the standard solution is NLT 10 mm.

System performance: Weigh 50 mg each of Potassium Guaiacolsulfonate and guaiacol and dissolve in 50 mL of the mobile phase. Perform the test with 5 μL of this solution under the above operating conditions; guaiacol and Potassium Guaiacolsulfonate are eluted in this order with the resolution of their peaks being NLT 4.0.

Time span of measurement: About twice the retention time of Potassium Guaiacolsulfonate.

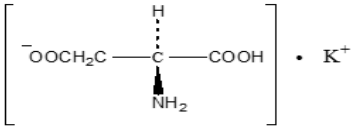
Water Between 3.0% and 4.5% (0.3 g, direct titration).

Assay Weigh accurately about 0.3 g of Potassium Guaiacolsulfonate, dissolve in 2.0 mL of formic acid, add 50 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid
= 24.229 mg of $C_7H_7KO_5S$

Packaging and storage Preserve in light-resistant, well-closed containers.

Potassium L-Aspartate
L-아스파르트산칼륨



$C_4H_6NO_4K$: 171.19
L-Aspartate potassium salt (1:1), [*14007-45-5*]

Potassium L-Aspartate contains NLT 74.6% and NMT 80.0% of L-aspartate ($C_4H_7NO_4$: 133.10) and NLT 21.9% and NMT 23.7% of potassium (K: 39.10), calculated on the anhydrous basis.

Description Potassium L-Aspartate occurs as a white powder. It is odorless and has a slightly characteristic taste.

Identification (1) A neutral solution (1 in 20) of Potassium L-Aspartate responds to the Qualitative Analysis (2) for potassium salt.

(2) To 5 mL of an aqueous solution (1 in 100) of Potassium L-Aspartate, add 1 mL of 2% ninhydrin solution, and heat for 3 minutes; the color of the resulting solution turns to a reddish purple color.

Optical rotation $[a]_D^{20}$: Between +19.0° and +22.6° (4.0 g, calculated on the anhydrous basis, 50 mL of 6 mol/L hydrochloric acid, 100 mm).

pH Dissolve 1.0 g of Potassium L-Aspartate in 10 mL of freshly boiled and cooled water. The pH of this solution

is between 6.0 and 7.5.

Purity (1) ***Clarity and color of solution*—**Perform the test with an aqueous solution (1 in 10) of Potassium L-Aspartate as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance at the wavelength 430 nm; the transmission rate is NLT 98.0%.

(2) ***Chloride*—**Perform the test with 0.5 g of Potassium L-Aspartate as directed under the Chloride. Prepare the control solution with 0.3 mL of 0.01 mol/L hydrochloric acid (NMT 0.021%).

(3) ***Sulfate*—**Perform the test with 0.6 g of Potassium L-Aspartate as directed under the Sulfate. Prepare the control solution with 0.35 mL of 0.05 mol/L sulfuric acid (NMT 0.028%).

(4) ***Iron*—**Prepare the test solution with 1.0 g of Potassium L-Aspartate according to Method 3 under the Iron and perform the test according to Method A. Prepare the control solution with 2.0 mL of iron standard solution (NMT 0.028%).

(5) ***Heavy metals*—**Proceed with 2.0 g of Potassium L-Aspartate as directed under Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(6) ***Arsenic*—**Prepare the test solution with 2.0 g of Potassium L-Aspartate according to Method 1 under the Arsenic and perform the test. Prepare the control solution with 2.0 mL of arsenic standard solution (NMT 1 ppm).

Water NMT 8.0% (0.2 g, volumetric titration, direct titration).

Other amino acids Weigh accurately 10.0 mg of Potassium L-Aspartate, dissolve in 200 mL of water, and use this solution as the test solution. To 1.0 mL of this solution, add water to make 100 mL, and use this solution as the control solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, water and acetic acid(100) (2 : 1 : 1) as the developing solvent, and air-dry the plate. Spray 2% ninhydrin-1-butanol solution on the plate, and heat the plate for 3 minutes. The principal spots obtained from the test solution are not greater or not more intense than the principal spot from the control solution (NMT 1%).

Assay (1) ***L-aspartate*—**Weigh accurately about 1.6 g of Potassium L-Aspartate, and add water to make 50 mL. Place 10.0 mL of this solution in a weakly acidic ion exchange resin column, and pass it at the efflux rate of 2 mL/min. Pass 90 mL of water through the column at the efflux rate of 2 mL/min to wash the column, and combine it with the effluent. Titrate this solution with 0.1 mol/L sodium hydroxide VS. Use 5 to 6 drops of bromothymol blue TS as the indicator. The endpoint is when the yellow color turns to a green color. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 13.310 mg of $C_4H_7NO_4$

Weakly acidic ion exchange resin column—Place about 50 g of weakly acidic ion exchange resin (H+ type, 30 μm to 1180 μm in particle diameter) in 300 mL of water for 24 hours, and pass it with water through a glass column for chromatography (about 25 mm in internal diameter and 30 cm in length). Pass 350 mL of 1 mol/L hydrochloric acid at the efflux rate of 2 mL/min, and pass water at the efflux rate of 2 mL/min. Add bromocresol green TS to the washings to wash the column until the green color turns to a blue color.

(2) ***Potassium*—**Weigh accurately about 0.1 g of Potassium L-Aspartate, dissolve in 25 mL of water, slowly add 25 mL of sodium tetraphenylborate solution (1 in 50) to mix, and allow to stand for 10 minutes. Filter the formed precipitate with a glass filter (G_4), and wash the precipitate 3 times with 5 mL of sodium tetraphenylborate solution (1 in 500) each time. Dry the residue at 105 ℃ for 1 hour, and weigh accurately the mass.

Amount (mg) of potassium (K)
= Amount (A mg) of potassium tetraphenylborate ($C_{24}H_{20}BK$) × 0.1091

Packaging and storage Preserve in tight containers.

Potassium Iodide
요오드화칼륨

KI: 166.00

Potassium Iodide [*7681-11-0*]

Potassium Iodide, when dried, contains NLT 99.0% and NMT 101.0% of potassium iodide (KI).

Description Potassium Iodide occurs as colorless or white crystals or a crystalline powder.
It is very soluble in water, soluble in ethanol(95), and practically insoluble in ether.
It is slightly deliquescent in humid air.

Identification A solution of Potassium Iodide (1 in 20) responds to the Qualitative Analysis for potassium salt and iodide.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Potassium Iodide in 2 mL of water; the solution is clear and colorless.

(2) ***Alkalinity***—Dissolve 1.0 g of Potassium Iodide in 10 mL of freshly boiled and cooled water, and add 0.50 mL of 0.005 mol/L sulfuric acid and 1 drop of phenolphthalein TS; the solution is colorless.

(3) ***Chloride, bromide and thiosulfate***—Dissolve 0.20 g of Potassium Iodide in 5 mL of ammonia TS, add 15.0 mL of 0.1 mol/L silver nitrate solution, shake to mix for 2 to 3 minutes, and filter. To 10 mL of the filtrate, add

15 mL of dilute nitric acid; the solution does not turn brown. Also, the turbidity of the solution is not more intense than that of the following control solution.

Control solution—To 0.30 mL of 0.01 mol/L hydrochloric acid, add 2.5 mL of ammonia TS, 7.5 mL of 0.1 mol/L silver nitrate VS, and 15 mL of dilute nitric acid.

(4) ***Nitrate, nitrite or ammonium***—Take 1.0 g of Potassium Iodide in a 40 mL test tube, add 5 mL of water, 5 mL of sodium hydroxide TS and 0.2 g of aluminum, and cover with absorbent cotton and carefully heat for 15 minutes on a steam bath; the gas produced does not change a moistened red litmus paper to blue.

(5) ***Cyanide***—Dissolve 0.5 of Potassium Iodide in 10 mL of water, add 1 drop of iron(II) sulfate TS and 2 mL of sodium hydroxide TS to 5 mL of this solution and warm, and add 4 mL of hydrochloric acid; the solution does not turn green.

(6) ***Iodate***—Dissolve 0.5 g of Potassium Iodide in 10 mL of freshly boiled and cooled water and add 2 drops of dilute sulfuric acid and 1 drop of starch TS; the solution does not turn blue immediately.

(7) ***Heavy metals***—Proceed with 2.0 g of Potassium Iodide as directed under Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(8) ***Sodium***—Dissolve 1.0 g of Potassium Iodide in 10 mL of water and perform the Flame Coloration (1); the solution does not exhibit a persistent yellow color.

(9) ***Barium***—Dissolve 0.5 g of Potassium Iodide in 10 mL of water, add 1 mL of dilute sulfuric acid and allow to stand for 5 minutes; no turbidity is produced.

(10) ***Arsenic***—Proceed with 0.40 g of Potassium Iodide as directed under Method 1 and perform the test (NMT 5 ppm).

Loss on drying NMT 1.0% (2 g, 105 ℃, 4 hours).

Assay Weigh accurately about 0.5 g of Potassium Iodide, previously dried, place in an iodine bottle, and dissolve in 10 mL of water. Add 35 mL of hydrochloric acid and 5 mL of chloroform and shake vigorously to mix; titrate with 0.05 mol/L potassium iodate VS until the purple color of the chloroform layer disappears. The endpoint is when the purple color of the chloroform layer does not reappear within 5 minutes after it is decolorized.

Each mL of 0.05 mol/L potassium iodate VS
= 16.600 mg of KI

Packaging and storage Preserve in light-resistant, tight containers.

Potassium Permanganate
과망간산칼륨

$KMnO_4$: 158.03

Potassium permanganate [*7722-64-7*]

Potassium Permanganate, when dried, contains NLT 99.0% and NMT 101.0% of potassium permanganate ($KMnO_4$).

Description Potassium Permanganate occurs as deep purple crystals and has a metallic luster.
It is soluble in water.
A solution of Potassium Permanganate (1 in 1000) is an astringent with a slightly sweet taste.

Identification A solution of Potassium Permanganate (1 in 100) responds to the Qualitative Analysis for permanganate.

Purity (1) ***Water insoluble matter***—Weigh 2.0 g of Potassium Permanganate, previously powdered, and dissolve in 200mL of water, filter it through a tared glass filter, wash with water until the last washings show no color, and dry at 105 ℃ for 2 hours; the mass of the residue is NMT 4 mg.

(2) ***Arsenic***—Weigh about 0.4 g of Potassium Permanganate and dissolve in 10mL of water, add 1 mL of sulfuric acid, put hydrogen peroxide(30) to completely decolorize, evaporate in a sand bath nearly to dryness, and dissolve the residue in 5 mL of water. Use this solution as the test solution and perform the test; it is not more intense than the following standard color (NMT 5 ppm).

Standard color—Pipet 10 mL of standard color water, add 1 mL of sulfuric acid and the same amount of hydrogen peroxide(30) as the preparation of the test solution, evaporate in a bath nearly to dryness, and add 2.0 mL of arsenic standard solution and water to make 5 mL, and use this solution as the test solution and perform the test.

Loss on drying NMT 0.5% (1 g, silica gel, 18 hours).

Assay Weigh accurately about 0.6 g of Potassium Permanganate, previously dried, and dissolve it in water to make exactly 200 mL. Use this solution as the test solution. Pipet 25 mL of 0.05 mol/L oxalic acid solution, put it into a 500-mL Erlenmeyer flask, add 200 mL of diluted sulfuric acid (1 in 20), and set the solution temperature to 30 to 35 ℃. Transfer the test solution in a burette, shake gently, add 23 mL quickly, and allow the flask to stand until the red color disappears. Then, warm it to 55 to 60 ℃ and titrate slowly until a red color persists for 30 seconds.

Each mL of 0.05 mol/L oxalic acid VS
= 3.1607 mg of $KMnO_4$

Packaging and storage Preserve in tight containers.

Povidone Ophthalmic Solution
포비돈 점안액

Povidone Ophthalmic Solution contains NLT 90.0% and NMT 110.0% of the labeled amount of povidone $(C_6H_9NO)_n$.

Method of preparation Prepare as directed under Ophthalmic Solutions, with Povidone.

Identification (1) Add 10 mL of water, 5 mL of dilute hydrochloric acid and 2 mL of 10% potassium dichromate solution to 2 mL of Povidone Ophthalmic Solution; a bright yellow precipitate is formed.

(2) Add 0.2 mL of 4-dimethylaminobenzaldehyde TS and 0.1 mL of sulfuric acid to 5 mL of Povidone Ophthalmic Solution; the resulting solution exhibits a pale orange color.

(3) Add 5 mL of water and 0.2 mL of 0.05 mol/L iodine solution to 5 mL of Povidone Ophthalmic Solution; the resulting solution exhibits a reddish brown color.

pH Between 6.0 and 8.0.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

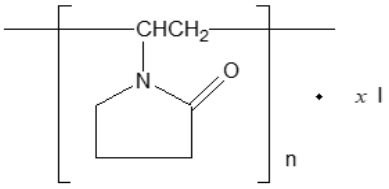
Insoluble particulate matter in ophthalmic solutions Meets the requirements.

Assay Pipet an amount of Povidone Ophthalmic Solution, equivalent to about 20 mg of povidone $(C_6H_9NO)_n$, and add water to make 100 mL. Pipet 10.0 mL of this solution, add water to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of povidone RS, dissolve in water to make 100 mL. Pipet 10.0 mL of this solution, add water to make 100 mL, and use this solution as the standard solution. Take 10.0 mL each of the test solution and the standard solution, put in a light-resistant container, add 5 mL of 0.2 mol/L citric acid TS and 2 mL of 0.003 mol/L iodine TS, shake to mix, and allow to stand for exactly 10 minutes. Perform the test with these solutions using the solution prepared in the same manner with 10 mL of water as the control solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbances, A_T and A_S, at the wavelength of 450 nm.

$$\text{Amount (mg) of povidone } (C_6H_9NO)_n = Amount\ (mg)\ of\ povidone\ RS \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers.

Povidone Iodine
포비돈요오드



$(C_6H_9NO)_n \cdot xI$

Poly(1-ethenylpyrrolidin-2-one)-iodine [*25655-41-8*]

Povidone Iodine is a complex of 1-vinyl-2-pyrrolidone polymer and iodine.

Povidone Iodine contains NLT 9.0% and NMT 12.0% of active iodine (I: 126.90) and NLT 9.0% and NMT 1 1.5% of nitrogen (N: 14.01), calculated on the dried basis.

Description Povidone Iodine occurs as a dark reddish brown powder and has a characteristic odor.
It is freely soluble in water or ethanol(99.5).
Dissolve 1.0 g of Povidone Iodine in 100 mL of water; the pH of the solution is between 1.5 and 3.5.

Identification (1) Add 1 drop of an aqueous solution of Povidone Iodine (1 in 10) to 10 mL of diluted starch TS (1 in 10); the resulting solution exhibits an dark blue color.

(2) To 1 mL of an aqueous solution of Povidone Iodine (1 in 100), add 1 mL of sodium thiosulfate TS, and add 1 mL of ammonium thiocyanate-cobalt nitrate TS and 2 drops of 1 mol/L hydrochloric acid TS; the resulting solution exhibits a blue color, and a blue precipitate gradually forms.

Purity (1) ***Clarity and color of solution***—Dissolve 0.30 g of Povidone Iodine in 100 mL of water; the resulting solution is brown and clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Povidone Iodine according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Povidone Iodine according to Method 4 and perform the test (NMT 2 ppm).

(4) ***Iodine ion***—Dissolve 0.5 g of Povidone Iodine in 100 mL of water, and add sodium bisulfite TS until the color of iodine disappears completely. Next, add exactly 25 mL of 0.1 mol/L silver nitrate, add 10 mL of nitric acid, shake well to mix, and titrate excess silver nitrate with 0.1 mol/L ammonium thiocyanate VS to determine the total amount of iodine (indicator: 1 mL of ammonium iron(III) sulfate TS). However, the endpoint of the titration is when the solution exhibits a reddish brown color. Perform a blank test in the same manner.

Each mL of 0.1 mol/L ammonium thiocyanate VS
= 12.690 mg of I

Determine the amount of iodide ion by subtracting the content (%) of active iodine from the total content (%) of iodine, calculated on the dried basis. The amount is NMT 6.6%.

Loss on drying NMT 8.0% (1 g, 100 ℃, 3 hours).

Residue on ignition NMT 0.05% (5 g).

Assay (1) ***Active iodine***—Weigh accurately about 0.5 g of Povidone Iodine, dissolve in 30 mL of water, and titrate with 0.02 mol/L sodium thiosulfate VS (indicator: 2 mL of starch TS).

Each mL of 0.02 mol/L sodium thiosulfate VS
= 2.5381 mg of I

(2) ***Nitrogen***—Weigh accurately about 1 g of Povidone Iodine, dissolve in water to make exactly 50 mL, and use this solution as the test solution. Pipet 1.0 mL of this solution, and perform the test as directed under the Nitrogen Determination.

Each mL of 0.005 mol/L sulfuric acid VS
= 0.14007 mg of N

Packaging and storage Preserve in tight containers.

Povidone Iodine Topical Solution
포비돈요오드 액

Povidone Iodine Topical Solution is a liquid of povidone iodine used in an external application. Povidone Iodine Topical Solution contains NLT 85.0% and NMT 120.0% of the labeled amount of iodine (I: 126.90). Povidone Iodine Topical Solution can contain a small amount of ethanol.

Method of preparation Prepare as directed under Liquids, with Povidone Iodine.

Identification (1) Take an amount of Povidone Iodine Topical Solution, equivalent to 50 mg of iodine according to the labeled amount, and add water to make 100 mL. To 1 mL of this solution, add 1 mL of starch TS and 9 mL of water; the resulting solution exhibits an dark blue color.

(2) Transfer 10 mL of Povidone Iodine Topical Solution into an Erlenmeyer flask without touching the inlet, cover the inlet with the filter paper, and moisten the filter paper with 1 drop of starch TS; it does not exhibit a blue color within 60 seconds.

Alcohol content If Povidone Iodine Topical Solution contains ethanol, perform the test according to Method 2 under the Alcohol Determination; Povidone Iodine Topical Solution contains NLT 90.0% and NMT 110.0% of the labeled amount of alcohol.

pH Between 1.5 and 6.5.

Assay Take exactly an amount of Povidone Iodine Topical Solution, equivalent to about 50 mg of iodine (I), transfer into a stoppered Erlenmeyer flask, add water to make NLT 30 mL in total, and titrate with 0.02 mol/L sodium thiosulfate VS (indicator: 3 mL of starch TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.02 mol/L sodium thiosulfate VS
= 2.5380 mg of I

Packaging and storage Preserve in tight containers.

Povidone-Iodine Vaginal Suppositories
포비돈요오드 질좌제

Povidone-Iodine Vaginal Suppositories contain NLT 85.0% and NMT 125.0% of the labeled amount of iodine (I : 126.90).

Method of preparation Prepare as directed under Suppositories, with Povidone-Iodine.

Identification (1) Dissolve Povidone-Iodine Vaginal Suppositories in alcohol to make an alcohol dilution containing 0.05% iodine. Add 1 mL of starch TS and 9 mL of water to 1 mL of this solution; the resulting solution exhibits a deep blue color.

(2) Weigh 10 g of Povidone-Iodine Vaginal Suppositories, put in a 50-mL beaker, while being careful not to get it on the beaker's wall. Cover the mouth of the beaker with a filter paper, and moisten the filter paper with 1 drop of starch TS; the resulting solution does not exhibit a blue color within 60 seconds.

Disintegration Meets the requirements.

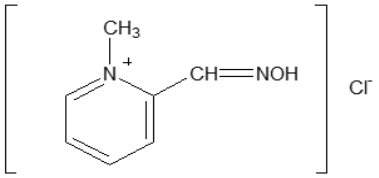
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Povidone-Iodine Vaginal Suppositories, break carefully into small pieces, and mix evenly. Weigh accurately about 40 mg of iodine to put in a 100-mL beaker, add water to make the total volume of NLT 30 mL, and shake to mix until the ointment dissolves. Titrate this solution with 0.02 mol/L sodium thiosulfate VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.02 mol/L sodium thiosulfate VS
= 2.5380 mg of I

Packaging and storage Preserve in tight containers.

Pralidoxime Chloride
프랄리독심염화물



$C_7H_9ClN_2O$: 172.61

[(*E*)-(1-Methylpyridin-2-ylidene)methyl]-oxoazanium chloride [*51-15-0*]

Pralidoxime Chloride contains NLT 97.0% and NMT 102.0% of pralidoxime chloride ($C_7H_9ClN_2$ O), calculated on the dried basis.

Description Pralidoxime Chloride occurs as a white to pale yellow crystalline powder, and is odorless.
It is freely soluble in water.
It is stable in air.

Identification (1) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

(2) Determine the infrared spectra of Pralidoxime Chloride and pralidoxime chloride RS, previously dried, as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit maxima at the same wavenumbers.

(3) An aqueous solution of Pralidoxime Chloride (1 in 10) responds to the Qualitative Analysis for chloride.

Melting point Between 215 and 225 ℃ (with decomposition).

Purity ***Heavy metals*—**Proceed with 1.0 g of Pralidoxime Chloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Loss on drying NMT 2.0% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.5% (1 g).

Assay Weigh accurately about 62.5 mg of Pralidoxime Chloride and dissolve in water to make exactly 50 mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh an appropriate amount of pralidoxime chloride RS and dissolve in water to make a solution containing 1.25 mg per mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 15 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas, A_T and A_S, of pralidoxime chloride for the test solution and the standard solution, respectively.

Amount (mg) of pralidoxime chloride ($C_7H_9ClN_2O$)
$$= C \times \frac{A_T}{A_S} \times 50$$

C: Concentration (mg/mL) of the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column 3 mm to 5 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and tetraethyl ammonium chloride solution (52 : 48).

Flow rate: 1.2 mL/min

System suitability

System performance: Dissolve pyridine-2-aldoxime in water to prepare a solution containing 0.65 mg per mL. To 2 mL of this solution, add 2 mL of a solution of pralidoxime chloride RS containing 1.25 mg per mL and the mobile phase to make 100 mL. Proceed with 15 μL of this solution according to the above conditions; pyridine-2-aldoxime and pralidoxime chloride are eluted in this order with the resolution between their peaks being NLT 4.0, and the number of theoretical plates and symmetry factor are NLT 4000 and NMT 2.5, respectively.

System repeatability: Repeat the test 6 times with 15 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of pralidoxime chloride is NMT 2.0%.

Tetraethylammonium chloride solution—Dissolve 0.17 g of tetraethylammonium chloride in 3.4 mL of diluted phosphoric acid (10 in 100), and add water to make 1000 mL.

Packaging and storage Preserve in well-closed containers.

Pralidoxime Chloride Tablets
프랄리독심염화물 정

Pralidoxime Chloride Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of pralidoxime chloride ($C_7H_9ClN_2O$: 172.61).

Method of preparation Prepare as directed under Tablets, with Pralidoxime Chloride.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Dissolution Perform the test with 1 tablet of Pralidoxime Chloride Tablets at 100 revolutions per minute according to Method 1, using 900 mL of water as the dissolution

medium. Take the dissolved solution after 60 minutes from start of the test, filter, dilute with the water, if necessary and use the solution as the test solution. Separately, weigh accurately an appropriate amount of pralidoxime chloride RS, dissolve in the dissolution medium to make a solution having the same concentration as the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as a control solution, and determine the absorbances at the absorbance maximum wavelength of about 293 nm.
The acceptable dissolution criterion is NLT 55% of Pralidoxime Chloride Tablets dissolved in 60 minutes.

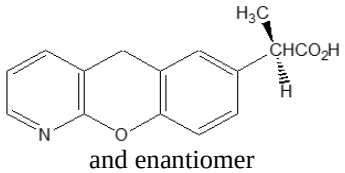
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Hydrocortisone Tablets, and reduce to powder. Take an accurately weighed portion of the powder, equivalent to about 0.25 g of pralidoxime chloride, add 150 mL of water and mechanically swirl for 30 minutes. Add water to make exactly 200 mL, centrifuge this solution, pipet 2 mL of the clear supernatant, add the mobile phase to make exactly 100 mL, and use it as the test solution. Separately, weigh accurately about 50 mg of pralidoxime chloride RS, and add water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Assay of Pralidoxime Chloride.

Amount (mg) of pralidoxime chloride ($C_7H_9ClN_2O$)
= Amount (mg) of pralidoxime chloride RS$\times \frac{A_T}{A_S} \times 5$

Packaging and storage Preserve in well-closed containers.

Pranoprofen
프라노프로펜



and enantiomer

$C_{15}H_{13}NO_3$: 255.27
2-(5*H*-Chromeno[2,3-b]pyridin-7-yl)propanoic acid [*52549-17-4*]

Pranoprofen, when dried, contains NLT 98.5% and NMT 101.0% of pranoprofen ($C_{15}H_{13}NO_3$).

Description Pranoprofen occurs as a white to pale yellowish white crystalline powder.
It is freely soluble in *N*,*N*-dimethylformamide, soluble in acetic acid(100), sparingly soluble in methanol, slightly soluble in acetonitrile, ethanol(95) or acetic anhydride, very slightly soluble in ether, and practically insoluble in water.
A solution of Pranoprofen in *N*,*N*-dimethylformamide (1 in 30) shows no optical rotation.

Identification (1) Dissolve 20 mg each of Pranoprofen and pranoprofen RS in 1 mol/L hydrochloric acid TS to make 100 mL each. To 10 mL each of the these solutions, add water to make 100 mL. Determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy, using 0.1 mol/L hydrochloric acid TS as the blank; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Pranoprofen and pranoprofen RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 186 and 190 ℃.

Purity (1) ***Chloride***—Dissolve 0.5 g of Pranoprofen in 40 mL of methanol, dissolve in 6 mL of dilute nitric acid and water to make 50 mL, and perform the test using this solution as the test solution. Prepare the control solution by adding 40 mL of methanol, 6 mL of dilute nitric acid and water to 0.30 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.021%).

(2) ***Heavy metals***—Proceed with 2.0 g of Pranoprofen according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 50 mg of Pranoprofen in 50 mL of the mobile phase, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area from each solution according to the automatic integration method; the peak area other than the major peak from the test solution is not greater than the peak area of the major peak of each standard solution, and the sum of all peaks is not more than twice the area of major peak from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 275 nm).

Column: A stainless steel column about 6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃

Mobile phase: Dissolve 7.02 g of sodium perchlorate in 1000 mL of water and adjust the pH to 2.5 with perchloric acid. To 2 volumes of this solution,

add 1 volume of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of pranoprofen is about 10 minutes.

System suitability

Detection sensitivity: Adjust the detection sensitivity so that the peak height of pranoprofen obtained from 10 μL of the standard solution is between 10 mm and 20 mm.

System performance: Dissolve 4 mg each of Pranoprofen and ethylparaben in 200 mL of the mobile phase. Proceed with 10 μL of this solution according to the above conditions; pranoprofen and ethylparaben are eluted in this order with the resolution being NLT 2.1.

Time span of measurement: About 3 times the retention time of pranoprofen.

Loss on drying NMT 0.5% (1 g, in vacuum, phosphorus pentoxide, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Pranoprofen, previously dried, dissolve in 70 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 25.527 mg of $C_{15}H_{13}NO_3$

Packaging and storage Preserve in light-resistant, tight containers.

Pranoprofen Syrup
프라노프로펜 시럽

Pranoprofen Syrup contains NLT 93.0% and NMT 107.0% of the labeled amount of pranoprofen ($C_{15}H_{13}NO_3$: 255.27).

Method of preparation Prepare as directed under Syrups, with Pranoprofen.

Identification (1) Take an amount of Pranoprofen Syrup, equivalent to 30 mg of pranoprofen, according to the labeled amount, and add 20 mL of water and 20 mL of ethyl acetate to extract. Take the ethyl acetate layer, dehydrate with anhydrous sodium sulfate, filter, then evaporate the filtrate to dryness in vacuum. Dissolve the residue in 20 mL of sulfuric acid, take 2 mL of the resulting solution, and heat under direct flame; the solution turns brown then a dark reddish purple. Separately, take 2 mL of the solution dissolved in sulfuric acid, and add 3 drops of potassium bichromate TS; the solution exhibits a reddish yellow color.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

pH Between 4.0 and 6.0.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Take exactly an amount of Pranoprofen Syrup, equivalent to about 75 mg of pranoprofen ($C_{15}H_{13}NO_3$), and add the mobile phase to make exactly 100 mL. Pipet 2 mL of this solution, add 5 mL of the internal standard solution, then add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 75 mg of pranoprofen RS, previously dried (in vacuum, phosphorus pentoxide, 4 hours), and proceed in the same manner as the test solution. Use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, of pranoprofen to that of internal standard, respectively.

Amount (mg) of pranoprofen ($C_{15}H_{13}NO_3$)
= Amount (mg) of pranoprofen RS × (Q_T / Q_S)

Internal standard solution—A solution of dimethyl phthalate in the mobile phase (1 in 870).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 278 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of phosphoric acid (1 in 600) and acetonitrile (3 : 2)

Flow rate: 2 mL/min

System suitability

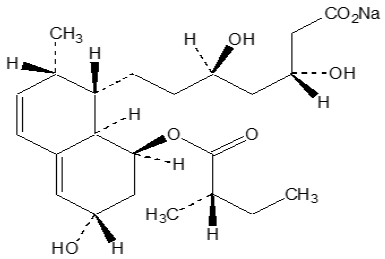
System performance: Proceed with 20 μL of the standard solution according to the above conditions; pranoprofen and the internal standard are eluted in this order with the resolution being NLT 2.

System suitability

System repeatability: Repeat the test 6 times with 20 μL each of pranoprofen standard solution according to the above conditions; the relative standard deviation is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Pravastatin Sodium
프라바스타틴나트륨



$C_{23}H_{35}NaO_7$: 446.51
Sodium(3*R*,5*R*)-3,5-dihydroxy-7-((1*S*,2*S*,6*S*,8*S*,8a*R*)-6-hydroxy-2-methyl-8-(((*S*)-2-methylbutanoyl)oxy)-1,2,6,7,8,8a-hexahydro-naphthalen-1-yl)heptanoate
[*81131-70-6*]

Pravastatin Sodium contains NLT 98.5% and NMT 101.0% of pravastatin sodium ($C_{23}H_{35}NaO_7$), calculated on the anhydrous and solvent-free basis.

Description Pravastatin Sodium occurs as a white or yellowish white powder or crystalline powder.
It is freely soluble in water or methanol, and soluble in ethanol(99.5).
It is hygroscopic.

Identification (1) Determine the absorption spectra of aqueous solutions of Pravastatin Sodium and pravastatin sodium RS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectrum of Pravastatin Sodium as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; it exhibits absorption at the wavenumbers of about 2970 cm^{-1}, 2880 cm^{-1}, 1727 cm^{-1} and 1578 cm^{-1}.

(3) A solution of Pravastatin Sodium (1 in 10) responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: +153° to +159° (on the anhydrous and solvent-free basis, 0.1 g, water, 20 mL, 100 mm).

pH Dissolve 1.0 g of Pravastatin Sodium in 20 mL of freshly boiled and cooled water; the pH of this solution is between 7.2 and 8.2.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Pravastatin Sodium according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Dissolve 0.1 g of Pravastatin Sodium in 100 mL of a mixture of water and methanol (11 : 9) and use this solution as the test solution. Pipet 10 mL of this solution, and add a mixture of water and methanol (11 : 9) to make exactly 100 mL. Pipet 5 mL of this solution, add a mixture of water and methanol (11 : 9) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution according to the automatic integration method; the peak area other than pravastatin from the test solution is not greater than 0.2 times the peak area of pravastatin from the standard solution. Also, the sum of peak area other than the major peak obtained from the test solution is not greater than the area of the major peak from the standard solution. Preserve the test solution and the standard solution at 15 ℃ or below.

Operating conditions

For the detector, column, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

Test for required detectability: Pipet 5 mL of the standard solution, and add a mixture of water and methanol (11 : 9) to make exactly 50 mL. Confirm that the peak area of pravastatin obtained from 10 μL of this solution is equivalent to 7% to 14% of that from the standard solution.

System performance: Dissolve 5 mg of pravastatin sodium in 50 mL of a mixture of water and methanol (11 : 9). Perform the test with 10 μL of this solution according to the above conditions; the number of theoretical plate and the symmetry factor of the peak of pravastatin are NLT 3500 and NMT 1.6, respectively.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of pravastatin is NMT 2.0%.

Time span of measurement: About 2.5 times the retention time of pravastatin after the solvent peak.

Water NMT 4.0% (0.5 g, volumetric titration, direct titration).

Assay Weigh accurately about 0.1 g of Pravastatin Sodium, and dissolve in a mixture of water and methanol (11 : 9) to make exactly 100 mL. Pipet 10 mL of this solution, add exactly 10 mL of the internal standard solution, add a mixture of water and methanol (11 : 9) to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 30 mg of pravastatin 1,1,3,3-tetramethylbutylammonium RS (previously determine the water with 0.5 g by direct titration in volumetric titration), and dissolve in a mixture of water and methanol (11 : 9) to make exactly 25 mL. Pipet 10 mL of this solution, add 10 mL of the internal standard solution exactly, add a mixture of water and methanol (11 : 9) to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak areas of pravastatin to that of the internal standard, Q_T and Q_S.

Amount (mg) of pravastatin sodium ($C_{23}H_{35}NaO_7$)

$$= W_S \times \frac{Q_T}{Q_S} \times 4 \times 1.0518$$

W_S: Amount (mg) of pravastatin in the amount of pravastatin 1,1,3,3-tetramethylbutylammonium RS taken, calculated on the anhydrous basis

Internal standard solution—A solution of ethyl p-hydroxybenzoate in a mixture of water and methanol (11 : 9) (3 in 4000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 238 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: A mixture of water, methanol, acetic acid(100) and triethylamine (550 : 450 : 1 : 1).

Flow rate: Adjust the flow rate so that the retention time of pravastatin is about 21 minutes.

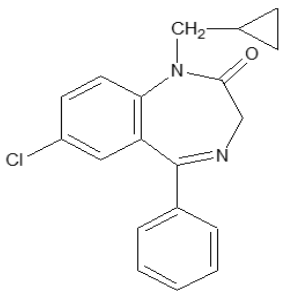
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the internal standard and pravastatin are eluted in this order with the resolution being NLT 10.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area ratios of pravastatin to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Prazepam
프라제팜



$C_{19}H_{17}ClN_2O$: 324.80

7-Chloro-1-(cyclopropylmethyl)-5-phenyl-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one [*2955-38-6*]

Prazepam, when dried, contains NLT 98.5% and NMT 101.0% of prazepam ($C_{19}H_{17}ClN_2$ O).

Description Prazepam occurs as white to pale yellow crystals or a crystalline powder and is odorless.
It is freely soluble in acetone, soluble in acetic anhydride, sparingly soluble in anhydrous ethanol or ether and practically insoluble in water.

Identification (1) Dissolve 10 mg of Prazepam in 3 mL of sulfuric acid and examine under ultraviolet light (wavelength of 365 nm); the resulting solution exhibits a grayish blue fluorescence.

(2) Dissolve 10 mg of each of Prazepam and prazepam RS in 1000 mL of a solution of sulfuric acid in anhydrous ethanol (3 in 1000), and determine the absorption spectra as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Prazepam and prazepam RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) Perform the test with Prazepam as directed under the Flame Coloration (2); it exhibits a green color.

Melting point Between 145 and 148 ℃.

Purity (1) ***Chloride***—Take 1.0 g of Prazepam, add 50 mL of water, and allow to stand for 1 hour with occasional shaking, and filter. Pipet 20 mL of the filtrate, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 40 mL of 0.01 mol/L hydrochloric acid (NMT 0.036%).

(2) ***Sulfate***—Take 20 mL of the filtrate obtained from (1) and add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid (NMT 0.048%).

(3) ***Heavy metal***—Proceed with 2.0 g of Prazepam according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Proceed with 1.0 g of Prazepam according to Method 3 and perform the test (NMT 2 ppm).

(5) ***Related substances***—Dissolve 0.40 g of Prazepam in 10 mL of acetone and use this solution as the test solution. Pipet 1 mL of this solution and add acetone to make exactly 20 mL. Pipet 1 mL of this solution, add acetone to make exactly 25 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform and acetone (9 : 1) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test

solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.2% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Prazepam, previously dried, dissolve in 60 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid
= 32.480 mg of $C_{19}H_{17}ClN_2O$

Packaging and storage Preserve in tight containers.

Prazepam Tablets
프라제팜 정

Prazepam Tablets contain NLT 93.0% and NMT 107.0% of prazepam ($C_{19}H_{17}ClN_2O$: 324.80).

Method of preparation Prepare as directed under Tablets, with Prazepam.

Identification (1) Weigh an amount of Prazepam Tablets, previously powdered, equivalent to 50 mg of prazepam according to the labeled amount, add 25 mL of acetone, shake to mix, and then filter. Take 5 mL of the filtrate, evaporate to dryness on a steam bath, and dissolve the residue in 3 mL of sulfuric acid. With this solution, perform the test as directed under the Identification (1) of Prazepam.

(2) Take a portion of powdered Prazepam Tablets, equivalent to 20 mg of prazepam according to the labeled amount, add 200 mL of a solution of sulfuric acid in dehydrated ethanol (3 in 1000), shake well and filter. To 5 mL of the filtrate and add a solution of sulfuric acid in dehydrated ethanol (3 in 1000) to make 50 mL, and determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry: it exhibits maxima between 241 nm and 245 nm, between 283 nm and 287 nm and between 363 nm and 367 nm and minima between 263 nm and 267 nm and between 334 nm and 338 nm.

Dissolution Perform the test with 1 tablet of Fluoxymesterone Tablets at 100 revolutions per minute according to Method 1, using 900 mL of 0.1 mol/L hydrochloric acid TS as the dissolution medium. Take 20 mL of the dissolved solution 30 minutes after starting the test, and filter through a membrane filter with a pore size of NMT 0.8 μm. Discard the first 10 mL of the filtrate, take exactly *V* mL of the subsequent filtrate, add 0.1 mol/L hydrochloric acid TS to make exactly *V'* mL of a solution containing about 5 μg of prazepam ($C_{19}H_{17}ClN_2O$) per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 5 mg of prazepam RS, previously dried at 105 ℃ for 2 hours, dissolve in 200 mL of 0.1 mol/L hydrochloric acid TS, shake to mix, and if necessary, sonicate to dissolve. Then, add 0.1 mol/L hydrochloric acid TS to make exactly 1000 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 240 nm as directed under the Ultraviolet-visible Spectroscopy.
The acceptable dissolution criterion is NLT 80% of Prazepam Tablets dissolved in 30 minutes.

Dissolution rate (%) of the labeled amount of prazepam ($C_{19}H_{17}ClN_2O$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{90}{C}$$

*W*s: Amount (mg) of the reference standard
C: Labeled amount (mg) of prazepam ($C_{19}H_{17}ClN_2O$) in 1 tablet

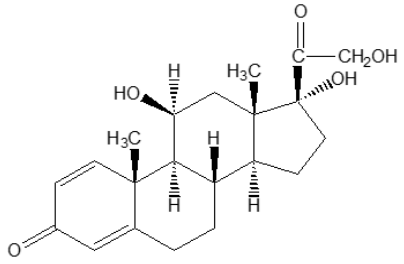
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Prazepam Tablets, and powder. Weigh accurately an amount of the powder, equivalent to about 50 mg of prazepam ($C_{19}H_{17}ClN_2O$), add 30 mL of acetone, shake well to mix, and then centrifuge. Take the clear supernatant. Repeat the same procedure 2 times using 30 mL of acetone, combine all the clear supernatant, and evaporate to dryness on a steam bath. Dissolve the residue in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.02 mol/L of perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.02 mol/L perchloric acid VS
= 6.496 mg of $C_{19}H_{17}ClN_2O$

Packaging and storage Preserve in tight containers.

Prednisolone
프레드니솔론



$C_{21}H_{28}O_5$: 360.44
(8*S*,9*S*,10*R*,11*S*,13*S*,14*S*,17*R*)-11,17-dihydroxy-17-(2-

hydroxyacetyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-3-one [*50-24-8*]

Prednisolone, when dried, contains NLT 97.0% and NMT 102.0% of prednisolone ($C_{21}H_{28}O_5$).

Description Prednisolone occurs as a white, crystalline powder.
It is soluble in methanol or ethanol(95), slightly soluble in ethyl acetate or chloroform, and very slightly soluble in water.

Melting point—About 235 ℃ (with decomposition).

Identification (1) To 2 mg of Prednisolone, add 2 mL of sulfuric acid; in 2 to 3 minutes, the resulting solution exhibits a deep red color with no fluorescence. Add 10 mL of water carefully to this solution; the color of the resulting solution fades and a gray, flocculent precipitate is formed.

(2) Determine the infrared spectra of Prednisolone and prednisolone RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the spectra, dissolve each in ethyl acetate, evaporate to dryness and perform the test in the same manner with the residues.

Optical rotation $[\alpha]_D^{20}$: Between +113° and +119° (0.2 g after drying, ethanol(95), 20 mL, 100 mm).

Purity (1) ***Selenium*—**To 0.10 g of Prednisolone, add 0.5 mL of a mixture of perchloric acid and sulfuric acid (1 : 1) and 2 mL of nitric acid. Then, heat the mixture until the brown gas no longer evolves and the reaction solution turns clear and exhibits a pale yellow color. After cooling, add 4 mL of nitric acid to this solution, add water to make exactly 50 mL, and use this solution as the test solution. Separately, pipet 3 mL of standard selenium stock solution, add 0.5 mL of a mixture of perchloric acid and sulfuric acid (1 : 1), 6 mL of nitric acid and water to make exactly 50 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Atomic Absorption Spectroscopy according to the following conditions, and determine the absorbance A_T for the test solution and A_S for the standard solution when the reading of the display/recording unit rapidly rises and, then, reaches a plateau; A_T is smaller than A_S (NMT 30 ppm).
This test is performed using a hydride generator and a heating cell.

Lamp: Selenium hollow-cathode lamp
Wavelength: 196.0 nm
Atomizing temperature: When an electric furnace is used, the temperature is set at about 1000 ℃.
Carrier gas: Nitrogen or argon

(2) ***Related substances*—**Weigh about 20.0 mg of Prednisolone, add exactly 2 mL of a mixture of methanol and chloroform (1 : 1), and use this solution as the test solution. Separately, weigh accurately 20.0 mg of hydrocortisone RS and 10.0 mg of prednisolone acetate RS, dissolve in a mixture of methanol and chloroform (1 : 1) to make exactly 100 mL, and use this solution as the standard solution (1) and the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution, the standard solution (1), and the standard solution (2) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of acetone, toluene, and diethylamine (55 : 45 : 2) as the developing solvent to a distance of about 15 cm, and air-dry the plate (However, do not put a filter paper into the developing chamber). Spray evenly alkaline blue tetrazolium TS; the spots obtained from the test solution at locations equivalent to the spots from the standard solution (1) and the standard solution(2) are not more intense than the spots obtained from the standard solution (1) and the standard solution (2). Also, spots other than the principal spot and those of hydrocortisone and prednisolone acetate do not appear in the test solution.

Loss on drying NMT 1.0% (0.5 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately about 25 mg each of Prednisolone and prednisolone RS, previously dried, dissolve each in 50 mL of methanol, and add exactly 25 mL each of the internal standard solution and methanol to make 100 mL. Take 1 mL each of these solutions, add the mobile phase to make respectively 10 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of prednisolone to the peak area of internal standard of each solution, respectively.

$$\text{Amount (mg) of prednisolone } (C_{21}H_{23}O_5) = \text{Amount (mg) of prednisolone RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of methyl *p*-hydroxybenzoate in methanol (1 in 2000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 247 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with fluorosilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: A mixture of water and methanol (13 : 7).

Flow rate: Adjust the flow rate so that the retention

time of prednisolone is about 15 minutes.

System suitability

System performance: Dissolve 25 mg of Prednisolone and 25 mg of hydrocortisone in 100 mL of methanol. To 1 mL of this solution, add the mobile phase to make 10 mL. Proceed with 25 μL of this solution according to the above conditions; hydrocortisone and prednisolone are eluted in this order with the resolution being NLT 1.5.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratios of prednisolone to the peak area of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Prednisolone Tablets
프레드니솔론 정

Prednisolone Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of prednisolone ($C_{21}H_{28}O_5$: 360.44).

Method of preparation Prepare as directed under Tablets, with Prednisolone.

Identification (1) Weigh an amount of Prednisolone Tablets, previously powdered, equivalent to 50 mg of prednisolone according to the labeled amount, add 10 mL of chloroform, shake to mix for 15 minutes, filter, and evaporate the filtrate to dryness on a steam bath. Perform the test with the residue, previously dried at 105 ℃ for 1 hour, as directed under the Identification (1) of Prednisolone.

(2) Determine the infrared spectra of the residue from (1) and prednisolone RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between these spectra, dissolve each in ethyl acetate, evaporate ethyl acetate, and perform the test with the residue in the same manner.

Dissolution Perform the test with 1 tablet of Prednisolone Tablets at 100 revolutions per minute according to Method 2, using 900 mL of water as the dissolution medium. Take NLT 20 mL of the dissolution medium 20 minutes after starting the test and filter through a membrane filter with a pore size of NMT 0.8 μm. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 10 mg of prednisolone RS, previously dried at 105 ℃ for 3 hours, and dissolve in ethanol(95) to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength at about 242 nm, as directed under the Ultraviolet-visible Spectroscopy.

It meets the requirements if the dissolution rate of Prednisolone Tablets in 20 minutes is NLT 70%.

$$\text{Dissolution rate (\%) of the labeled amount of prednisolone } (C_{21}H_{23}O_5) = W_S \times \frac{A_T}{A_S} \times \frac{45}{C}$$

Ws: Amount (mg) of the reference standard

C: Labeled amount (mg) of prednisolone ($C_{21}H_{28}O_5$) in 1 tablet

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following procedure.

Take 1 tablet of Prednisolone Tablets, and shake to mix with 10 mL of water until the tablet is disintegrated. Next, add 50 mL of methanol, shake for 30 minutes to mix, then add methanol to make exactly 100 mL, and centrifuge. Pipet χ mL of the clear supernatant, add methanol to make *V* mL of a solution containing about 10 μg of prednisolone ($C_{21}H_{28}O_5$) per mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of prednisolone RS, previously dried at 105 ℃ for 3 hours, dissolve in 10 mL of water and 50 mL of methanol, and then add methanol to make exactly 100 mL. Pipet 5 mL of this solution, add methanol to make 50 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 242 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) prednisolone } (C_{21}H_{23}O_5) = \text{Amount (mg) of prednisolone RS} \times \frac{A_T}{A_S} \times \frac{V}{10} \times \frac{1}{x}$$

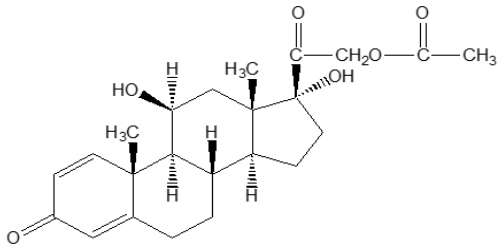
Assay Weigh accurately the mass of NLT 20 tablets of Prednisolone Tablets, and powder using an agate mortar. Weigh accurately a portion of the powder, equivalent to about 5 mg of prednisolone ($C_{21}H_{28}O_5$), add 1 mL of water, and shake gently. Then, add exactly 5 mL of the internal standard solution, add 15 mL of methanol, and shake vigorously for 20 minutes to mix. To 1.0 mL of this solution add the mobile phase to make exactly 10 mL, and filter through a membrane filter with a pore size NMT 0.45 μm. Discard the first 3 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 25 mg of prednisolone RS, previously dried at 105 ℃ for 3 hours, dissolve in 50 mL of methanol, add exactly 25 mL of the internal standard solution, and add methanol to make 100 mL. To 1 mL of this solution, add the mobile phase to make 10 mL, and use this solution as the standard solution. Perform the test as directed under the Assay of Prednisolone.

$$\text{Amount (mg) prednisolone } (C_{21}H_{23}O_5) = \text{Amount (mg) of prednisolone RS} \times \frac{Q_T}{Q_S} \times \frac{1}{5}$$

Internal standard solution—A solution of methyl parahydoxybenzoate in methanol (1 in 2000).

Packaging and storage Preserve in tight containers.

Prednisolone Acetate
프레드니솔론아세테이트



$C_{23}H_{30}O_6$: 402.48

2-((8*S*,9*S*,10*R*,11*S*,13*S*,14*S*,17*R*)-11,17-Dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl acetate [*52-21-1*]

Prednisolone Acetate, when dried, contains NLT 96.0% and NMT 102.0% of prednisolone acetate ($C_{23}H_{30}O_6$).

Description Prednisolone Acetate occurs as a white crystalline powder.
It is slightly soluble in methanol, ethanol(95), ethanol(99.5) or chloroform, and practically insoluble in water.

Melting point—About 235 ℃ (with decomposition).

Identification (1) To 2 mg of Prednisolone Acetate, add 2 mL of sulfuric acid; in 2 to 3 minutes, the resulting solution exhibits a deep red color and a gray, flocculent precipitate is produced.

(2) Determine the infrared spectra of Prednisolone Acetate and prednisolone acetate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the two spectra, dissolve each in ethanol(99.5), evaporate the ethanol(99.5), and perform the test in the same manner with the residues.

Optical rotation $[\alpha]_D^{20}$: Between +128° and +137° (after drying, 70 mg, methanol, 20 mL, 100 mm).

Purity ***Related substances***—Dissolve 0.20 g of Prednisolone Acetate in 10 mL of a mixture of chloroform and methanol (9 : 1), and use this solution as the test solution. Separately, weigh 20 mg each of prednisolone, cortisone acetate and hydrocortisone acetate, and dissolve in exactly 10 mL of a mixture of chloroform and methanol (9 : 1). Pipet 1 mL of this solution, add a mixture of chloroform and methanol (9 : 1) to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of dichloromethane, ether, methanol and water (385 : 75 : 40 : 6) as the developing solvent to a distance of about 15 cm and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the spots obtained from the test solution corresponding to those from the standard solution is not more intense than that obtained from the standard solution. Also, any spot other than the principal spot and the spots of prednisolone, cortisone acetate and hydrocortisone acetate do not appear from the test solution.

Loss on drying NMT 1.0% (0.5 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately about 10 mg each of Prednisolone Acetate and prednisolone acetate RS, previously dried, dissolve in 60 mL of methanol, add exactly 2 mL each of the internal standard solution, and add methanol to make exactly 100 mL. Use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution according to the following conditions as directed under the Liquid Chromatography, and calculate the peak height ratios, Q_T and Q_S, of prednisolone acetate to that of the peak height of the internal standard.

$$\text{Amount (mg) prednisolone acetate } (C_{23}H_{30}O_6) = \text{Amount (mg) of prednisolone acetate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of butylparaben in methanol (3 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: A mixture of water and acetonitrile (3 : 2).

Flow rate: Adjust the flow rate so that the retention time of prednisolone acetate is about 10 minutes.

System suitability

System performance: Proceed with 10 mL of the standard solution according to the above conditions; prednisolone acetate and the internal standard are eluted in this order with the resolution being NLT 10.

System repeatability: Repeat the test 6 times with 10 mL each of the standard solution according to the above conditions; the relative standard deviation of the

peak height ratios of prednisolone acetate to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Prednisolone Sodium Succinate for Injection
주사용 프레드니솔론숙시네이트나트륨

Prednisolone Sodium Succinate for Injection is a preparation for injection which is reconstituted before use. Prednisolone Sodium Succinate for Injection contains NLT 72.4% and NMT 83.2% of prednisolone sodium succinate ($C_{25}H_{31}NaO_8$: 482.51) and the equivalent of NLT 90.0% and NMT 110.0% of the labeled amount of prednisolone ($C_{21}H_{28}O_5$: 360.44).

The amount of Prednisolone Sodium Succinate for Injection is labeled as the amount of prednisolone ($C_{21}H_{28}O_5$)

Method of preparation Prepare as directed under Injections with Prednisolone Succinate, adding dried sodium carbonate or sodium hydroxide. Prednisolone Sodium Succinate for Injection contains a suitable buffering agent.

Description Prednisolone Sodium Succinate for Injection occurs as a white powder or light, porous mass.
It is freely soluble in water.
It is hygroscopic.

Identification (1) Add 2 mL of sulfuric acid to 2 mg of Prednisolone Sodium Succinate for Injection; the solution exhibits a dark red color after 2 to 3 minutes and does not exhibit fluorescence. To this solution add 10 mL of water cautiously: the color disappears and a gray, flocculent precipitate is formed.

(2) Dissolve 10 mg of Prednisolone Sodium Succinate for Injection in 1 mL of methanol, add 1 mL of Fehling's TS and heat; an orange to red precipitate is formed.

(3) Dissolve 0.1 g of Prednisolone Sodium Succinate for Injection in 2 mL of sodium hydroxide TS, allow to stand for 10 minutes and filter. Filter the precipitate, add 1 mL of dilute hydrochloric acid to the filtrate and shake to mix, filter as needed, adjust the pH to about 6 by adding diluted ammonia TS (1 in 10), and add 2 to 3 drops of iron(III) chloride TS; a brown precipitate is formed.

(4) Prednisolone Sodium Succinate for Injection responds to the Qualitative Analysis (1) for sodium salt.

pH Dissolve 1 g of Prednisolone Sodium Succinate for Injection in 40 mL of water; the pH of this solution is between 6.5 and 7.2.

Purity ***Clarity and color of solution***—Dissolve 0.25 g of Prednisolone Sodium Succinate for Injection in 10 mL of water; the solution is clear and colorless.

Loss on drying NMT 2.0% (0.15 g, in vacuum, phosphorus pentoxide, 60 ℃, 3 hours).

Sterility Meets the requirements.

Bacterial endotoxins Less than 2.4 EU per mg of prednisolone.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Take a number of Prednisolone Sodium Succinate for Injection equivalent to about 0.10 g of prednisolone ($C_{21}H_{28}O_5$), dissolve the contents in diluted methanol (1 in 2), and put in a 100-mL volumetric flask. Wash each container with diluted methanol (1 in 2), combine the washings in a volumetric flask, then add diluted methanol (1 in 2) to make exactly 100 mL. Pipet 4 mL of this solution, and add diluted methanol (1 in 2) to make exactly 50 mL. Pipet 5.0 mL of this solution, add exactly 5 mL of the internal standard solution, shake to mix, and use this solution as the test solution. Separately, weigh accurately about 25 mg of prednisolone succinate RS (previously dried under vacuum at 60 ℃ for 6 hours in a phosphorus pentoxide desiccator) and dissolve in methanol to make exactly 25 mL. Pipet 5 mL of this solution, and add diluted methanol (1 in 2) to make exactly 50 mL. Pipet 5 mL of this solution, add exactly 5 mL of the internal standard solution, mix by shaking and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak area of prednisolone succinate to that of the internal standard Q_T and Q_S.

$$\text{Amount (mg) of prednisolone sodium succinate } (C_{25}H_{31}NaO_8) = \text{Amount (mg) of prednisolone succinate RS } (C_{25}H_{32}O_8) \times \frac{Q_T}{Q_S} \times 5 \times 1.048$$

$$\text{Amount (mg) of prednisolone } (C_{21}H_{28}O_5) = \text{Amount (mg) of prednisolone succinate RS } (C_{25}H_{32}O_8) \times \frac{Q_T}{Q_S} \times 5 \times 0.783$$

Internal standard solution—A solution of propyl p-hydroxybenzoate in diluted methanol (1 in 2) (1 in 25000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octa-

decylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 0.32 g of tetra n-butylammonium bromide, 3.22 g of sodium monohydrogen phosphate and 6.94 g of potassium dihydrogen phosphate in 1000 mL of water. To 840 mL of this solution, add 1160 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of prednisolone succinate is about 15 minutes.

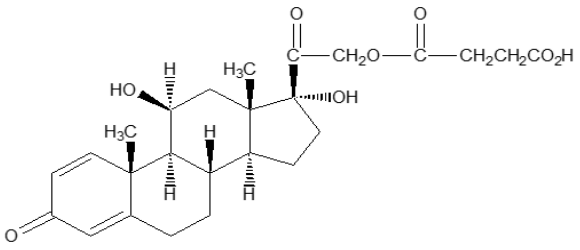
System suitability

When the procedure is run with 10 μL of the standard solution under the above operating conditions, prednisolone succinate and the internal standard are eluted in this order with the resolution between their peaks being NLT 6.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak area ratios of prednisolone succinate to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in hermetic containers.

Prednisolone Succinate
프레드니솔론숙시네이트



$C_{25}H_{32}O_8$: 460.52

4-(2-((8*S*,9*S*,10*R*,11*S*,13*S*,14*S*,17*R*)-11,17-dihydroxy-10,13-dimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a]phenanthren-17-yl)-2-oxoethoxy)-4-oxobutanoic acid [*2920-86-7*]

Prednisolone Succinate, when dried, contains NLT 97.0% and NMT 103.0% of prednisolone succinate ($C_{25}H_{32}O_8$).

Description Prednisolone Succinate occurs as a white, fine, crystalline powder and is odorless.

It is freely soluble in methanol, soluble in ethanol(95), and very slightly soluble in water or ether.

Melting point—About 205 °C (with decomposition).

Identification (1) To 2 mg of Prednisolone Succinate, add 2 mL of sulfuric acid; in 2 to 3 minutes, the resulting solution exhibits a deep red color with no fluorescence. Add 10 mL of water carefully to this solution; the deep red color of the solution fades and a gray, flocculent precipitate is produced.

(2) Determine the infrared spectra of Prednisolone Succinate and prednisolone succinate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +114° and +120° (67 mg, after drying, methanol, 10 mL, 100 mm).

Purity ***Related substances***—Weigh 0.10 g of Prednisolone Succinate, dissolve in methanol to make exactly 10 mL, and use this solution as the test solution. Separately, weigh 30 mg of prednisolone and dissolve in methanol to make exactly 10 mL, pipet 1 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate and ethanol(95) (2 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, phosphorus pentoxide, 60 °C, 6 hours).

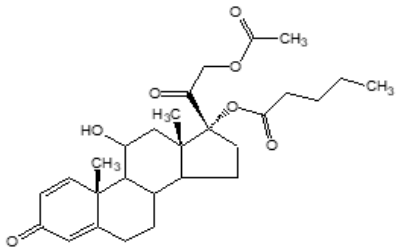
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 10 mg each of Prednisolone Succinate and prednisolone succinate RS, previously dried, and dissolve by adding methanol to make exactly 100 mL. Pipet 5 mL each of these solutions, add methanol to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 242 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of prednisolone succinate } (C_{25}H_{32}O_8) = \text{Amount (mg) of prednisolone succinate RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers.

Prednisolone Valeroacetate
프레드니솔론발레로아세테이트



$C_{28}H_{38}O_7$: 486.60

[(8*S*,9*S*,10*R*,11*S*,13*S*,14*S*,17*R*)-17-(2-Acetyloxyacetyl)-11-hydroxy-10,13-dimethyl-3-oxo-7,8,9,11,12,14,15,16-octahydro-6*H*-cyclopenta[a]phenanthren-17-yl] pentanoate, [*72064-79-0*]

Prednisolone Valeroacetate, when dried, contains NLT 98.0% and NMT 101.0% of prednisolone valeroacetate ($C_{28}H_{38}O_7$).

Description Prednisolone Valeroacetate occurs as a white, crystalline powder. It is odorless.
It is freely soluble in acetone, ethyl acetate, and chloroform, soluble in methanol or ethanol(99.5), slightly soluble in ether, and practically insoluble in water or hexane.

Identification (1) Add 4 mL of isoniazid TS to 1 mL of a solution of Prednisolone Valeroacetate in methanol (1 in 10000), and heat on a steam bath for 2 minutes; the resulting solution exhibits a yellow color.

(2) Add 2 mL of sulfuric acid to 2 mg of Prednisolone Valeroacetate; the resulting solution gradually exhibits a yellow or yellowish brown color without fluorescence.

(3) Dissolve 10 mg of Prednisolone Valeroacetate in 2 mL of methanol, add 1 mL of Fehling's TS, and heat; an orange or red precipitate is formed.

(4) Add 2 mL of sodium hydroxide-ethanol TS to 50 mg of Prednisolone Valeroacetate, and heat on a steam bath for 5 minutes. After cooling, add 2 mL of diluted sulfuric acid (2 in 7), and heat slowly for 1 minute; the odor of ethyl valerate is perceptible.

(5) Weigh accurately 0.3 g of Prednisolone Valeroacetate, and dissolve in 2000 mL of methanol. Take 10 mL of this solution, add methanol to make exactly 100 mL, and determine the absorption spectrum of the resulting solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 242 nm and 244 nm.

(6) Determine the infrared spectra of 1 mg each of Prednisolone Valeroacetate and prednisolone valeroacetate RS, previously dried at 105 ℃ for 3 hours, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the spectra, dissolve each in acetone, respectively, evaporate to dryness, and perform the test in the same manner with the residues.

Melting point Between 184 and 188 ℃.

Optical rotation $[\alpha]_D^{20}$: Between +45° and +49° (after drying, 0.1 g, ethanol(95), 10 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Add 0.2 g of Prednisolone Valeroacetate to 10 mL of ethanol(99.5), and warm to dissolve; the solution is colorless and clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Prednisolone Valeroacetate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Prednisolone Valeroacetate according to Method 3, and perform the test (NMT 2 ppm).

(4) ***Other steroids*—**Weigh 0.1 g of Prednisolone Valeroacetate, dissolve in methanol to make exactly 10 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of n-hexane, ethyl acetate and methanol (6 : 5 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly alkaline blue tetrazolium TS on the plate; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (0.5 g, 105 ℃, 3 hours).

Assay Weigh accurately about 50 mg each of Prednisolone Valeroacetate and prednisolone valeroacetate RS, previously dried, dissolve in methanol to make exactly 50 mL. Pipet 5 mL each of these solutions, add exactly 5 mL each of the internal standard solution, add methanol to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and calculate the peak area ratios, Q_T and Q_S, of prednisolone valeroacetate to that of the internal standard.

$$\text{Amount (mg) of prednisolone valeroacetate } (C_{28}H_{38}O_7) = \text{Amount (mg) of prednisolone valeroacetate RS (mg)} \times (Q_T / Q_S)$$

Internal standard solution—A solution of dexamethasone acetate in methanol (1 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 243 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 ℃.

Mobile phase: A mixture of methanol and water (10 : 3).

Flow rate: Adjust the flow rate so that the retention time of prednisolone valeroacetate is about 10 minutes.

System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; the internal standard and prednisolone valeroacetate are eluted in this order with the resolution being NLT 8.

Packaging and storage Preserve in tight containers.

Prednisolone Valeroacetate Cream
프레드니솔론발레로아세테이트 크림

Prednisolone Valeroacetate Cream contains NLT 90.0% and NMT 110.0% of the labeled amount of prednisolone valeroacetate ($C_{28}H_{38}O_7$: 486.60).

Method of preparation Prepare as directed under Creams, with Prednisolone Valeroacetate.

Identification (1) Take 20 mL of the test solution obtained from the Assay and evaporate to dryness on a steam bath under a nitrogen atmosphere. Dissolve the residue in 1 mL of methanol, and use this solution as the test solution. Separately, weigh 6 mg of prednisolone valeroacetate RS, dissolve in 10 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution onto a plate made of silica gel with fluorescence indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, ethyl acetate and methanol (50 : 10 : 3) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray the plate evenly with alkaline blue tetrazolium TS; the R_f value and the color of the spots obtained from the test solution and the standard solutions are the same.

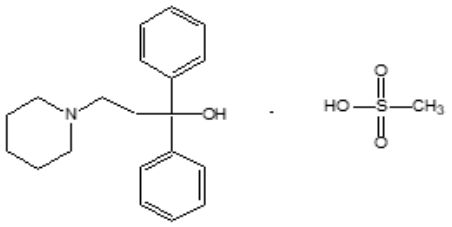
(2) The test solution from the Assay exhibits a yellow color, and measure the absorption spectra as directed under Ultraviolet-visible Spectroscopy using the blank test solution in the Assay as the control solution; it exhibit a maximum at the wavelength of around 406 nm.

Assay Weigh accurately an amount of Prednisolone Valeroacetate Cream, equivalent to about 1.5 mg of prednisolone valeroacetate ($C_{28}H_{38}O_7$), add 10 mL of hexane and 10 mL of a mixture of methanol and water (9 : 1), shake well to mix, then centrifuge. Take the methanol and water mixture layer, then extract the hexane layer again in the same manner using 10 mL and 5 mL of a mixture of methanol and water (9 : 1), then combine the methanol and water mixture layer. To this solution, add 10 mL of water and extract with 10 mL and 5 mL of chloroform, combine the extracts, add 10 mL of water, shake well to mix, and then centrifuge. Discard the water layer, take the chloroform layer, and concentrate the chloroform layer in vacuum on a steam bath. Dissolve the residue in methanol and pipet 25 mL, and use this solution as the test solution. Centrifuge, if necessary, and use the clear supernatant as the test solution. Separately, weigh accurately about 30 mg of prednisolone valeroacetate RS, and add methanol to make exactly 50 mL. Pipet 1 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the standard solution. Pipet 2 mL each of the standard solution and the test solution, add 7.0 mL of isoniazid TS, respectively, seal, and heat for 60 minutes on a steam bath maintained at 50 ℃. After cooling, add methanol to make exactly 10 mL. Separately, determine the absorbances, A_T and A_S, at the wavelength of 406 nm as directed under Ultraviolet-visible Spectroscopy, using a solution prepared by proceeding with methanol in the same manner as the control solution.

Amount (mg) of prednisolone valeroacetate ($C_{28}H_{38}O_7$)
= Amount (mg) of prednisolone valeroacetate RS
× (A_T / A_S) × 0.05

Packaging and storage Preserve in tight containers.

Pridinol Mesilate
프리디놀메실산염



$C_{20}H_{25}NO \cdot CH_3SO_3H$: 391.52

1,1-Diphenyl-1-piperidinepropanol·methanesulfonate (1:1), [*6856-31-1*]

Pridinol Mesilate, when dried, contains NLT 98.0% and NMT 101.0% of pridinol mesilate ($C_{20}H_{25}NO \cdot CH_4O_3S$).

Method of preparation If there is any possibility of alkyl methanesulfonate esters (methyl, ethyl, isopropyl, etc.) to be introduced as potential impurities by the manufacturing process of Pridinol Mesilate, take caution with starting materials, manufacturing process, and intermediate materials and control them to minimize the residue of impurities in consideration of risk assessment results. If necessary, the manufacturing process may be verified by the test data proving that no quality risk exists in the final drug substance.

Description Pridinol Mesilate occurs as a white fine power with a faint characteristic odor.

It is freely soluble in chloroform, sparingly soluble in water or ethanol(95), slightly soluble in acetone, and practically insoluble in ether or petroleum ether.

The pH of an aqueous solution of Pridinol Mesilate (1 in 50) is between 5.0 and 6.0.

Identification (1) Dissolve 0.1 g of Pridinol Mesilate in 5 mL of water and add 2 mL of ammonia TS; a precipitate is produced. Collect the precipitates, wash with water, and dry at 105 °C for 1 hour; the melting point of the precipitates is between 120 and 121 °C.

(2) Add 2 to 3 drops of reinecke salt TS to 1 mL of an aqueous solution of Pridinol Mesilate (1 in 500); a pale red precipitate is produced.

(3) Place 0.1 g of Pridinol Mesilate in a porcelain crucible and add 0.3 g of potassium nitrate. Mix well and melt carefully. Add 2 to 3 mL of water, boil for a while, and add 1 mL of barium nitrate TS; a milky white precipitate is produced.

Barium nitrate TS—Dissolve 6.5 g of barium nitrate in water to make 100 mL (0.25 mol/L).

(4) Determine the absorption spectrum of an aqueous solution of Pridinol Mesilate (1 in 2500) as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 251 nm and 254 nm (A_1), and between 256 nm and 259 nm (A_2), respectively, and the ratio of the maximum absorbances, A_1/A_2, is between 0.85 and 0.89.

(5) Pridinol Mesilate responds to the Qualitative Analysis for mesylate.

Melting point Between 160 and 162 °C.

Purity (1) ***Clarity and color of solution***—Add 5 mL of water to 0.10 g of Pridinol Mesilate and shake to dissolve; the solution is clear.

(2) ***Chloride***—Dissolve 0.5 g of Pridinol Mesilate in 30 mL of methanol and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding water to 30 mL of methanol, 6 mL of dilute nitric acid and 0.40 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.028%).

(3) ***Sulfate***—Dissolve 0.5 g of Pridinol Mesilate in 30 mL of methanol and add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding water to 30 mL of methanol, 1 mL of dilute hydrochloric acid and 0.40 mL of 0.005 mol/L sulfuric acid to make 50 mL (NMT 0.038%).

(4) ***Heavy metals***—Proceed with 1.0g of Pridinol Mesilate according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(5) ***Arsenic***—Proceed with 1.0 g of Pridinol Mesilate according to Method 3 and perform the test (NMT 2 ppm).

Loss on drying NMT 1.0% (0.5 g, 105 °C, 3 hours).

Residue on ignition NMT 0.3% (0.5 g).

Assay Weigh accurately about 0.5 g of Pridinol Mesilate, previously dried, dissolve in 50 mL of a mixture of acetic acid(100) for nonaqueous titration and acetic anhydride (1 : 4), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 39.152 mg of $C_{20}H_{25}NO{\cdot}CH_3SO_3H$

Packaging and storage Preserve in well-closed containers.

Pridinol Mesilate Injection
프리디놀메실산염 주사액

Pridinol Mesilate Injection contains NLT 95. 0% and NMT 105.0% of the labeled amount of pridinol mesilate ($C_{20}H_{25}NO{\cdot}CH_3SO_3H$: 391.53).

Method of preparation Prepare as directed under Injections, with Pridinol Mesilate.

Identification Take an amount of Pridinol Mesilate Injection equivalent to 4 mg of pridinol mesilate according to the labeled amount, add ethanol to make 2 mL, and use this solution as the test solution. Separately, add 20 mL of ethanol to 40 mg of pridinol mesilate RS, heat to dissolve, and use this solution as the standard solution. With these solutions, spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography as directed under the Thin Layer Chromatography, develop the plate with a mixture of methanol and strong ammonia water (100 : 1.5) (as the developing solvent) to a distance about 10 cm, and air-dry the plate. Spray hexachloroplatinic (IV) acid-potassium iodide TS on the plate; the spot of the test solution exhibits an R_f value and color corresponding to that of the standard solution.

pH Between 5.0 and 7.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 150 EU per mg of pridinol mesilate.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Pridinol Mesilate Injection, equivalent to about 4 mg of pridinol mesilate ($C_{20}H_{25}NO \cdot CH_3SO_3H$), dissolve in a mixture of methanol and diluted phosphoric acid (1 in 1000) (1 : 1) to make exactly 100 mL, filter, and use this solution as the test solution Separately, weigh accurately about 20 mg of pridinol mesilate RS and dissolve in a mixture of methanol and diluted phosphoric acid (1 in 1000) (1 :1) to make exactly 100 mL. Pipet 10 mL of this solution, add a mixture of methanol and diluted phosphoric acid (1 in 1000) (1 : 1) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of the test solution and the standard solution, respectively.

$$\text{Amount (mg) of pridinol mesilate } (C_{20}H_{25}NO \cdot CH_3SO_3H) = \text{Amount (mg) of pridinol mesilate RS} \times \frac{A_T}{A_S} \times \frac{1}{5}$$

Operating condition

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of methanol with 0.005 mol/L sodium 1-octanesulfonate and diluted phosphoric acid (1 in 1000) (3 : 2).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in light-resistant, hermetic containers.

Pridinol Mesilate Tablets
프리디놀메실산염 정

Pridinol Mesilate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of pridinol mesilate ($C_{20}H_{25}NO \cdot CH_3SO_3H$: 391.52).

Method of preparation Prepare as directed under Tablets, with Pridinol Mesilate.

Identification Weigh an amount of Pridinol Mesilate Tablets, previously powdered, equivalent to 40 mg of pridinol mesilate according to the labeled amount, add 50 mL of sodium monohydrogen phosphate-citric acid buffer solution, pH 4.0, shake well to mix, and filter. Perform the test with the filtrate as directed below.

(1) Add 2 mL of Reinecke salt TS to 10 mL of the filtrate; a pale red precipitate is formed.

(2) Add 2 mL of sodium hydroxide TS to 10 mL of the filtrate; a white precipitate is formed. Add 30 mL of ether and shake well to mix. Take the ether layer, wash it with 10 mL of water, add 0.5 g of anhydrous sodium sulfate, shake well to mix, and filter. Evaporate the ether solution to dryness on a steam bath, and dissolve the residue by adding 1 mL of sulfuric acid; the resulting solution exhibits an orange-red color. Add 10 mL of water again; it is decolorized.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Pridinol Mesilate Tablets, and powder them. Weigh accurately an amount of the powder, equivalent to 40 mg of pridinol mesilate ($C_{20}H_{25}NO \cdot CH_3SO_3H$), add 50 mL of diluted phosphoric acid (1 in 1000), and shake for 30 minutes using an ultrasonic shaker. Add 10.0 mL of internal standard solution to this solution, add methanol to make 100 mL, filter it through a membrane filter (pore size of 0.45 μm), and use this solution as the test solution. Separately, weigh accurately about 20 mg of pridinol mesilate RS, previously dried at 105 ℃ for 3 hours, add 5.0 mL of internal standard solution, add a mixture of methanol and diluted phosphoric acid (1 in 1000) (1 : 1) to make 50 mL, and use this solution as the standard solution. Perform the test with 3 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of the peak area of pridinol mesilate to that of the internal standard solution.

$$\text{Amount (mg) of pridinol mesilate } (C_{20}H_{25}NO \cdot CH_3SO_3H) = \text{Amount (mg) of pridinol mesilate RS} \times \frac{Q_T}{Q_S} \times 2$$

Internal standard solution—A solution of butyl p-hydroxybenzoate in methanol (13 in 5000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column, about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography.

Column temperature: A constant temperature of about 55 ℃.

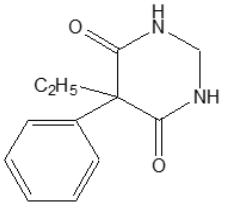
Mobile phase: A mixture of methanol with 0.005 mol/L sodium 1-octanesulfonate and diluted phosphoric acid (1 in 1000) (3 : 2).

Flow rate: Adjust the flow rate so that the retention time of pridinol mesilate is about 6 minutes.

Selection of column: Proceed with 3 μL of the standard solution according to the above conditions; use a column where pridinol mesilate and internal standard are eluted in this order with the resolution being NLT 2.

Packaging and storage Preserve in well-closed containers.

Primidone
프리미돈



$C_{12}H_{14}N_2O_2$: 218.25
5-Ethyl-5-phenyldihydropyrimidine-4,6(1*H*,5*H*)-dione
[*125-33-7*]

Primidone, when dried, contains NLT 98.5% and NMT 101.0% of primidone ($C_{12}H_{14}N_2O_2$).

Description Primidone occurs as a white crystalline powder or granule. It is odorless and has a slightly bitter taste.
It is soluble in *N*,*N*-dimethylformamide, sparingly soluble in pyridine, slightly soluble in ethanol(95), very slightly soluble in water, and practically insoluble in ether.

Identification (1) Heat 0.5 g of Primidone with 5 mL of diluted sulfuric acid (1 in 2); the odor of formaldehyde is perceptible.

(2) Mix 0.2 g of Primidone with 0.2 g of anhydrous sodium carbonate and heat; the gas evolved changes wet red litmus paper to blue.

Melting point Between 279 and 284 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Primidone in 10 mL of *N*,*N*-dimethylformamide; the solution is colorless and clear.

(2) ***Heavy metals***—Proceed with 2.0 g of Primidone according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***2-ethyl-2-phenylmalonediamide***—Dissolve 0.10 g of Primidone in 2 mL of pyridine, add exactly 2.0 mL of the internal standard solution, then add 1 mL of bistrimethylsilyl acetamide, shake well to mix, and heat at 100 °C for 5 minutes. Cool, add pyridine to make 10 mL, and use this solution as the test solution. Separately, dissolve 50 mg of 2-ethyl-2-phenylmalonediamide in pyridine to make exactly 100 mL. Pipet 2.0 mL of this solution, add exactly 2.0 mL of the internal standard solution, proceed in the same manner as the test solution, and use this solution as the standard solution. Perform the test with each 2 μL of the test solution and the standard solution as directed under the Gas Chromatography according to the following operating conditions and determine the ratios, Q_T and Q_S, of the peak area of 2-ethyl-2-phenylmalonediamide to that of the internal standard for the test solution and the standard solution, respectively; Q_T is not larger than Q_S.

Internal standard solution—A solution of stearyl alcohol in pyridine (1 in 2000).

Operating conditions

Detector: A flame ionization detector

Column: A column, about 3 mm in internal diameter and about 1.5 m in length, packed with diatomaceous earth for gas chromatography (125 μm to 150 μm in particle diameter) coated with 50% phenylmethlysilicone polymer for gas chromatography (3% of diatomaceous earth).

Column temperature: A constant temperature of about 195 °C.

Carrier gas: Nitrogen

Flow rate: Adjust the flow rate so that the retention time of stearyl alcohol is 8 - 9 minutes.

System suitability

System performance: Perform the test with 2 μL of the standard solution according to the above operating conditions; 2-ethyl-2-phenylmalondiamide and the internal standard are eluted in this order, and the peak resolution is NLT 3.

System repeatability: Repeat the test 5 times with 2 μL of the standard solution under the above operating conditions; the relative standard deviation of the ratio of the peak area of 2-ethyl-2-phenylmalondiamide to that of the internal standard is NMT 1.5%.

(4) ***Related substances***—Weigh accurately about 100 mg of Primidone, dissolve in methanol to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 100 mg of primidone RS, dissolve in methanol to make exactly 100 mL, and use this solution as the standard solution (1). To 0.1 mL of the standard solution (1), add methanol to make exactly 100 mL and use this solution as the standard solution (2). Perform the test with each 10 μL of the test solution and the standard solution (2) as directed under the Liquid Chromatography according to the following conditions. Determine individual peak area of each solution by the automatic integration method and calculate the amount of related substances in the test solution; primidone related substance I {2-ethyl-2-phenylmalonamide}, phenobarbital, primidone related substance II {2-phenylbutyramide}, 2-cyano-2-phenylbutylamide and 2-phenylbutyric acid, appearing at a relative retention time of about 0.5, about 1.4, about 1.6, about 1.8, and about 2.0 to primidone, respectively, are NMT 0.1%, and phenylpropylpimidone appearing at a relative retention time of about 2.8, is NMT 0.3%. Any other related substance is NMT 0.1%, and the total amount of related substances is NMT 0.5%. Exclude any related substance the percent peak area of which is NMT 0.05%. Determine the peak areas of primidone related substance I, primidone related substance II, 2-cyano-2-phenylbutylamide and 2-phenylbutyric acid by dividing the peak areas determined by the automatic integration method by their relative response factors, 0.67, 0.67, 0.71, and 0.77, respectively.

Content (%) of each related substance

$$= 100 \times \frac{A_i}{A_S} \times \frac{C_S}{C_T}$$

A_i: Peak area of each related substance in the test solution

A_S: Peak area of primidone in the standard solution

C_S: Concentration (μg/mL) of primidone in the standard solution

C_T: Concentration (μg/mL) of primidone in the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Adjust the mobile phase using a stepwise change or gradient elution by mixing mobile phase A and mobile phase B as directed under the following table.

Mobile phase A: Dissolve 1.36 g of potassium dihydrogen phosphate in 1000 mL of water.

Mobile phase B: Methanol

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 1.0	75	25
1.0 - 6.0	75 → 40	25 → 60
6.0 - 8.0	40	60
8.0 - 8.5	40 → 75	60 → 25
8.5 - 10.0	75	25

Flow rate: 3.2 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution (2) according to the above operating conditions; the symmetry factor of the primidone peak is NMT 2. Dissolve 0.1 mg of phenobarbital RS and 0.1 mg of primidone related substance II RS in 10 mL of the standard solution (1) and use this solution as the system suitability solution. Proceed with 10 μL of the system suitability solution according to the above operating conditions, phenobarbital and primidone related substance II are eluted in this order with the resolution of the two peaks being NLT 2.5.

System repeatability: Perform the test 5 times with each 10 μL of the standard solution (2) according to the above operating conditions; the relative standard deviation of the primidone peak area is NMT 5.0%.

Loss on drying NMT 0.5% (1 g, 105 °C, 2 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about each 20 mg of Primidone and primidone RS, previously dried, dissolve each in 20 mL of ethanol(95) by warming. After cooling, add ethanol(95) to make exactly 25 mL and use these solutions as the test solution and the standard solution, respectively. With these solutions, determine the absorbance at the absorbance maximum wavelength of about 257 nm (A_1) and at the absorbance minimum wavelength of about 254 nm and 261 (A_2 and A_3, respectively) as directed under the Ultraviolet-visible Spectroscopy, using ethanol(95) as the control solution.

$$\text{Amount (mg) of primidone } (C_{12}H_{14}N_2O_2) = \text{Amount (mg) of primidone RS} \times \frac{(2A_1-A_2-A_3)_T}{(2A_1-A_2-A_3)_S}$$

where $(2A_1\text{-}A_2\text{-}A_3)_T$ refers to the values from the test solution, and $(2A_1\text{-}A_2\text{-}A_3)_S$ refers to the values from the standard solution.

Packaging and storage Preserve in tight containers.

Primidone Tablets
프리미돈 정

Primidone Tablets contain NMT 95.0% and NLT 105.0% of the labeled amount of primidone ($C_{12}H_{14}N_2O_2$: 218.25).

Method of preparation Prepare as directed under Tablets, with Primidone.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Purity ***Related substances*—**Weigh accurately the mass of NLT 20 tablets of Primidone Tablets, and power them. Weigh accurately an amount of the powder equivalent to about 250 mg of primidone ($C_{12}H_{14}N_2O_2$), and dissolve in 90mL of methanol. Sonicate this solution for 15 minutes, then shake and mix for about 20 minutes until all solid materials are dispersed. Next, cool this solution at room temperature, and add water to make exactly 250 mL. Filter through a filter with a pore size of 0.45 μm, discard the first 5 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately about 5 mg of primidone RS, dissolve in methanol to make exactly 100 mL, use this solution as the standard solution (1). Add diluent to 2 mL of standard solution (1) to make exactly 50 mL, and use this solution as standard solution (2). Perform the test with 20 μL each of the test solution and the standard solution (2) as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of each solution as directed in the automatic integration method, and calculate the amount of each related substance in the test solution; the amounts of primidone related substance I {2-ethyl-2-phenylmalonamide} with a relative retention time to primidone of about 0.5, phenobarbital with that of

about 1.6, primidone-related substance II {2-phenylbutyramide} with that of about 1.9 and 2-phenylbutyric acid with that of about 4.1 are NMT 0.1%. Any other related substance is NMT 0.1%, and the total amount of related substances is NMT 0.3%. However, exclude the related substances accounting for NMT 0.025%. To calculate the peak areas of primidone related substance I, primidone related substance II and 2-phenylbutyric acid, divide the areas determined by the automatic integration method by the correction factors of 0.76, 0.92, and 0.91, respectively.

$$\text{Content (\%) of each related substance} = 100 \times \frac{A_{\mathrm{i}}}{A_{\mathrm{S}}} \times \frac{C_{\mathrm{S}}}{C_{\mathrm{T}}}$$

A_T: Peak area of each related substance in the test solution

A_S: Peak area of primidone in the standard solution

C_S: Concentration (μg/mL) of primidone in the standard solution

C_T: Concentration (μg/mL) of primidone in the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column 4.6 mm in internal diameter and about 10 cm in length with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of potassium dihydrogen phosphate solution (6.8 in 1000), tetrahydrofuran and methanol (65 : 0.5 : 35).

Flow rate: 1.3 mL/min

System suitability

System performance: Dissolve 20 mg of primidone related substance I RS in 100 mL of methanol. Add diluent to 10 mL of this solution to make exactly 100 mL, and use this solution as the primidone related substance I standard solution. Dissolve 1 mL of primidone related substance I standard solution and 0.8 mL of standard solution (2) in the diluent to make exactly 20 mL, and use this solution as the system suitability solution. Proceed with 20 μL of this solution under the above operating conditions; the resolution of primidone related substance I and primidone is NLT 4.0.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solution (2) according to the above operating conditions; the relative standard deviation of the peak areas of primidone is NMT 5.0%.

Diluent—A mixture of methanol and water (35 : 65).

Dissolution Perform the test with 1 tablet of Primidone Tablets at 50 revolutions per minute according to Method 2, using 900 mL of water as the dissolution medium. Take the dissolved solution after 60 minutes from starting of the test, filter, dilute with the dissolution solution, if necessary and use this solution as the test solution. Separately, weigh accurately a portion of Primidone RS, previously dried at 105 ℃ for 2 hours, add the water to make the same concentration with the dissolution solution and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as a control solution, and determine the absorbances at the absorbance maximum wavelength of around 257 nm.

It meets the requirements if the dissolution rate of Primidone Tablets in 60 minutes is NLT 75%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Primidone Tablets, and powder them. Weigh accurately an amount of the powder equivalent to about 0.25 g of primidone ($C_{12}H_{14}N_2O_2$), place it in a 250-mL volumetric flask, add exactly 125 mL of methanol, and sonicate for 15 minutes. Shake for at least 20 minutes to sufficiently dissolve, add methanol to make exactly 250 mL, and filter through a filter with a pore size of 0.45 μm. Discard the first 5 mL of the filtrate, and collect NLT 10 mL of the subsequent filtrate. Take exactly 2.5 mL of the filtrate, add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg of primidone RS (previously dried at 105 °C for 2 hours), add methanol to make exactly 50 mL, and use this solution as the standard stock solution. Pipet 1 mL of this solution, add the mobile phase to it make exactly 10 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of both solutions as directed in the automatic integration method, and calculate the peak area ratios, A_T and A_S, of primidone.

$$\text{Content (\%) of primidone } (C_{12}H_{14}N_2O_2) = 100 \times A_T / A_S \times C_S / C_T$$

A_T: Peak area of primidone in the test solution

A_S: Peak area of primidone in the standard solution

C_S: Concentration (μg/mL) of primidone in the standard solution

C_T: Concentration (μg/mL) of primidone in the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless-steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: 35 °C

Flow rate: 1.0 mL/min

Mobile phase: A mixture of potassium dihydrogen phosphate solution (6.8 in 1000), tetrahydrofuran and methanol (650 : 5 : 350).

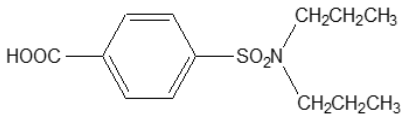
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the number of theoretical plates is NLT 3000 plates with the symmetry factor being NMT 2.0.

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above conditions; the relative standard deviation of the peak areas for primidone is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Probenecid
프로베네시드



$C_{13}H_{19}NO_4S$: 285.36

4-(Dipropylsulfamoyl)benzoic acid [*57-66-9*]

Probenecid, when dried, contains NLT 98.0% and NMT 101.0% of probenecid ($C_{13}H_{19}NO_4$ S: 285.36).

Description Probenecid occurs as white crystals or a crystalline powder. It is odorless and has a slightly bitter taste initially, followed by unpleasant bitter taste.

It is sparingly soluble in ethanol(95), slightly soluble in ether and practically insoluble in water.

It dissolves in sodium hydroxide TS or ammonia TS.

Melting point—Between 198 and 200 ℃.

Identification (1) Heat Probenecid; the odor of sulfur dioxide is perceptible.

(2) Determine the absorption spectra of solutions of Probenecid and probenecid RS in ethanol(95) (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Purity (1) ***Acid***—Dissolve 2.0 g of Probenecid in 100 mL of water and heat on a steam bath for 30 minutes with occasional shaking. After cooling, filter the solution, add 1 drop of phenolphthalein TS and 0.50 mL of 0.1 mol/L sodium hydroxide solution to the filtrate; the resulting solution exhibits a red color.

(2) ***Chloride***—Take 1.0 g of Probenecid, add 100 mL of water and 1 mL of nitric acid, and heat on a steam bath for 30 minutes with occasional shaking. After cooling, if necessary, add water to make 100 mL, and filter. Use 50 mL of the filtrate as the test solution and perform the test. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.021%).

(3) ***Sulfate***—To 1.0 g of Probenecid, add 100 mL of water and 1 mL of hydrochloric acid and heat on a steam bath for 30 minutes with occasional shaking. After cooling, if necessary, add water to make 100 mL, and filter. Use 50 mL of the filtrate as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid VS (NMT 0.038%).

(4) ***Heavy metals***—Proceed with 2.0 g of Probenecid according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (10 ppm).

(5) ***Arsenic***—Proceed with 1.0 g of Probenecid according to Method 3 and perform the test (NMT 2 ppm).

(6) ***Selenium***—Weigh accurately 0.1 g of Probenecid, add 0.1 g of magnesium oxide to mix, put into a combustion flask and combust as directed under the Oxygen Flask Combustion, using 25 mL of diluted nitric acid (1 in 30) as an absorbent. Use a combustion flask with a volume of 1000 mL, combust, wash the stopper and the inner wall of the flask with 10 mL of water, and use 20 mL of water to transfer the solution in the combustion flask into a 150-mL beaker. Heat lightly until it boils, boil for 10 minutes, allow it to cool down at room temperature, and use this solution as the test solution. Separately, pipet 3.0 mL of standard selenium stock solution, add 25 mL of diluted nitric acid (1 in 30) and 25 mL of water, and use this solution as the standard solution. Add diluted ammonia water(28) (1 in 2) to each of the test and standard solutions, adjust the pH to 2.0 ± 0.2, add water to dilute exactly to 60 mL, and add 10 mL of water to transfer to a separatory funnel. Then, wash the separatory funnel with 10 mL of water. To each, add 0.2 g of hydroxylamine hydrochloride, and stir to dissolve. Then, immediately add 5.0 mL of 2,3-diaminonaphthalene TS, put a stopper, stir to mix, and allow to stand at the room temperature for 100 minutes. To the resulting mixture, add 5.0 mL of cyclohexane, shake vigorously for two minutes, and allow to stand. If the layer is separated, remove the water layer, centrifuge cyclohexane extracts, remove water, and take the cyclohexane layer. With these solutions and a control solution prepared by adding 25 mL of water to 25 mL of diluted nitric acid (1 in 30) proceeding in the same manner, perform the test as directed under the Ultraviolet-visible Spectroscopy. Determine the absorbance at the absorbance maximum wavelength around 380 nm; the absorbance of the solution obtained from the test solution is not larger than the absorbance from the standard solution (NMT 30 ppm).

(7) ***Related substances***—Weigh accurately 50 mg of Probenecid, add the mobile phase to make 100 mL, and use this solution as the test solution. Perform the test with 20 μL each of the test solution as directed under the Liquid Chromatography according to the following operating conditions, determine each peak area other than the solvent by the automatic integration method, and calculate the amount of each related substance by the percentage peak area method; the amount of each related substance is NMT 0.5% and the amount of total related substances is NMT 2.0%.

Content (%) of each related substance

$$= 100 \times \frac{A_i}{A_S}$$

A_i: Peak area of each related substance obtained from the test solution

A_S: Total area of all peaks from the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30cm in length, packed with phenyl silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of sodium phosphate solution and a solution of acetic acid(100) in acetonitrile (1 in 100) (1 : 1).

Flow rate: 1 mL/min

System suitability

System performance: Weigh accurately about 50 mg of probenecid RS, dissolve in the mobile phase to make 100 mL, and use this solution as the system suitability solution. With 20 μL of this solution, proceed according to the above conditions; the number of theoretical plate and the symmetry factor are NLT 3900 and NMT 2.3, respectively.

System repeatability: Repeat the test 6 times with 20 μL each of the system suitability solution according to the above conditions; the relative standard deviation is NMT 1.5%.

Sodium phosphate solution: Prepare a 0.05 mol/L solution of dibasic sodium phosphate using a solution of acetic acid(100) (1 in 100) as the solvent, and then adjust the pH to 3.0 with phosphoric acid.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Probenecid, previously dried, dissolve in 50 mL of neutralized ethanol, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of phenolphthalein TS).

Each mL of 0.1 mol/L sodium hydroxide VS
= 28.536 mg of $C_{13}H_{19}NO_4S$

Packaging and storage Preserve in well-closed containers.

Probenecid Tablets
프로베네시드 정

Probenecid Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of probenecid ($C_{13}H_{19}NO_4S$: 285.36).

Method of preparation Prepare as directed under Tablets, with Probenecid.

Identification (1) Weigh an amount of Probenecid Tablets, previously powdered, equivalent to 0.5 g of probenecid according to the labeled amount, add 50 mL of ethanol(95) and 1 mL of 1 mol/L hydrochloric acid TS, shake to mix, and filter. Evaporate the filtrate on a steam bath to make about 20 mL. After cooling, filter the resulting precipitate, recrystallize with 50 mL of dilute ethanol, and dry at 105 ºC for 4 hour; the melting point of the crystals is between 198 and 200 ºC. With the precipitate, perform the test as directed under the Identification (1) of Probenecid.

(2) Determine the absorption spectrum of an ethanol(95) solution (1 in 50000) of dried crystals of (1) as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima at the wavelengths between 224 nm and 226 nm and between 247 nm and 249 nm, and a minimum between 234 nm and 236 nm.

Dissolution Perform the test with 1 tablet of Probenecid Tablets at 50 revolutions per minute according to Method 2, using 900 mL of Solution 2 for dissolution test as the dissolution medium. Take NLT 30 mL of the dissolution medium 30 minutes after starting the test and filter through a membrane filter with a pore size of NMT 0.8 μm. Discard the first 10 mL of the filtrate, take exactly *V* mL of the subsequent filtrate, add Solution 2 for dissolution test to make exactly *V'* mL, so that each mL contains about 14 μg of probenecid ($C_{13}H_{19}NO_4S$) according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 70 mg of probenecid RS, previously dried at 105 ℃ for 4 hours, and dissolve in Solution 2 for dissolution test to make exactly 100mL. Pipet 1 mL of this solution, add Solution 2 for dissolution test to make exactly 50 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 244 nm as directed under the Ultraviolet-visible Spectroscopy.

Meets the requirements if the dissolution rate of Probenecid Tablets in 30 minutes is NLT 80%.

Dissolution rate (%) of the labeled amount of probenecid ($C_{13}H_{19}NO_4S$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 18$$

W_S: Amount (mg) of probenecid RS

C: Labeled amount (mg) of probenecid ($C_{13}H_{19}NO_4S$) per tablet

Uniformity of dosage units Meets the requirements.

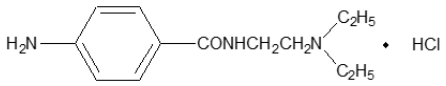
Assay Weigh accurately the mass of NLT 20 tablets of Probenecid Tablets, and powder them. Weigh accurately an amount of the powder equivalent to about 0.25 g of probenecid ($C_{13}H_{19}NO_4S$), dissolve in 30 mL of water and 2 mL of 1 mol/L hydrochloric acid TS, and then dissolve in 30 mL of ethanol(99.5). Next, add ethanol(99.5)

to make exactly 100 mL, centrifuge this solution, take exactly 3 mL of the supernatant, and add 1 mL of 0.1 mol/L hydrochloric acid TS and ethanol(99.5) to make exactly 50 mL. Take exactly 5 mL of this solution again, add ethanol(99.5) to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 0.125 g of probenecid RS, previously dried at 105 °C for 4 hours, and dissolve in 1 mL of 1 mol/L hydrochloric acid TS and 15 mL of water, and add ethanol(99.5) to make exactly 50 mL. Take exactly 3 mL of this solution, dissolve in 2 mL of 1 mol/L hydrochloric acid TS, add ethanol(99.5) to make exactly 50 mL. Take exactly 5 mL of this solution, add ethanol(99.5) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using a solution prepared by adding ethanol(99.5) to 1 mL of 0.1 mol/L hydrochloric acid TS to make exactly 50 mL as a control solution, and determine the absorbances, A_T and A_S at the wavelength of 248 nm.

$$\text{Amount (mg) of probenecid } (C_{13}H_{19}NO_4S) = \text{Amount (mg) of probenecid RS} \times \frac{A_T}{A_S} \times 2$$

Packaging and storage Preserve in well-closed containers.

Procainamide Hydrochloride
프로카인아미드염산염



$C_{13}H_{21}N_3O \cdot HCl$: 271.79

4-Amino-*N*-(2-diethylaminoethyl)benzamide hydrochloride [*614-39-1*]

Procainamide Hydrochloride, when dried, contains NLT 98.0% and NMT 101.0% of procainamide hydrochloride ($C_{13}H_{21}N_3O \cdot HCl$).

Description Procainamide Hydrochloride occurs as a white to pale yellow crystalline powder.
It is very soluble in water and soluble in ethanol(99.5).
It is hygroscopic.

Identification (1) Determine the infrared spectra of Procainamide Hydrochloride and procainamide hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Procainamide Hydrochloride (1 in 20) responds to the Qualitative Analysis for chloride.

Melting point Between 165 and 169 °C.

pH Dissolve 1.0 g of Procainamide Hydrochloride in 10 mL of water; the pH of this solution is between 5.0 and 6.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Procainamide Hydrochloride in 10 mL of water; the resulting solution is clear.

(2) ***Heavy metals***—Proceed with 2.0 g of Procainamide Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Procainamide Hydrochloride according to Method 1 and perform the test. (NMT 2 ppm).

(4) ***Related substances***—Weigh 50 mg of Procainamide Hydrochloride, dissolve in 100 mL of the mobile phase, and use this solution as the test solution. Pipet 1 mL of this solution, and add the mobile phase to make exactly 50 mL. Next, pipet 2 mL of this solution, add the mobile phase to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution by the percentage peak area method under the Liquid Chromatography according to the following conditions; the sum of peak areas other than the peak area of procainamide hydrochloride obtained from the test solution is not greater than the peak area of procainamide hydrochloride from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of pH 3.0 0.02 phosphate buffer solution and methanol (9 : 1).

Flow rate: Adjust the flow rate so that the retention time of procainamide hydrochloride is 9 minutes.

System suitability

Test for required detectability: Pipet 10 mL of the standard solution and add the mobile phase to make exactly 20 mL. Confirm that the peak area of procainamide obtained from 10 μL of this solution is equivalent to 40 to 60% of the peak area of procainamide from the standard solution.

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the number of theoretical plates and the symmetry factor of the peak of procainamide are NLT 10000 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of procainamide is NMT 2.0%.

Time span of measurement: About 2 times the retention time of procainamide.

Loss on drying NMT 0.3% (2 g, 105 °C, 4 hours).

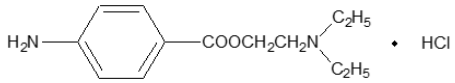
Residue on ignition NMT 0.1% (2 g).

Assay Weigh accurately about 0.5 g of Procainamide Hydrochloride, previously dried, and dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 27.179 mg of $C_{13}H_{21}N_3O \cdot HCl$

Packaging and storage Preserve in tight containers.

Procaine Hydrochloride
프로카인염산염



$C_{13}H_{20}N_2O_2 \cdot HCl$: 272.77
2-(Diethylamino)ethyl4-aminobenzoate hydrochloride
[*51-05-8*]

Procaine Hydrochloride, when dried, contains NLT 99.0% and NMT 101.0% of procaine hydrochloride ($C_{13}H_{20}N_2O_2 \cdot HCl$).

Description Procaine Hydrochloride occurs as white crystals or a crystalline powder.
It is very soluble in ethanol(95), soluble in ethanol(95) and practically insoluble in ether.

Identification (1) Determine the absorption spectra of aqueous solutions of Procaine Hydrochloride and procaine hydrochloride RS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Procaine Hydrochloride and procaine hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Procaine Hydrochloride (1 in 10) responds to the Qualitative Analysis for chloride.

Melting point Between 155 and 158°C.

pH Dissolve 1.0 g of Procaine Hydrochloride in 20 mL of water; the pH of this solution is between 5.0 and 6.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Procaine Hydrochloride in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Procainamide Hydrochloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Weigh 1.0 g of Procainamide Hydrochloride, add 5 mL of ethanol(95), shake well to mix and dissolve, add water to make exactly 10 mL, and use this solution as the test solution. Separately, weigh 0.010 g of 4-aminobenzoic acid, dissolve in ethanol(95) to make exactly 20 mL. Pipet 1 mL of this solution, add 4 mL of ethanol(95) and water to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of dibutyl ether, n-hexane, and acetic acid(100) (20 : 4 : 1) as the developing solvent to a distance of about 10 cm, air-dry the plate, and then heat further at 105 °C for 10 minutes. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution However, the principal spot from the test solution remains at the origin.

Loss on drying NMT 0.5% (1 g, silica gel, 4 hours).

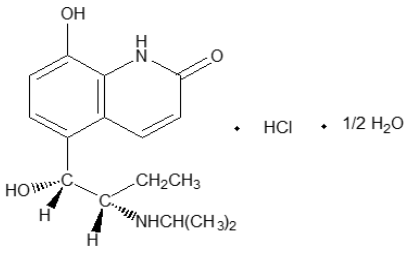
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Procainamide Hydrochloride, previously dried, dissolve in 5 mL of hydrochloric acid and 60 mL of water, add 10 mL of potassium bromide solution (3 in 10), and cool at NMT 15 °C. Then, titrate with 0.1 mol/L sodium nitrite VS (potentiometric titration under the Titrimetry).

Each mL of 0.1 mol/L sodium nitrite VS
= 27.277 mg of $C_{13}H_{20}N_2O_2 \cdot HCl$

Packaging and storage Preserve in well-closed containers.

Procaterol Hydrochloride Hydrate
프로카테롤염산염수화물



and enantiomer

Procaterol Hydrochloride

$C_{16}H_{22}N_2O_3 \cdot HCl \cdot ½H_2O$: 335.83

(1*RS*,2*SR*)-8-Hydroxy-5-[1-hydroxy-2-(isopropylamino)butyl]-quinolin-2(1*H*)-one hydrochloride hemihydrate [*62929-91-3, anhydrous*]

Procaterol Hydrochloride Hydrate contains NLT 98.5% and NMT 101.0% of procaterol hydrochloride ($C_{16}H_{22}N_2O_3 \cdot HCl$: 326.82), calculated on the anhydrous basis.

Description Procaterol Hydrochloride Hydrate occurs as white to pale yellowish white crystals or a crystalline powder.

It is soluble in water, formic acid or methanol, slightly soluble in ethanol(95), and practically insoluble in ether.

The pH of a solution of 1.0 g of Procaterol Hydrochloride Hydrate dissolved in 100 mL of water is between 4.0 and 5.0.

It is gradually colored by light.

An aqueous solution of Procaterol Hydrochloride Hydrate (1 in 20) shows no optical rotation.

Melting point—About 195 °C (with decomposition).

Identification (1) Determine the absorption spectra of aqueous solutions of Procaterol Hydrochloride Hydrate and procaterol hydrochloride hydrate RS (7 in 1000000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Procaterol Hydrochloride Hydrate and procaterol hydrochloride hydrate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) An aqueous solution of Procaterol Hydrochloride Hydrate (1 in 50) responds to the Qualitative Analysis for chloride.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Procaterol Hydrochloride Hydrate in 30 mL of water; the resulting solution is clear. The color of this solution is not more intense than that of the following control solution.

Control solution—Take 3.0 mL of colorimetric stock solution of iron(III) chloride hexahydrate and add water to make 50 mL.

(2) ***Heavy metals***—Proceed with 2.0 g of Procaterol Hydrochloride Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 0.10 g of Procaterol Hydrochloride Hydrate in 100 mL of diluted methanol (1 in 2) and use this solution as the test solution. Pipet 1 mL of this solution, add diluted methanol (1 in 2) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 2 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the total area of peaks other than procaterol from the test solution is not larger than the peak area of procaterol from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Add 230 mL of methanol and 10 mL of acetic acid(100) into 760 mL of a solution of 0.87 g of sodium 1-heptanesulfonate dissolved in 1000 mL of water.

Flow rate: Adjust the flow rate so that the retention time of procaterol is about 15 minutes.

System suitability

Detection sensitivity: Adjust the sensitivity so that the peak height of procaterol obtained from 2 μL of the standard solution is NLT 10 mm.

System performance: Dissolve 20 mg each of Procaterol Hydrochloride Hydrate and threoprocaterol hydrochloride in 100 mL of diluted methanol (1 in 2) Pipet 15 mL of this solution, and add diluted methanol (1 in 2) to make 100 mL. Proceed with 2 μL of this solution as directed under the above operating conditions; procaterol and threoprocaterol hydrochloride are eluted in this order with the resolution being NLT 3.

Time span of measurement: About 2.5 times the retention time of procaterol after the solvent peak.

Water Between 2.5% and 3.3% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.25 g of Procaterol Hydrochloride Hydrate, add 2 mL of formic acid, warm to dissolve, add exactly 15 mL of 0.1 mol/L perchloric acid, add 1 mL of acetic anhydride, and heat on a steam bath

for 30 minutes. After cooling, add 60 mL of acetic anhydride, and titrate the excess perchloric acid with 0.1 mol/L sodium acetate VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner.

Each mL of 0.1 mol/L perchloric acid VS
= 32.682 mg of $C_{16}H_{22}N_2O_3 \cdot HCl$

Packaging and storage Preserve in light-resistant, well-closed containers.

Procaine Hydrochloride Injection
프로카인염산염 주사액

Procaine Hydrochloride Injection is an aqueous solution for injection. Procaine Hydrochloride Injection contains NLT 95.0% and NMT 105.0% of the labeled amount of procaine hydrochloride ($C_{13}H_{20}N_2O_2 \cdot HCl$: 272.77).

Method of preparation Prepare as directed under Injections, with Procaine Hydrochloride.

Description Procaine Hydrochloride Injection occurs as a clear, colorless liquid.

Identification (1) Take an amount of Procaine Hydrochloride Injection, equivalent to 10 mg of procaine hydrochloride according to the labeled amount, and determine the absorption spectra as directed under Ultraviolet-visible Spectroscopy; it exhibits maxima at the between 219 nm and 223 nm and between 289 nm and 293 nm.

(2) Procaine Hydrochloride Injection responds to the Qualitative Tests (2) for chloride.

pH Between 3.3 and 6.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.6 EU per mg of procaine hydrochloride. As for injections administered within the spinal canal, procaine hydrochloride is less than 0.02 EU per mg.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Procaine Hydrochloride Injection equivalent to about 20 mg of procaine hydrochloride ($C_{13}H_{20}N_2O_2 \cdot HCl$), and add the mobile phase to make exactly 20 mL. Pipet 5 mL of the resulting solution, add exactly 5 mL of the internal standard solution, and then add the mobile phase to make 20 mL. Use this solution as the test solution. Separately, weigh accurately about 20 mg of Procaine Hydrochloride RS, previously dried in a desiccator (silica gel) for 4 hours and dissolve in the mobile phase to make exactly 20 mL. Pipet 5 mL of this solution, add exactly 5 mL of the internal standard solution, add the mobile phase to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak area of procaine to that of the internal standard Q_T and Q_S.

Amount (mg) of procaine hydrochloride ($C_{13}H_{20}N_2O_2 \cdot HCl$)
= Amount (mg) of procaine hydrochloride RS $\times \frac{Q_T}{Q_S}$

Internal standard solution—A solution of caffeine in the mobile phase (1 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Add phosphoric acid to 0.05 mol/L potassium dihydrogen phosphate TS to adjust the pH to 3.0. With this solution, prepare an 800 mL of solution containing 0.1% of sodium 1-pentanesulfonate and add 200 mL of methanol.

Flow rate: Adjust the flow rate so that the retention time of procaine is about 10 minutes.

System suitability

System performance: Proceed with 5 μL of the standard solution under the above operating conditions; procaine and the internal standard are eluted in this order with the resolution being NLT 8.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution according to the above conditions; the relative standard deviation of ratios of the peak area of procaine to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in hermetic containers.

Procaterol Hydrochloride Tablets
프로카테롤염산염 정

Procaterol Hydrochloride Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of procaterol hydrochloride hydrate ($C_{16}H_{22}N_2O_3 \cdot HCl \cdot 1/2H_2O$: 335.83).

Method of preparation Prepare as directed under Tablets, with Procaterol Hydrochloride Hydrate.

Identification (1) Weigh an amount of Procaterol Hydrochloride Tablets, equivalent to about 2 mg of procaterol hydrochloride hydrate according to the labeled amount, add 5 mL of water, shake to mix, and centrifuge. Filter, if necessary, and use the filtrate as the test solution. Spot 15 μL of the test solution onto filter paper while air-drying, and then spray Dragendorff's TS for spraying evenly; the spot exhibits an orange color.

(2) Weigh an amount of Procaterol Hydrochloride Tablets, equivalent to about 0.1 mg of procaterol hydrochloride according to the labeled amount, add 20 mL of 0.01 mol/L hydrochloric acid TS, shake to mix, and filter. Determine the absorption spectrum of the filtrate as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima at wavelengths of around 233 nm, and between 293 nm and 297 nm.

Dissolution Perform the test with 1 tablet of Procaterol Hydrochloride Tablets at 50 revolutions per minute according to Method 2, using 500 mL of water as the dissolution medium. Take the dissolution medium 30 minutes after starting the dissolution test, and filter it. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add water to make exactly *V*′ mL so that each mL contains about 0.1 μg of procaterol hydrochloride according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 10 mg of procaterol hydrochloride RS, and dissolve in the mobile phase to make exactly 200 mL. Pipet 2 mL of this solution and add the mobile phase to make exactly 100 mL. Take exactly 5 mL of this solution, add the dissolution medium to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of procaterol hydrochloride (C16H22N2O3 HCl) in each solution. Meets the requirements if the dissolution rate of Procaterol Hydrochloride Tablets in 30 minutes is NLT 70%.

Dissolution rate (%) of the labeled amount of procaterol hydrochloride hydrate (C16H22N2O3 HCl.1/2H2O)

$$= W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 0.5 \times 1.0276$$

*W*s: Amount (mg) of procaterol hydrochloride RS

C: Labeled amount (mg) of ($C_{16}H_{22}N2O_3$·HCl·1/2H_2O) per tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of sodium 1-pentanesulfonate solution (0.87 in 1000), methanol and acetic acid(100) (76 : 23 : 1).

Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 50 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of procaterol hydrochloride is NMT 2.0%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Procaterol Hydrochloride Tablets, and powder them. Weigh accurately an amount of the powder equivalent to about 0.2 mg of procaterol hydrochloride hydrate ($C_{16}H_{22}N_2O_3$·HCl·1/2 H_2O), and add 10.0 mL of the internal standard solution. Next, add 1/300 mol/L phosphoric acid to make 100 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 50 mg of procaterol hydrochloride RS (previously measure the moisture content), and add 1/300 mol/L phosphoric acid to make 100 mL. Take exactly 4.0 mL of this solution and add 1/300 mol/L phosphoric acid to make 100 mL. Pipet 10.0 mL of this solution, add 10.0 mL of the internal standard solution, add 1/300 mol/L phosphoric acid to make 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, of procaterol hydrochloride to the peak area of the internal standard solution.

Amount (mg) of procaterol hydrochloride ($C_{16}H_{22}N_2O_3$·HCl)

= Amount (mg) of procaterol hydrochloride RS, calculated on the anhydrous basis $\times \frac{Q_T}{Q_S} \times \frac{1}{250} \times 1.0276$

Internal standard solution—Weigh 10 mg of *N*-phenylglycine, dissolve in 70 mL of water, add 1 mL of 1/3 mol/L phosphoric acid, and add water to make 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

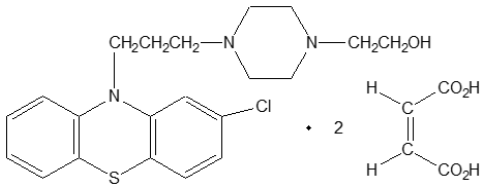
Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of 2% acetic acid,·methanol and acetonitrile (8: 1.5 : 0.5).

Flow rate: 1 mL/min

Packaging and storage Preserve in well-closed containers.

Prochlorperazine Maleate
프로클로르페라진말레산염



$C_{20}H_{24}ClN_3S \cdot 2C_4H_4O_4$: 606.09
2-Chloro-10-[3-(4-methyl-1-piperazinyl)propyl]-10*H*-phenothiazine (*Z*)-but-2-enedioate [*84-02-6*]

Prochlorperazine Maleate, when dried, contains NLT 98.0% and NMT 101.0% of prochlorperazine maleate ($C_{20}H_{24}ClN_3S \cdot 2C_4H_4O_4$).

Description Prochlorperazine Maleate occurs as a white to pale yellow powder. It is odorless and has a slightly bitter taste.
It is slightly soluble in acetic acid(100), very slightly soluble in water or ethanol(95), and practically insoluble in ether.
It is gradually colored to red by light.

Melting point—Between 195 and 203 ℃ (with decomposition).

Identification (1) Dissolve 5 mg of Prochlorperazine Maleate in 5 mL of sulfuric acid; the resulting solution exhibits a red color, and this color slowly get more intense.
Take half of this solution and heat it; the resulting solution exhibits a purple color. Add a drop of potassium dichromate TS to the remaining solution; a greenish brown color develops, and changes to a brown color if allowed to stand.

(2) Dissolve 0.2 g of Prochlorperazine Maleate in 5 mL of sodium hydroxide (1 in 10) and extract 3 times with 3 mL each of ether [the aqueous layer is used in the test in (4)]. Combine the ether extracts and evaporate to dryness on a steam bath. Add 10 mL of methanol to the residue, warm to dissolve, add this solution to 30 mL of a solution of 2,4,6-trinitrophenol in methanol (1 in 75), warmed to 50 ℃, and allow to stand for 1 hour. Filter and collect the crystals, wash with a small amount of methanol, and dry at 105 ℃ for 1 hour; the crystals melt between 252 and 258℃ (with decomposition).

(3) Add 10 mL of hydrobromic acid to 0.5 g of Prochlorperazine Maleate, and heat under a reflux condenser for 10 minutes. After cooling, add 100 mL of water and filter using a glass filter (G 4). Wash the residue three times with 10 mL each of water and dry at 105 ℃ for 1 hour; it melts between 195 and 198 ℃ (with decomposition).

(4) To the aqueous layer in (2), add boiling stones and heat on a steam bath for 10 minutes. After cooling, add 2 mL of bromine TS, heat on a steam bath for 10 min, and then heat further to boiling. After cooling, add 2 drops of this solution to 3 mL of a solution of resorcinol in sulfuric acid (1 in 300) dropwise, and heat on a steam bath for 15 minutes; the resulting solution exhibits a purple color.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Prochlorperazine Maleate according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Weigh accurately 100 mg of Prochlorperazine Maleate, dissolve in 10 mL of a mixture of methanol and 1 mol/L sodium hydroxide (9 : 1) and use this solution as the test solution. Separately, weigh accurately 10 mg of prochlorperazine maleate RS, dissolve in 50 mL of a mixture of methanol and 1 mol/L sodium hydroxide (9 : 1) and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the plate made of silica gel with fluorescent indicator for thin-layer chromatography, develop the plate with a mixture of methanol and ammonia water(28) (100 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelengths: 254 nm and 365 nm); the spots other than the principal spot obtained from the test solution are not larger or not more intense than the spots from the standard solution (NMT 2.0%). Disregard the spots left on the origin.

Loss on drying NMT 1.0% (1 g, 105℃, 3 hours)

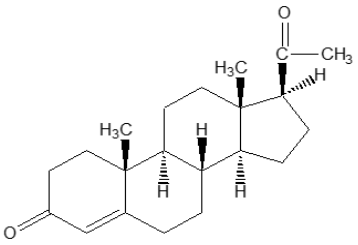
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Prochlorperazine Maleate, previously dried, add 60 mL of acetic acid(100), warm while stirring to dissolve, and cool. Then, titrate with 0.05 mol/L perchloric acid VS (indicator: 0.5 mL of 1-naphtholbenzein TS). However, the endpoint of the titration is when the solution changes from an orange color to a green color. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L perchloric acid VS
= 15.152 mg of $C_{20}H_{24}ClN_3S \cdot 2C_4H_4O_4$

Packaging and storage Preserve in light-resistant, tight containers.

Progesterone
프로게스테론



$C_{21}H_{30}O_2$: 314.46

(8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-17-Acetyl-10,13-dimethyl-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-3-one [*57-83-0*]

Progesterone, when dried, contains NLT 97.0% and NMT 103.0% of progesterone ($C_{21}H_{30}O_2$).

Description Progesterone occurs as white crystals or a crystalline powder.
It is soluble in methanol or ethanol(99.5) and practically insoluble in water.

Identification (1) Determine the absorption spectra of the solutions of Progesterone and progesterone RS in ethanol(99.5) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Progesterone and progesterone RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the two spectra, dissolve each in ethanol(95), evaporate, and perform the test in the same manner with the residues.

Optical rotation $[\alpha]_D^{20}$: Between +184° and +194° (after drying, 0.2 g, ethanol(99.5), 10 mL, 100 mm).

Melting point Between 128 and 133 ℃ or 120 and 122 ℃.

Purity ***Related substances***—Weigh 80 mg of Progesterone, dissolve in 2 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform and diethylamine (19 : 1) as the developing solvent to a distance of about 15 cm and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (0.5 g, in vacuum, phosphorus pentoxide, 4 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately about 10 mg each of Progesterone and progesterone RS, previously dried, and dissolve in ethanol(99.5), respectively, to make exactly 100 mL. Pipet 5.0 mL each of these solutions, add ethanol(99.5) to make exactly 50 mL and use these solutions as the test solution and the standard solution, respectively. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength around 241 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of progesterone } (C_{21}H_{30}O_2) = \text{Amount (mg) of progesterone RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in light-resistant, tight containers.

Progesterone Injection
프로게스테론 주사액

Progesterone Injection is an oily injection and contains NLT 95.0% and NMT 105.0% of the labeled amount of progesterone ($C_{21}H_{30}O_2$: 314.46).

Method of preparation Prepare as directed under Injections, with Progesterone.

Description Progesterone Injection occurs as a clear, colorless to pale yellow distillate.

Identification Take 1 mL of Progesterone Injection, add 1 mL of diluted ethanol (9 in 10), shake well to mix, take the ethanol layer, add 1 mL of petroleum benzene, shake to mix, and take the ethanol layer. Use this solution as the test solution. Separately, weigh about 5 mg of progesterone RS, dissolve in 1 mL of ethanol(99.5), and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ether and diethylamine (19 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly sulfuric acid on the plate, and heat at 105 ℃ for 10 minutes; the R_f values of the spots obtained from the test solution and the standard solution are the same.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay First, measure the specific gravity of Progesterone Injection. Weigh accurately a mass equivalent to 1 mL of Progesterone Injection, add 2 mL of tetrahydrofuran and shake to mix, and then add ethanol(99.5) to make exactly *V* mL of a solution containing 0.5 mg of progesterone ($C_{21}H_{30}O_2$). Pipet 2 mL of this solution, add exactly 10 mL of the internal standard solution, and add ethanol(99.5) to make exactly 20 mL. Use this solution as the test solution. Separately, weigh accurately about 10 mg of progesterone RS (dried previously under vacuum for 4 hours in a phosphorus pentoxide desiccator), dissolve in 2 mL of tetrahydrofuran, and add ethanol(99.5) to make exactly 20 mL. Pipet 2 mL of this solution, add 10 mL of internal standard solution, then add ethanol(99.5) to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratio of the peak area of progesterone to that of the internal standard Q_T and Q_S.

Amount (mg) of progesterone ($C_{21}H_{30}O_2$) per mL of progesterone injection

$$= \text{Amount (mg) of progesterone RS} \times \frac{Q_T}{Q_S} \times \frac{V}{20}$$

Internal standard solution—A solution of testosterone propionate in ethanol(99.5) (1 in 4000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 241 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of acetonitrile and water (7 : 3).

Flow rate: Adjust the flow rate so that the retention time of progesterone is about 6 minutes.

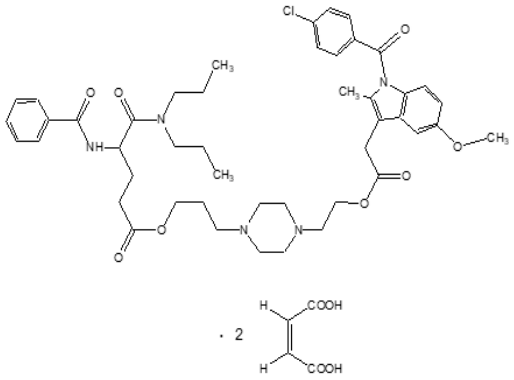
System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; progesterone and the internal standard are eluted in this order with the resolution being NLT 9.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution according to the above conditions; the relative standard deviation of ratios of the peak area of progesterone to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, hermetic containers.

Proglumetacin Dimaleate
프로글루메타신말레산염



$C_{46}H_{58}ClN_5O_8 \cdot 2C_4H_4O_4$: 1076.59

2-[4-[3-[[4-(Benzoylamino)-5-(dipropylamino)-1,5-dioxopentyl]oxy]propyl]-1-piperazinyl]ethyl 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid ester·(2*Z*)-2-butenedioate (1:2), [*59209-40-4*]

Proglumetacin Dimaleate contains NLT 97.5% and NMT 101.0% of proglumetacin dimaleate ($C_{46}H_{58}ClN_5O_8 \cdot 2C_4H_4O_4$), calculated on the anhydrous basis.

Description Proglumetacin Dimaleate occurs as a pale yellow crystalline powder.

It is freely soluble in dimethylformamide, dimethylsulfoxide, and acetic acid(100), soluble in chloroform and methanol, slightly soluble in ethanol and 1,2-propylene glycol and practically insoluble in water.

Melting point—Between 145 and 148 °C.

Identification Weigh 0.15 g of Proglumetacin Dimaleate, dissolve in methanol to make 15 mL, and use this solution as the test solution. Separately, weigh 0.15 g of proglumetacin dimaleate RS, dissolve in methanol to make 15 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescence indicator). Develop the plate with a mixture of 1-butanol, water and acetic acid (100) (5 : 2 : 2) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm) or spray Dragendorff's TS; the spot of the test solution exhibits an Rf value and color corresponding to that of the standard solution.

Purity (1) ***Chloride***—Weigh 0.5 g of Proglumetacin Dimaleate, and perform the test as directed under the Chloride. Prepare the control solution with 3.5 mL of 0.02 mol/L hydrochloric acid (NMT 0.5%).

(2) ***Sulfate***— Weigh 0.5 g of Proglumetacin Dimaleate, and perform the test as directed under the Sulfate. Prepare the control solution with 2.5 mL of 0.01

mol/L sulfuric acid (NMT 0.5%).

(3) ***Heavy metals***—Proceed with 2.0 g of Proglumetacin Dimaleate according to Method 2 under the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Proceed with 1.0 g of Proglumetacin Dimaleate according to Method 3 under the Arsenic (NMT 2 ppm).

Water NMT 0.5%.

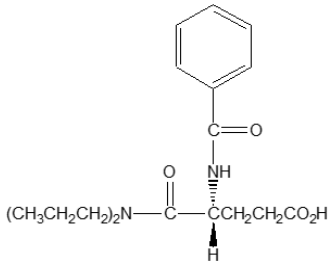
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.6 g of Proglumetacin Dimaleate, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 53.83 mg of $C_{46}H_{58}N_4O_8 \cdot 2C_4H_4O$

Packaging and storage Preserve in well-closed containers.

Proglumide
프로글루미드



and enantiomer

$C_{18}H_{26}N_2O_4$: 334.41

(4*RS*)-4-Benzamido-5-(dipropylamino)-5-oxo-pentanoic acid [*6620-60-6*]

Proglumide, when dried, contains NLT 98.5% and NMT 101.0% of proglumide ($C_{18}H_{26}N_2O_4$).

Description Proglumide occurs as white crystals or a crystalline powder.
It is freely soluble in methanol, soluble in ethanol(95), slightly soluble in ether and practically insoluble in water.
A solution of Proglumide in methanol (1 in 10) shows no optical rotation.

Identification (1) Put 0.5 g of Proglumide in a round-bottomed ampoule, add 5 mL of hydrochloric acid, seal the ampoule and heat carefully at 120 ºC for 3 hours. After cooling, collect crystals produced, wash the crystals with 50 mL of water, and dry at 100 ºC for 1 hour; the melting point of the crystals is between 121 and 124 ºC.

(2) Determine the infrared spectra of Proglumide and proglumide RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 148 and 150 ºC.

Absorbance $E_{1cm}^{1\%}$ (225 nm): Between 384 and 414 (4 mg after drying, methanol, 250 mL).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Proglumide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Weigh 1.0 g of Proglumide, add 10 mL of a solution of magnesium nitrate in ethanol(95) (1 in 10) and 1.5 mL of hydrogen peroxide, burn the ethanol, proceed according to Method 3 and perform the test (NMT 2 ppm).

(3) ***Related substances***—Dissolve 0.10 g of Proglumide in 5 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of cyclohexane, ethyl acetate, acetic acid(100) and methanol (50 : 18 : 5 : 4) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 366 nm); any spot other than the principal spot obtained from the test solution is not more intense than the spot from the standard solution.

Loss on drying NMT 0.1% (1 g, in vacuum, phosphorus pentoxide, 60 ºC, 3 hours).

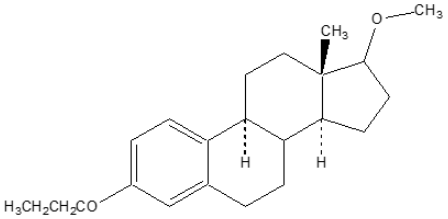
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.16 g of Proglumide, previously dried, dissolve in 40 mL of methanol, add 40 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 33.441 mg of $C_{18}H_{26}N_2O_4$

Packaging and storage Preserve in well-closed containers.

Promestriene
프로메스트리엔



$C_{22}H_{32}O_2$: 328.49

(8*R*,9*S*,13*S*,14*S*)-17-Methoxy-13-methyl-3-propoxy-6,7,8,9,11,12,14,15,16,17-decahydrocyclopenta[a]phenanthrene, [*39219-28-8*]

Promestriene, when dried, contains NLT 97.0% and NMT 103.0% of promestriene ($C_{22}H_{32}O_2$).

Description Promestriene occurs as a white to creamy crystalline powder.
It is soluble in methanol, ethanol(95) and chloroform and petroleum ether and practically insoluble in water.

Identification (1) Determine the absorption spectrum of a solution of Promestriene in methanol (1 in 100) as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum around the wavelength of 288 nm.

(2) Determine the infrared spectra of Promestriene and promestriene RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 10 mg of Promestriene in 1 mL of methanol, and use this solution as the test solution. Weigh 10 mg of promestriene RS, dissolve in 1 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of benzene and ethyl acetate (19 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray 20% sulfuric acid on the plate; the spot of the test solution exhibits an Rf value corresponding to that of the standard solution.

Melting point Between 65 and 67 °C.

Optical rotation $[\alpha]_D^{20}$: Between +60° and + +69° (after drying, 0.2 g, ethanol(95), 10 mL, 100 mm).

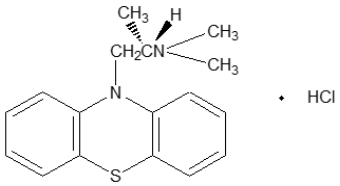
Loss on drying NMT 1.0% (0.5 g, in vacuum, phosphorus pentoxide, 50 °C, 3 hours)

Assay Weigh accurately about 10 mg of Promestriene, previously dried, dissolve in ethanol(99.5) to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of promestriene RS, add ethanol(99.5) to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances for the test solution and the standard solution, A_T and A_S, at 288 nm as directed under the Ultraviolet-visible Spectroscopy, using ethanol(99.5) as the control solution.

Amount (mg) of promestriene ($C_{22}H_{32}O_2$)
= Amount (mg) of promestriene RS × (A_T / A_S)

Packaging and storage Preserve in tight containers.

Promethazine Hydrochloride
프로메타진염산염



and enantiomer

$C_{17}H_{20}N_2S{\cdot}HCl$: 320.88

(*RS*)-*N*,*N*-dimethyl-1-(10*H*-phenothiazin-10-yl)propan-2-amine hydrochloride [*58-33-3*]

Promethazine Hydrochloride, when dried, contains NLT 98.0% and NMT 101.0% of promethazine hydrochloride ($C_{17}H_{20}N_2O{\cdot}HCl$).

Description Promethazine Hydrochloride occurs as a white to pale yellow powder.
It is very soluble in water, freely soluble in ethanol(95) or acetic acid(100), slightly soluble in acetic anhydride and practically insoluble in ether.
It is gradually colored by light.
An aqueous solution of Promethazine Hydrochloride (1 in 25) shows no optical rotation.

Melting point—About 223 °C (with decomposition).

Identification (1) Determine the absorption spectra of aqueous solutions of Promethazine Hydrochloride and promethazine hydrochloride RS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Promethazine Hydrochloride and promethazine hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 0.5 g of Promethazine Hydrochloride in 5 mL of water, add 2 mL of ammonia TS, and filter. To 5 mL of the filtrate, add dilute nitric acid to acidify; the solution responds to the Qualitative Analysis (2) for chloride.

pH Dissolve 1.0 g of Promethazine Hydrochloride in 10

mL of water; the pH of this solution is between 4.0 and 5.5.

Purity (1) ***Clarity and color of solution***—Perform the test while protected from direct sunlight. Dissolve 1.0 g of Promethazine Hydrochloride in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Promethazine Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Perform the test while protected from direct sunlight Dissolve 0.10 g of Promethazine Hydrochloride in 5 mL of ethanol(95) and use this solution as the test solution. Pipet 1 mL of this solution, add ethanol(95) to make exactly 200 mL, and use this solution as the standard solution (1). Separately, weigh 20 mg of isopromethazine hydrochloride RS, dissolve in ethanol(95) to make 100 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution, standard solution (1) and standard solution (2) on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of methanol and diethylamine (19 : 1) as the developing solvent to a distance of about 12 cm and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the spot obtained from the test solution at a location equivalent to the spot obtained from the standard solution (2) is not more intense than the spot of the standard solution (2). Also, the spots other than the principal spot from the test solution are not more intense than those obtained from the standard solution (1).

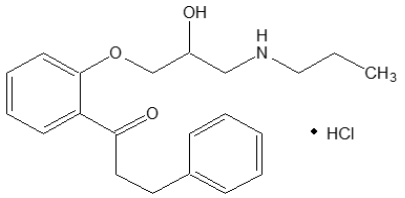
Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours)

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Promethazine Hydrochloride, previously dried, and dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Packaging and storage Preserve in light-resistant, tight containers.

Propafenone Hydrochloride
프로파페논염산염



$C_{21}H_{27}NO_3 \cdot HCl$: 377.91

1-{2-[2-Hydroxy-3-(propylamino)propoxy] phenyl}-3-phenylpropan-1-one hydrochloride [*14222-60-7*]

Propafenone Hydrochloride contains NLT 98.0% and NMT 102.0% of propafenone hydrochloride ($C_{21}H_{27}NO_3 \cdot HCl$), calculated on the dried basis.

Description Propafenone Hydrochloride occurs as a white powder.
It is soluble in methanol or hot water, slightly soluble in ethanol(95) or chloroform, very slightly soluble in acetone, and practically insoluble in ether or toluene.

Identification (1) Determine the infrared spectra of Propafenone Hydrochloride and propafenone hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve 0.5 g of Propafenone Hydrochloride in 50 mL of water by heating and adjust the pH to 9.5 - 10.0 with 0.1 mol/L sodium hydroxide TS; a precipitate is formed. After cooling, filter, and add 1 mL of 6 mol/L nitric acid and 2 to 3 drops of 0.1 mol/L silver nitrate TS to the filtrate; a precipitate is formed, and it dissolves upon the addition of 2 to 3 drops of ammonia water(28).

Melting point Between 171 and 175 ℃.

pH Dissolve 0.5 g of Propafenone Hydrochloride in 100 mL of water; the pH of the solution is between 5.0 and 6.2.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Propafenone Hydrochloride in 30 mL of hot water; the resulting solution is clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Propafenone Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Weigh accurately about 0.10 g of Propafenone Hydrochloride, dissolve in 20 mL of the mobile phase from the operating conditions 1, and use this solution as the test solution. Pipet 2 mL of this solution and dissolve in 50 mL of the mobile phase from the operating conditions 1. Pipet 2.5 mL of this solution, add 2.5 mL of a solution of diphenylphthalate in methanol (1 in 2000), add the mobile phase from the operating conditions 1 to make exactly 100 mL, and use this solution as the standard solution. Perform the test with each 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to

operating conditions 1 and operating conditions 2. Determine the area of each peak from the test solution by the automatic integration method. The area of any peak other than the propafenone peak from the test solution is not larger than the peak area of propafenone from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 4.6 g of sodium 1-nonanesulfonate and 2.3 g of phosphoric acid in water to make exactly 1000 mL and filter with a membrane filter with a pore size of 0.45 μm. To 900 mL of this solution, add 600 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of diphenylphthalate is about 39 minutes.

System suitability

System performance: Dissolve 12 mg of propafenone hydrochloride and 50 mg of isopropyl benzoate in 100 mL of methanol. Proceed with 10 μL of this solution according to the above operating conditions; propafenone and isopropyl benzoate are eluted in this order with the resolution of these peaks being NLT 5.

System repeatability: Perform the test 6 times with each 10 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of propafenone is NMT 2.0%.

Time span of measurement: About as long as the retention time of diphenylphthalate after the solvent peak.

Operating conditions 2

Detector, column and column temperature: Proceed as directed under the operating condition 1.

Column: A stainless steel column, about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 7.33 g of sodium 1-nonanesulfonate and 2.3 g of phosphoric acid in water to make exactly 1000 mL and filter with a membrane filter with a pore size of 0.45 μm. To 700 mL of this solution, add 700 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of diphenylphthalate is about 11 minutes.

System suitability

System performance: Dissolve 12 mg of propafenone hydrochloride and 50 mg of isopropyl benzoate in 100 mL of methanol. Proceed with 10 μL of this solution according to the above operating conditions; propafenone and isopropyl benzoate are eluted in this order with the resolution of these peaks being NLT 21.

System repeatability: Perform the test 6 times with each 10 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of propafenone is NMT 2.0%.

Time span of measurement: About 2.5 times the retention time of the diphenylphthalate after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 ℃, constant mass).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.25 g of Propafenone Hydrochloride and propafenone hydrochloride RS (previously measure the loss on drying in the same manner as Propafenone Hydrochloride), dissolve each in the mobile phase to make exactly 200 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with each 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the areas, A_T and A_S, of propafenone hydrochloride from each solution.

Amount (mg) of propafenone hydrochloride ($C_{21}H_{27}NO_3 \cdot HCl$)
= Amount (mg) of propafenone hydrochloride RS, calculated on the dried basis $\times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 1.36 g of potassium dihydrogen phosphate in 980 mL of water, adjust the pH to 3.0 with phosphoric acid, and add water to make 1000 mL. To 570 mL of this solution, add 430 mL of acetonitrile.

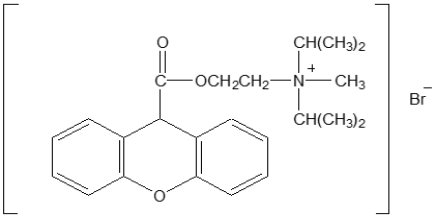
Flow rate: Adjust the flow rate so that the retention time of propafenone hydrochloride is about 5 minutes.

System suitability

System repeatability: Perform the test 6 times with 20 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of propafenone hydrochloride is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Propantheline Bromide
프로판텔린브롬화물



$C_{23}H_{30}BrNO_3$: 448.39

N-Isopropyl-*N*-methyl-*N*-{2-[(9*H*-xanthen-9-ylcarbonyl)oxy]ethyl}propan-2-aminium bromide [*50-34-0*]

Propantheline Bromide, when dried, contains NLT 98.0% and NMT 102.0% of propantheline bromide ($C_{23}H_{30}BrNO_3$).

Description Propantheline Bromide occurs as a white to yellowish white crystalline powder. It is odorless and has a very bitter taste.

It is very soluble in water, acetic acid(100), ethanol(95) or chloroform, soluble in acetic anhydride, and practically insoluble in ether.

Dissolve about 1.0 g of Propantheline Bromide in 50 mL of water; the pH of the solution is between 5.0 and 6.0.

Melting point—About 161 ºC (with decomposition, after drying).

Identification (1) To 5 mL of an aqueous solution of Propantheline Bromide (1 in 50), add 10 mL of sodium hydroxide TS, heat to boiling. Again, continue heating for 2 minutes, cool to 60 °C, and add 5 mL of dilute hydrochloric acid. After cooling, collect the precipitates, wash thoroughly with water, recrystallize from dilute ethanol, and dry at 105 °C for 1 hour; the melting point of the crystals is between 217 and 222 °C.

(2) Dissolve 10 mg of the crystals obtained from (1) in 5 mL of sulfuric acid; the solution exhibits a vivid yellow to yellowish red color.

(3) To 5 mL of an aqueous solution of Propantheline Bromide (1 in 50), add 2 mL of dilute nitric acid; the solution responds to the Qualitative Analysis (1) for bromide.

Purity ***Related substances***—Weigh accurately about 60 mg of Propantheline Bromide, dissolve in the mobile phase to make exactly 200 mL, and use this solution as the test solution. Separately, weigh accurately a suitable amount of 9-bromohydroxypropantheline RS, xanthantanoic acid RS and xanthon RS, dissolve in the mobile phase to obtain a solution containing 6.0 μg of 9-bromohydroxypropantheline and 1.5 μg each of xanthantanoic acid and xanthon per mL, and use this solution as the standard solution. Perform the test with each 50 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas, A_T and A_S, from the test solution and the standard solution, respectively; xanthantinoic acid and xanthone are NMT 0.5%, 9-bromohydroxyproprntheline is NMT 2.0%, and among the peaks, except the solvent peak other than the major peak from the test solution, the total area of the peaks of which the percentage area is NLT 0.1% is NMT 3.0%.

$$\text{Content (\%) of related substances} = 20 \times \frac{C}{C_X} \times \frac{A_T}{A_S}$$

C: Concentration (μg/mL) of each related substance in the standard solution

C_x: Concentration (μg/mL) of propantheline bromide in the test solution

$$\text{Content (\%) of all unidentified related substances, which is NLT 0.1\%} = \frac{A_i}{A_t}$$

A_i: Peak area of any unidentified peak

A_t: Total area of all peaks

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 mm).

Column: A stainless steel column, about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and pH 3.5 buffer solution (55 : 45).

Flow rate: 2.0 mL/min

System suitability

System performance: Proceed with 50 μL of the standard solution according to the above operating conditions; the resolution between the least resolved peaks is NLT 1.2.

System repeatability: Perform the test 6 times with each 50 μL of the standard solution according to the above operating conditions; the relative standard deviation of each peak area is NMT 6.0%.

pH 3.5 buffer solution—Prepare as directed under the Assay under Propantheline Bromide Tablets.

Loss on drying NMT 0.5% (2 g, 105 ºC, 4 hours).

Residue on ignition NMT 0.1% (1 g).

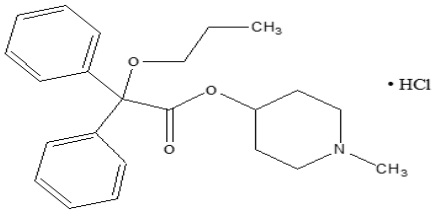
Assay Weigh accurately about 1.0 g of Propantheline Bromide, previously dried, dissolve in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 44.84 mg of $C_{23}H_{30}BrNO_3$

Packaging and storage Preserve in well-closed contain-

ers.

Propiverine Hydrochloride
프로피베린염산염



$C_{23}H_{29}NO_3 \cdot HCl$: 403.94

α-Phenyl-α-propoxy-benzeneacetic acid 1-methyl-4-piperidinyl ester hydrochloride, [*54556-98-8*]

Propiverine Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of propiverine hydrochloride ($C_{23}H_{29}NO_3 \cdot HCl$).

Description Propiverine Hydrochloride occurs as white crystals or a crystalline powder. It is freely soluble in methanol, chloroform, or acetic acid(100), soluble in water or anhydrous ethanol, sparingly soluble in acetonitrile, slightly soluble in acetone, and practically insoluble in ethyl acetate, ether or hexane.

Identification (1) Determine the infrared spectra of Propiverine Hydrochloride and propiverine hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) To 5 mL of an aqueous solution of Propiverine Hydrochloride (1 in 100), add 6 mL of ethyl acetate and 3 drops of silver nitrate TS; a white precipitate is formed. The precipitate does not dissolve in 0.5 mL of dilute nitric acid and dissolves on addition of 2 mL of ammonia TS with shaking to mix.

Melting point Between 212 and 216 °C.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Propiverine Hydrochloride in 20 mL of methanol; the solution is colorless and clear.

(2) ***Sulfate*—**Proceed with 0.4 g of Propiverine Hydrochloride according to the Sulfate in the General tests and perform the test. Prepare the control solution with 0.4 mL of 0.005 mol/L sulfuric acid (NMT 0.048%).

(3) ***Heavy metals***—Proceed with 1.0 g of Propiverine Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic*—**Proceed with 1.0g of Propiverine Hydrochloride according to Method 3 and perform the test. Prepare the control solution with 2.0 mL of arsenic standard solution (NMT 2 ppm).

(5) ***Related substances*—**Weigh accurately 50 mg of Propiverine Hydrochloride, dissolve in 100 mL of the mobile phase, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with each 15 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas of each peak from the test solution and the standard solution by the automatic integration method; the area of the peak at the relative retention time of about 0.28 to the propiverine peak from the test solution is not larger than 3/10 of the propiverine peak area from the standard solution. The total area of the peaks other than the propiverine peak and the peaks above from the test solution is not larger than 1/10 of the propiverine peak area from the standard solution. The total area of the peaks other than the propiverine peak from the test solution is not larger than 1/2 of the propiverine peak from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

Time span of measurement: About 2.5 times the retention time of propiverine, beginning after the solvent peak

System suitability

Test for required detectability: Pipet 1 mL of the standard solution and add the mobile phase to make exactly 20 mL. Confirm that the peak area of propiverine obtained from 15 μL of this solution is equivalent to 3.5% to 6.5% of that obtained from propiverine of the standard solution.

System performance: Perform the test with 15 μL of the standard solution according to the above operating conditions; the number of theoretical plates and symmetry factor of the propiverine peak are NLT 7000 and NMT 1.5, respectively.

System repeatability: Perform the test 6 times with each 15 μL of the standard solution according to the above operating conditions; the relative standard deviation of the propiverine peak area is NMT 2.0%.

Loss on drying NMT 1.0% (1 g, 105 °C, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about each 50 mg of Propiverine Hydrochloride and propiverine hydrochloride RS, previously dried, and dissolve in the mobile phase to make exactly 100 mL. Pipet each 10 mL of these solutions, add the mobile phase to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with each 15 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the propiverine peak areas, A_T and A_S.

Amount (mg) of propiverine hydrochloride ($C_{23}H_{29}NO_3 \cdot HCl$)
= Amount (mg) of propiverine hydrochloride RS $\times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and 15 cm in length, packed with phenylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of mobile phase A and acetonitrile (29 : 21).

Mobile phase A—Dissolve 2.21 g of potassium dihydrogen phosphate and 1.51 g of 1-sodium octanesulfonate in 650 mL of water and adjust pH to 3.2 with phosphoric acid.

Flow rate: 1.0 mL/min

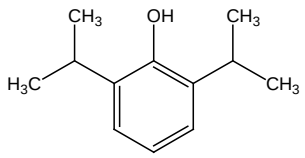
System suitability

System performance: Proceed with 15 μL of the standard solution and perform the test; the number of theoretical plates and symmetry factor of the propiverine peak are NLT 6000 and NMT 2.0, respectively.

System repeatability: Perform the test 6 times with each 15 μL of the standard solution according to the above operating conditions; the relative standard deviation of the propiverine peak area is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Propofol
프로포폴



$C_{12}H_{18}O$: 178.27

2,6-Diisopropylphenol [*2078-54-8*]

Propofol contains NLT 98.0% and NMT 102.0% of propofol ($C_{12}H_{18}O$).

Description Propofol occurs as a clear, colorless or pale yellow liquid.

It is very soluble in methanol or ethanol(95), slightly soluble in cyclohexane or 2-propanol, and very slightly soluble in water.

Identification (1) Determine the infrared spectra of Propofol and propofol RS as directed under the liquid film method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Refractive index n_D^{20}: Between 1.5125 and 1.5145.

Purity (1) ***Related substance I***—Weigh accurately 0.5 g of Propofol, dissolve in hexane to make exactly 10 mL, and use this solution as the test solution. Separately, dissolve exactly 5 mg of propofol related substance I [(2,6-bis(1-methylethyl)-1,4-benzoquinone] in hexane to make exactly 100 mL and use this solution as the standard solution. Perform the test with each 20 μL of the test solution and the standard solution according to the operating conditions in the Assay as directed under the Liquid Chromatography. The peak area of related substance I from the test solution is NMT 5 times that of related substance I from the standard solution.

Time span of measurement: About 6 times the retention time of propofol

(2) ***Related substances***—Weigh accurately 1.0 g of Propofol, dissolve in hexane to make exactly 10 mL, and use this solution as the test solution. Pipet 1.0 mL of the test solution, dilute with hexane to make exactly 100 mL. Pipet 1.0 mL of the resulting solution, dilute with to make exactly 10 mL, and use this solution as the standard solution. Perform the test with each 10 μL of the test solution and the standard solution according to the operating conditions in the Assay as directed under the Liquid Chromatography. The peak area of propofol related substance II [2-(1-methylethoxy)-1,3-bis(1-methylethyl)benzene] is NMT 0.4 times the peak area of propofol from the standard solution (0.2%, response factor of 0.2). The peak area of propofol related substance III [3,3',5,5'-tetrakis(1-methylethyl)biphenyl-4,4'-diol} is NMT 0.4 times the peak area of propofol from the standard solution (0.01%, response factor of 4.0). Total area of the peaks other than propofol and two related substances above is NMT 0.5 time the peak area of propofol from the standard solution (0.05%); the total amount of all related substances, including related substance II and III, is NMT 0.3%. Exclude any peaks of which the peak area is NMT 0.25 times the peak area of propofol from the standard solution.

Assay Weigh accurately about 0.24 g of Propofol, dissolve in hexane to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.24 g of propofol RS, dissolve in hexane to make exactly 100 mL, and use this solution as the standard solution. Perform the test with each 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak areas, A_T and A_S, of propofol from each solution.

Amount (mg) of propofol ($C_{12}H_{16}O$)
= Amount (mg) of propofol RS $\times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer

(wavelength: 275 nm).

Column: A stainless steel column, about 5 mm in internal diameter and about 20 cm in length, packed with silica gel for liquid chromatography (50 μm in particle diameter).

Mobile phase: A mixture of hexane, acetonitrile and ethanol(95) (990 : 7.5 : 1).

Flow rate: 2.0 mL/min

System suitability

System performance: Proceed with 10 μL of the system suitability solution (I) according to the above operating conditions; related substance I (retention time: about 2.5 minutes) and propofol (retention time: about 3 minutes) are eluted in this order with the resolution being NLT 4.0. Proceed with 10 μL of the system suitability solution (II) according to the above operating conditions; the relative retention times of related substance II and III to that of propofol is about 0.5 and about 5, respectively.

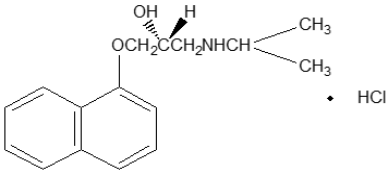
Time span of measurement: About 5 times the retention time of propofol.

System suitability solution (I)—Dissolve 5 mg of propopol RS and 15 mg of related substance I RS in hexane to make 50 mL.

System suitability solution (II)—Dissolve 1.0 g of propopol RS in hexane to make 10 mL.

Packaging and storage Preserve in light-resistant, tight containers, filled with inert gas.

Propranolol Hydrochloride
프로프라놀롤염산염



and enantiomer

$C_{16}H_{21}NO_2 \cdot HCl$: 295.80

(*RS*)-1-(Isopropylamino)-3-(naphthalen-1-yloxy)propan-2-ol hydrochloride [*318-98-9*]

Propranolol Hydrochloride, when dried, contains NLT 99.0% and NMT 101.0% of propranolol hydrochloride ($C_{16}H_{21}NO_2 \cdot HCl$).

Description Propranolol Hydrochloride occurs as a white crystalline powder. It is odorless and has a bitter taste.

It is freely soluble in methanol, soluble in water, acetic acid(100) or ethanol(95), sparingly soluble in chloroform, and practically insoluble in ether.

The pH of a solution of 1.0 g of Propranolol Hydrochloride dissolved in 100 mL of water is between 5.0 and 6.0.

It is colored by light.

Identification (1) Determine the absorption spectra of solutions of Propranolol Hydrochloride and propranolol hydrochloride RS in methanol (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Propranolol Hydrochloride and propranolol hydrochloride RS, previously dried, as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy, respectively; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Propranolol Hydrochloride (1 in 50) responds to the Qualitative Analysis (2) for chloride.

Melting point Between 163 and 166 ℃.

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Propranolol Hydrochloride in 20 mL of water; the solution is colorless and clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Propranolol Hydrochloride according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve 20 mg of Propranolol Hydrochloride in 10 mL of the mobile phase and use this solution as the test solution. Pipet 2 mL of this solution and add the mobile phase to make exactly 100 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 10 mL, and use this solution as the standard solution. Perform the test with each exactly 20 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas of each solution by the automatic integration method; the area of any peak other than the propranolol peak from the test solution is not larger than 1/2 times the area of the propranolol peak from the standard solution. The total area of the peaks other than the propranolol peak from the test solution is not larger than 2 times the area of the propranolol peak from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 292 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 1.6 g of sodium lauryl sulfate and 0.31 g of tetrabutylammonium phosphate in 450 mL of water, add 1 mL of sulfuric acid and 550 mL of acetonitrile for liquid chromatography, and adjust the pH to 3.3 with 2 mol/L sodium hydroxide TS.

Flow rate: Adjust the flow rate so that the retention time of propranolol is about 4 minutes.

System suitability

Test for required detectability: Take exactly 5 mL of the standard solution and add the mobile phase to make exactly 20 mL. Confirm that the peak area of propranolol obtained from 20 μL of this solution is between 17% and 33% of that of propranolol from the standard solution.

System performance: Proceed with 20 μL of the standard solution according to the above operating conditions and perform the test; the number of theoretical plates and symmetry factor of the propranolol peak are NLT 3000 plates and NMT 2.0, respectively.

System repeatability: Perform the test 6 times with each 20 μL of the standard solution according to the above operating conditions; the relative standard deviation of the area of the propranolol peak is NMT 2.0%.

Time span of measurement: About 5 times the retention time of propranolol.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

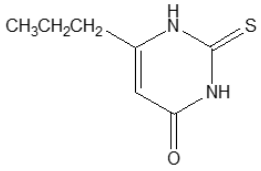
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Propranolol Hydrochloride, previously dried, and dissolve it in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 29.580 mg of $C_{16}H_{21}NO_2 \cdot HCl$

Packaging and storage Preserve in light-resistant, well-closed containers.

Propylthiouracil
프로필티오우라실



$C_7H_{10}N_2OS$: 170.23
6-Propyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one [*51-52-5*]

Propylthiouracil, when dried, contains NLT 98.0% and NMT 101.0% of propylthiouracil ($C_7H_{10}N_2OS$).

Description Propylthiouracil occurs as a white powder. It is odorless and has a bitter taste.
It is sparingly soluble in ethanol(95) and very slightly soluble in water or ether.
It dissolves in sodium hydroxide TS or ammonia TS.

Identification (1) To 20 mg of Propylthiouracil, add 7 mL of bromine TS, shake well to mix for 1 minute, and heat until the color of bromine TS disappears. Cool, filter, and add 10 mL of barium hydroxide TS to the filtrate; a white precipitate is produced. The color of the precipitate does not turn purple within 1 minute.

(2) Take 5 mL of a hot saturated solution of Propylthiouracil, add 2 mL of a solution of sodium pentacyanoammine ferroate (1 in 100); a green color develops.

Melting point Between 218 and 221 ℃.

Purity (1) ***Sulfate***—Triturate Propylthiouracil to very finely powder, take 0.75 g of the Propylthiouracil powder, add 25 mL of water, and heat on a steam bath for 10 minutes. Cool, filter, and wash the residue with water to obtain 30 mL of the filtrate. To 10 mL of the filtrate, add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution to perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid (NMT 0.077%).

(2) ***Heavy metals***—Proceed with 1.0 g of Propylthiouracil according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Selenium***—Proceed with 0.2 g of Propylthiouracil as directed under the Oxygen Flask Combustion, using 25 mL of diluted nitric acid (1 in 30) as absorbent. Use a 1 L combustion flask. After combustion, wash the stopper and the inside of the flask with 10 mL of water. Transfer the liquid inside the flask to a 150-mL beaker using 20 mL of water. Heat gently to boil, boil for another 10 minutes, cool to room temperature, and use this solution as the test solution. Separately, pipet 6 mL of standard selenium stock solution, add 25 mL of diluted nitric acid (1 in 30) and 25 mL of water, and use this solution as the standard solution. Adjust the pH of the test solution and standard solution to 2.0 ± 0.2 with diluted ammonia water(28) (1 in 2), add water to make exactly 60 mL, transfer to a separatory funnel using 10 mL of water, and wash the separatory funnel with 10 mL of water. Add 0.2 g of hydroxylamine, dissolve by stirring, immediately add 5 mL of 2,3-diaminonaphthalene TS, and put a stopper. Mix by stirring and allow to stand at room temperature for 100 minutes. Add 5.0 mL of cyclohexane, shake vigorously for 2 minutes, and allow to stand until the layers are separated. Remove the water layer, centrifuge the cyclohexane extract to remove water, and take the cyclohexane layer. With these solutions and the control solution prepared in the same way with 25 mL of water added to 25 mL of diluted nitric acid (1 in 30), perform the test as directed under the Ultraviolet-visible Spectroscopy. Determine the absorption at the absorbance maximum wavelength of about 380 nm; the absorption of the solution prepared with the test solution is not greater than the absorption from the standard solution (NMT 30 ppm).

(4) ***Related substances***—Weigh accurately about 100 mg of Propylthiouracil, dissolve in methanol to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately 10 mg of propylthiouracil RS, dissolve in methanol to make exactly 50 mL, and use this solution as the standard solution. With these solu-

tions, perform the test as directed under the Thin Layer Chromatography. Spot each 10 μL of the test solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of toluene, ethyl acetate and formic acid (10 : 9 : 1) to a distance of about 15 cm and air-dry the plate. Examine the plate under ultraviolet light (main wavelengths: 254 nm and 365 nm); the spots other than the principal spot obtained from the test solution are not larger or not more intense than those from the standard solution (NMT 2.0%). Disregard any spots remaining at the starting line.

(5) ***Thiourea***—To 0.30 g of Propylthiouracil, add 50 mL of water, attach a reflux condenser, and heat to dissolve for 5 minutes. Cool and filter. To 10 mL of the filtrate, add 3 mL of ammonia TS, shake well, and add 2 mL of silver nitrate TS; the color of the resulting solution is not more intense than the following control solution.

Control solution—Weigh accurately 60 mg of thiourea and dissolve in water to make exactly 100 mL. Pipet 2 mL of this solution and add water to make exactly 100 mL. Take 10 mL of this solution and proceed in the same manner.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Propylthiouracil, previously dried, and add 30 mL of water. Add 30 mL of 0.1 mol/L sodium hydroxide to this solution, heat to boil, and dissolve by stirring. Wash down the solid residue inside the flask with a small volume of water and add 50 mL of 0.1 mol/L silver nitrate with stirring. Boil gently for 5 minutes, add 1 mL to 2 mL of bromothymol blue TS, and titrate with 0.1 mol/L sodium hydroxide VS until a persistent bluish green color develops. Determine the total volume of 0.1 mol/L sodium hydroxide VS consumed.

Each mL of 0.1 mol/L sodium hydroxide VS
= 8.512 mg of $C_7H_{10}N_2OS$

Packaging and storage Preserve in light-resistant, well-closed containers.

Propylthiouracil Tablets
프로필티오우라실 정

Propylthiouracil Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of propylthiouracil ($C_7H_{10}N_2OS$: 170.23).

Method of preparation Prepare as directed under Tablets, with Propylthiouracil.

Identification Weigh an amount of Propylthiouracil Tablets, previously powdered, equivalent to 0.3 g of propylthiouracil ($C_7H_{10}N_2OS$) according to the labeled amount, add 5 mL of ammonia TS, and allow to stand for 5 minutes shaking occasionally. Then add 10 mL of water and centrifuge. Add acetic acid to the clear supernatant, collect the resulting precipitates by filtering, recrystallize with water, and dry at 105 °C for 1 hour; the melting point is 218 to 221 °C. With the precipitates, perform the test as directed under the Identification of Propylthiouracil.

Dissolution Perform the test with 1 tablet of Propylthiouracil Tablets at 75 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of Solution 2 for dissolution test as the dissolution medium. Take NLT 20 mL of the dissolution medium 30 minutes after starting the test and filter through a membrane filter with a pore size of NMT 0.8 μm. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 50 mg of propylthiouracil RS, previously dried at 105 ℃ for 3 hours, dissolve in Solution 2 for dissolution test to make exactly 1000 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 274 nm as directed under the Ultraviolet-visible Spectroscopy.
Meets the requirements if the dissolution rate of Propylthiouracil Tablets in 30 minutes is NLT 80%.

Dissolution rate (%) of the labeled amount of propylthiouracil ($C_7H_{10}N_2OS$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 90$$

*W*s: Amount (mg) of reference standards
C: Labeled amount (mg) of propylthiouracil ($C_7H_{10}N_2OS$) per tablet

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Propylthiouracil Tablets, and powder them. Weigh accurately an amount of the powder equivalent to about 50 mg of propylthiouracil ($C_7H_{10}N_2OS$), add 150 mL of Solution 2 for dissolution test, sonicate to disperse the particles into small pieces, and add Solution 2 for dissolution test to make exactly 200 mL. Filter this solution through a membrane filter with a pore size of NMT 0.45 μm. Discard the first 5 mL of the filtrate, take exactly 2 mL of the subsequent filtrate, add Solution 2 for dissolution test to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of propylthiouracil RS, dried at 105 °C for 2 hours, and dissolve in Solution 2 for dissolution test to make exactly 200 mL. Pipet 2 mL of this solution, add Solution 2 for dissolution test to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at 274 nm as directed under the

Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of propylthiouracil } (C_7H_{10}N_2OS) = \text{Amount (mg) of propylthiouracil RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in light-resistant, well-closed containers.

Protamine Sulfate
프로타민황산염

Protamine Sulfate is a sulfate of protamine, obtained from the mature seminal glands of fish of the family *Salmonidae*. Protamine Sulfate binds with heparin, and binds to NLT 100 units heparin sodium per mg of protamine sulfate, calculated on the dried basis.

Description Protamine Sulfate occurs as a white to pale yellowish gray powder.
It is sparingly soluble in water and practically insoluble in ethanol(95) or ether.

Identification (1) Dissolve 1 mg of Protamine Sulfate in 2 mL of water, add 5 drops of 0.1 g of 1-naphthol dissolved in 100 mL of diluted ethanol (7 in 10) and 5 drops of sodium hypochlorite TS, and add sodium hydroxide TS to alkalize; the resulting solution exhibits a vivid red color.

(2) Add 5 mg of Protamine Sulfate to 1 mL of water, dissolve by warming, and add 1 drop of sodium hydroxide solution (1 in 10) and 2 drops of copper(II) sulfate TS; the resulting solution exhibits a purple color.

(3) A solution of Protamine Sulfate (1 in 20) responds to the Qualitative Analysis for sulfate.

pH Dissolve 1.0 g of Protamine Sulfate in 100 mL of water; the pH of this solution is between 6.5 and 7.5.

Absorbance Measure the absorbance of a 1.0% aqueous solution of Protamine Sulfate as directed under Ultraviolet-visible Spectroscopy using water as the control solution; the difference in absorbance at the wavelengths of 260 nm and 280 nm is NMT 0.1.

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Protamine Sulfate in 10 mL of water; the resulting solution is clear and colorless.

(2) ***Heavy metals***—Weigh 1.0 g of Protamine Sulfate, add 0.5 g of magnesium oxide to mix, and carbonize. After cooling, ignite for 1 hour at NMT 800 ℃ to incinerate. Cool, then dissolve the residue in a mixture of hydrochloric acid and water (1 :1). Add 0.1 mL of phenolphthalein TS and add ammonia water(28) dropwise until the solution turns pale red. Allow to cool, add acetic acid(100) until the color disappears, and add another 0.5 mL. Filter and wash, if necessary. Add water to make 20 mL and use this solution as the test solution. Separately, proceed in the same manner as in the test solution using 2.0 mL of lead standard solution instead of Protamine Sulfate. To 10 mL of this solution, add 2 mL of the test solution and use this solution as the control solution. Separately, add 2 mL of the test solution to 10 mL of water and use this solution as the blank test solution. To 12 mL each of the test solution, the control solution and the blank test solution, add 2 mL of acetate buffer solution, pH 3.5, mix, add 1.2 mL of thioacetamide TS, and immediately mix. Allow the mixture to stand for 2 minutes; the color of the test solution is not more intense than that of the control solution (NMT 20 ppm).

System suitability—The control solution exhibits a faint brown color compared to the blank test solution. To the test solution, add 2.0 mL of lead standard solution. Then, to 10 mL of this solution, add 2 mL of the test solution, and use this solution as the system suitability solution. The system suitability solution is more intense than or equal to the control solution.

(3) ***Mercury***—Weigh 2.0 g of Protamine Sulfate, put in a 250-mL Erlenmeyer flask with a glass stopper, then add 20 mL of a mixture of nitric acid and sulfuric acid (1 : 1). Connect a reflux condenser and boil for 1 hour. Cool, then carefully add water to dilute. Boil again until nitric acid fumes are no longer produced. Cool, carefully add water to make 200 mL, then filter. Transfer 50 mL of the filtrate to a separatory funnel, and extract multiple times using a small amount of chloroform until the chloroform layer becomes colorless. Discard the chloroform layer, add 25 mL of dilute sulfuric acid, 115 mL of water and 10 mL of hydroxylamine hydrochloride solution (2 in 10), then titrate with dithizone solution; vigorously shake the mixture to mix, and titrate until a bluish green color is produced (NMT 10 ppm).

Each mL of dithizone solution = 1 μg of Hg

Dithizone solution—Dissolve 40.0 mg of dithizone in 1000 mL of chloroform. Pipet 30.0 mL of this solution and add chloroform to make 100 mL.

Loss on drying NMT 5.0% (1 g, 105 ℃, 3 hours).

Abnormal toxicity Dissolve 0.5 mg of Protamine Sulfate in 0.5 mL of water for injection, and inject intravenously for 15 to 30 seconds to each of 5 healthy mice weighing 17 to 24 g. Use animals in which no abnormalities are observed for NLT 5 days prior to the test. No animals die when observed for 24 hours after administration. If one animal dies, repeat the test with 5 animals, and make sure no animal dies during the 24 hour post-dosage observation.

Nitrogen content Weigh accurately about 10 mg of Protamine Sulfate, and perform the test as directed under the Nitrogen Determination; the amount of nitrogen (N: 14.01) is NLT 22.5% and NMT 25.5%, calculated on the dried basis.

Sulfate Weigh accurately about 0.150 g of Protamine Sulfate, dissolve in 75 mL of water, add 5 mL of hydrochloric acid TS, and boil while slowly adding 10 mL of barium chloride TS. Close the lid, allow to stand for 1 hour on a steam bath, then filter. Wash the residue with hot water several times, dry, then ignite to a constant mass. Multiply 0.4117 to the amount of residue obtained; the amount is NLT 16% and NMT 22%, calculated on the dried basis.

Heparin-binding test (1) ***Test solution A***—Weigh accurately 15 mg of Protamine Sulfate, dissolve in water to make exactly 100 mL, and use this solution as the test solution. Prepare 3 of the same test solution, and use these solutions as the test solutions (A1), (A2) and (A3).

(2) ***Test solution B***—Pipet 10 mL each of test solutions (A1), (A2) and (A3), add exactly 5 mL of water to each, and use these solutions as test solutions (B1), (B2) and (B3).

(3) ***Test solution C***—Pipet 10 mL each of test solutions (A1), (A2) and (A3), add exactly 20 mL of water to each, and use these solutions as test solutions (C1), (C2) and (C3).

(4) ***Standard heparin sodium solution***—Weigh accurately a certain amount of heparin sodium RS, dissolve in water to prepare a solution containing 20 units per mL, and use this solution as the standard solution.

(5) ***Procedure***—Pipet 2 mL of the test solution, put in a cell for spectrophotometry, add standard heparin sodium solution dropwise, and mix. Then measure the transmission rate at 500 nm as directed under the Ultraviolet-visible Spectroscopy. Determine the amount *V* mL of standard solution consumed until a sudden change in transmission rate is observed. Repeat 2 times for each ***test*** solution to carry out a total of 18 tests.

(6) ***Calculation***—Using the amount consumed (mL) of the standard solution obtained from each test solution, calculate the amount of heparin binding to 1 mg of Protamine Sulfate according to the following formula, and calculate the average for the 18 total tests. Here, the test is valid when the relative standard deviation of the 6 results obtained from test solutions A, B and C is NMT 5%, and the relative standard deviation of the 6 results from each of the test solution combinations (A1, B1, C1), (A2, B2, C2) and (A3, B3, C3) is NMT 5%.

$$\text{Amount (heparin units) of heparin binding to 1 mg of Protamine Sulfate} = \text{Concentration of the standard solution (heparin units/mL)} \times V \frac{50}{W_T} \times d$$

W_T: Amount (mg) of sample, calculated on the anhydrous basis

d: Dilution factor of each test solution with respect to test solution (A)

Packaging and storage Preserve in tight containers.

Protamine Sulfate Injection
프로타민황산염 주사액

Protamine Sulfate Injection is an aqueous solution for injection. Protamine Sulfate Injection contains NLT 92.0% and NMT 108.0% of the labeled amount of protamine sulfate and binds to NLT 100 units of heparin sodium per mg of protamine sulfate.

Method of preparation Prepare as directed under Injections, with Protamine Sulfate.

Description Protamine Sulfate Injection occurs as a colorless liquid, and is odorless or has the odor of the preservative.

Identification (1) Take an amount of Protamine Sulfate Injection equivalent to 1 mg of Protamine Sulfate according to the labeled amount, add water to make 2 mL, and proceed as directed under the Identification (1) under Protamine Sulfate.

(2) Take an amount of Protamine Sulfate Injection equivalent to 5 mg of Protamine Sulfate according to the labeled amount, add water to make 1 mL, and proceed as directed under the Identification (2) under Protamine Sulfate.

(3) Protamine Sulfate Injection responds to the Qualitative Analysis for sulfate.

pH Between 5.0 and 7.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 6.0 EU per mg of protamine sulfate.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay (1) ***Protein content***—Weigh accurately an amount of Protamine Sulfate Injection equivalent to about 10 mg of Protamine Sulfate, put in a Kjeldahl flask, and evaporate to dryness on a steam bath through air, and perform the test according to the Nitrogen Determination. Determine the amount protein, calculating 0.24 mg of nitrogen (N : 14.01) as 1 mg of protein.

(2) ***Heparin binding capacity test***—Perform the test as directed under the Heparin binding capacity test under Protamine sulfate, and determine the amount of reactive heparin sodium binding per mg of protein. The test solution for (A) is prepared as follows. Weigh accurately an amount of Protamine Sulfate Injection equivalent to 15.0 mg of Protamine Sulfate, add water to make exactly 100

mL, and use this solution as the test solution. Prepare 3 units of the same test solution, and use these as test solutions (A1), (A2) and (A3). The amount of reactive heparin sodium per mg of Protamine Sulfate Injection according to the labeled amount is NLT 100 units.

Packaging and storage Preserve in hermetic containers.

Protease
프로테아제

Protease is an enzyme preparation with protein digestion activity, prepared from a useful mycetoma of the genus *Bacillus*, the genus *Aspegillus* or the genus *Streptomyces*, and contains NLT 90.0% of the digestive power unit of the labeled amount.

Description Protease occurs as a white to pale yellow or pale brown powder and has a characteristic odor.

Identification Weigh about 10 mg of Protease, add it to 10 mL of gelatin solution (2 in 10), previously warmed to 40℃, shake to mix, and makes it reaction at 40 ℃ for 5 minutes; the viscosity of the solution decreases.

pH Dissolve 1.0 g of Protease in 100 mL of water; the pH of this solution is between 6.7 and 8.3.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Protease according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Protease according to Method 3, and perform the test (NMT 1 ppm).

Loss on drying NMT 5.0% (1 g, 105℃, 2 hours).

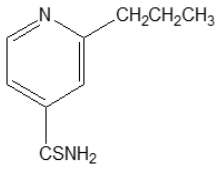
Assay (1) ***Test solution***—Dissolve Protease in phosphate buffer solution, pH 7.4, to adjust to contain 15 to 25 protein digestion activity units per mL, and use this solution as the test solution.

(2) ***Substrate solution***—Use the substrate solution 2 in the Assay for protein digestion activity under the Digestive Power. However, adjust the pH to 7.4.

(3) ***Procedure***—Proceed as directed under the Assay for protein digestion activity under the Digestive Power. However, use trichloroacetic acid B as the precipitation TS.

Packaging and storage Preserve in tight containers.

Prothionamide
프로티온아미드



$C_9H_{12}N_2S$: 180.27
2-Propylpyridine-4-carbothioamide [*14222-60-7*]

Prothionamide, when dried, contains NLT 98.0% and NMT 101.0% of prothionamide ($C_9H_{12}N_2S$).

Description Prothionamide occurs as yellow crystals or a crystalline powder and has a slightly distinctive odor.
It is freely soluble in methanol or acetic acid(100), soluble in ethanol(95), slightly soluble in ether, and practically insoluble in water.
It dissolves in dilute hydrochloric acid or dilute sulfuric acid.

Identification (1) Mix 50 mg of Prothionamide with 0.1 g of 1-chloro-2,4-dinitrobenzene, transfer about 10 mg of the mixture to a test tube, and heat over a small flame for several seconds to melt. After cooling, add 3 mL of potassium hydroxide-ethanol TS; the resulting solution exhibits a red to orange color.

(2) Put 0.5 g of Prothionamide in a 100-mL beaker, add 20 mL of sodium hydroxide TS, and heat to dissolve while shaking occasionally; the generated gas changes a moistened red litmus paper to blue. Again, gently boil this solution until it reaches 3 - 5 mL, cool it, then slowly add 20 mL of acetic acid(100) and heat it on a steam bath; the generated gas changes the moistened lead acetate paper to black. Concentrate the solution to 3 - 5 mL while blowing air on a steam bath, cool, add 10 mL of water, mix well, filter with suction, quickly recrystallize the residue with water, and dry in a desiccator (in vacuum, silica gel) for 6 hours; the melting point is 198 to 203 ℃ (with decomposition).

Melting point Between 142 and 145 ºC.

Purity (1) ***Clarity and color of solution***—Dissolve about 0.5 g of Prothionamide in 20 mL of ethanol(95); the resulting solution clear and yellow.

(2) ***Acidity***—Dissolve 3.0 g of Prothionamide in 20 mL of methanol by warming, add 100 mL of water, shake to mix in iced water to precipitate crystals, then filter. Take 80 mL of the filtrate, bring it to room temperature, add 0.8 mL of cresol red TS and 0.20 mL of 0.1 mol/L sodium hydroxide TS; the resulting solution exhibits a red color.

(2) ***Heavy metals***—Proceed with 1.0 g of Prothionamide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic***—Proceed with 0.6 g of Prothionamide

according to Method 3 and perform the test. However, add 10 mL of a solution of magnesium nitrate in ethanol(95) (1 in 50), add 1.5 mL of hydrogen peroxide(30), and ignite to burn (NMT 3.3 ppm).

Loss on drying NMT 0.5% (1 g, 80 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Prothionamide, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 mL of 1-naphtholbenzein TS). However, the endpoint of the titration is when the color changes from orange to dark reddish brown. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 18.03 mg of $C_9H_{12}N_2S$

Packaging and storage Preserve in light-resistant, well-closed containers.

Prothionamide Tablets
프로티온아미드 정

Prothionamide Tablets contain NLT 92.5% and NMT 107.5% of the labeled amount of prothionamide ($C_9H_{12}N_2S$: 180.27).

Method of preparation Prepare as directed under Tablets, with Prothionamide.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Dissolution Perform the test with 1 tablet of Prothionamide Tablets at 100 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of Solution 1 for dissolution test as the dissolution medium. Take the dissolved solution 45 minutes after starting the dissolution test, and filter it. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add dissolution medium to obtain exactly V' mL of a solution containing about 100 μg of prothionamide ($C_9H_{12}N_2S$) according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 10 mg of prothionamide RS, dissolve in dissolution medium to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of prothionamide ($C_9H_{12}N_2S$) in each solution. Meets the requirements if the dissolution rate of Prothionamide Tablets in 45 minutes is NLT 80%.

Dissolution rate (%) of the labeled amount of prothionamide ($C_9H_{12}N_2S$)

$$= W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 900$$

W_S: Amount (mg) of prothionamide RS
C: Labeled amount (mg) of prothionamide ($C_9H_{12}N_2S$) per tablet

Operating conditions
Detector: An ultraviolet absorption photometer (wavelength: 254 nm).
Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).
Column temperature: A constant temperature of about 40 °C.
Mobile phase: A mixture of 0.1 mol/L sodium dihydrogen phosphate TS, acetonitrile and anhydrous acetic acid (72 : 28 : 1).
Flow rate: 1.0 mL/min
System suitability
System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak areas of prothionamide is NMT 2.0%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately and finely powder NLT 20 tablets of Prothionamide Tablets. Weigh accurately an amount of the powder, equivalent to about 20 mg of prothionamide ($C_9H_{12}N_2S$), add methanol to make exactly 200 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of prothionamide RS, transfer it into 200-mL volumetric flask, prepare in the same manner as the test solution, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and determine the peak areas, A_T and A_S, of prothionamide, respectively, in each solution.

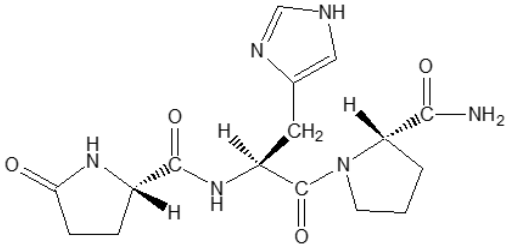
Amount (mg) of prothionamide ($C_9H_{12}N_2S$)

$$= Amount\ (mg)\ of\ \text{prothionamide RS} \times \frac{A_T}{A_S}$$

Operating conditions
Detector: An ultraviolet absorption photometer (wavelength: 254 nm).
Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).
Column temperature: A constant temperature of about 30 °C.
Mobile phase: A mixture of 0.1 mol/L sodium dihydrogen phosphate TS, acetonitrile and acetic acid(100) (720 : 280 : 10).
Flow rate: 1 mL/min

Packaging and storage Preserve in well-closed containers.

Protirelin
프로티렐린



$C_{16}H_{22}N_6O_4$: 362.38
(2*S*)-*N*-{(2*S*)-1-[(*S*)-2-Carbamoylpyrrolidin-1-yl]-3-(1*H*-imidazol-4-yl)-1-oxopropan-2-yl}-5-oxopyrrolidine-2-carboxamide [*24305-27-9*]

Protirelin contains NLT 98.5% and NMT 101.0% of protirelin ($C_{16}H_{22}N_6O_4$), calculated on the anhydrous basis.

Description Protirelin occurs as a white powder.
It is freely soluble in water, methanol, acetic acid(100) or ethanol(95).
It is hygroscopic.

Identification (1) Put 10 mg of Protirelin in a hard glass test tube, add 0.5 mL of 6 mol/L hydrochloric acid TS, seal the top of the test tube, and carefully heat it at 110 °C for 5 hours. After cooling, open it, transfer the contents to a beaker, and evaporate to dryness on a steam bath. Dissolve the residue in 1 mL of water and use this solution as the test solution. Separately, dissolve 80 mg of L-glutamic acid, 0.12 g of L-histidine hydrochloride and 60 mg of L-proline in 20 mL of water, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, water, acetic acid (100) and pyridine (4: 1: 1 : 1) as the developing solvent to a distance of about 12 cm, and dry the plate at 100 °C for 30 minutes. Spray a solution of ninhydrin in acetone (1 in 50) evenly on the plate and heat the plate at 80 ℃ for 5 minutes; the three spots obtained from the test solution have the same color and R_f value as each corresponding spot obtained from the standard solution.

(2) Determine the infrared spectra of Protirelin and protirelin RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

Optical rotation $[\alpha]_D^{20}$: Between -66.0° and -69.0° (0.1 g calculated on the anhydrous basis, water, 20 mL, 100 mm).

pH Dissolve 0.2 g of Protirelin in 10 mL of water; the pH of this solution is between 7.5 and 8.5.

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g of Protirelin in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Protirelin according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve 0.20 g of Protirelin in 10 mL of water, and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution onto the plate (1) made of silica gel for thin-layer chromatography, and drop 5 μL of the test solution onto the plate (2) made of silica gel for thin-layer chromatography. Next, develop the plates with a mixture of 1-butanol, water, acetic acid(100), and pyridine (4: 2: 1 : 1) as the developing solvent to a distance of about 12 cm, and dry the plates at 100 °C for 30 minutes. Spray a mixture of a solution of sulfamic acid in 1 mol/L hydrochloric acid TS (1 in 200) and sodium nitrite solution (1 in 20) (1 : 1) evenly onto the plate (1) and air-dry the plate. Spray a sodium carbonate solution (1 in 10) evenly onto the plate; the spots other than the principal spot from the test solution are not more intense than the spot from the standard solution. Additionally, spay an solution of ninhydrin in acetone (1 in 50) evenly onto the plate (2) and heat at 80 °C for 5 minutes; no colored spot appear.

Water NMT 5.0% (0.1 g, volume titration, direct titration).

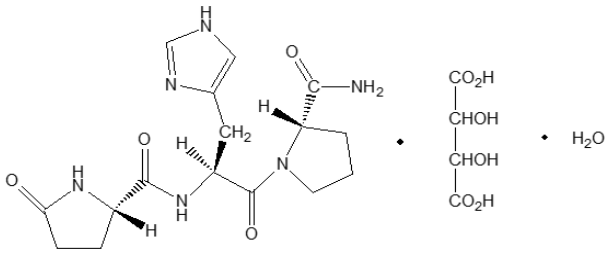
Residue on ignition NMT 0.3% (0.2 g).

Assay Weigh accurately about 70 mg of Protirelin, dissolve it in 50 mL of acetic acid(100) and titrate with 0.02 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.02 mol/L perchloric acid VS
= 7.248 mg of $C_{16}H_{22}N_6O_4$

Packaging and storage Preserve in tight containers.

Protirelin Tartrate Hydrate
프로티렐린타르타르산염수화물



Protirelin Tartrate $C_{16}H_{22}N_6O_4 \cdot C_4H_6O_6 \cdot H_2O$: 530.49
(2*S*)-*N*-{(2*S*)-1-[(*S*)-2-Carbamoylpyrrolidin-1-yl]-3-(1H-imidazol-4-yl)-1-oxopropan-2-yl}-5-oxopyrrolidine-2-carboxamide
(2*R*,3*R*)-2,3-dihydroxybutanedioate hydrate [*53935-32-3*, anhydride]

Protirelin Tartrate Hydrate contains NLT 98.5% and NMT 101.0% of protirelin tartrate ($C_{16}H_{22}N_6O_4 \cdot C_4H_6O_6$: 512.47), calculated on the anhydrous basis.

Description Protirelin Tartrate Hydrate occurs as white to pale yellowish white crystals or a crystalline powder.
It is freely soluble in water, sparingly soluble in acetic acid(100), and practically insoluble in ethanol(95) or ether.

Melting point—About 187 °C (with decomposition).

Identification (1) To 1 mL of an aqueous solution of Protirelin Tartrate Hydrate (1 in 1000), add 2 mL of a solution of 4-nitrobenzenediazonium fluoroborate (1 in 2000) and 2 mL of boric acid-potassium chloride-sodium hydroxide buffer solution, pH 9.0; the resulting solution exhibits a red color.

(2) Dissolve 30 mg of Protirelin Tartrate Hydrate in 5 mL of sodium hydroxide TS and put 1 drop of copper(II) sulfate TS; the resulting solution exhibits a violet color.

(3) Weigh 0.2 g of Protirelin Tartrate Hydrate, add 5.0 mL of 6 mol/L hydrochloric acid TS, and boil under a reflux condenser for 7 hours. After cooling, take 2.0 mL of this solution, evaporate to dryness on a steam bath, dissolve the residue in 2.0 mL of water, and use the solution as the test solution. Separately, weigh 22 mg of L-glutamic acid, 32 mg of L-histidine hydrochloride and 17 mg of L-proline, add 2.0 mL of 0.1 mol/L hydrochloric acid TS, warm to dissolve, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, water, acetic acid(100) and pyridine (4: 1: 1 : 1) as the developing solvent to a distance of about 12 cm, and dry the plate at 100 °C for 30 minutes. Spray a solution of ninhydrin in acetone (1 in 50) evenly onto the plate and heat the plate at 80 °C for 5 minutes; the three spots from the test solution have the same color and R_f value as each corresponding spot from the standard solution.

(4) An aqueous solution of Protirelin Tartrate Hydrate (1 in 40) responds to the Qualitative Analysis for tartrate.

Optical rotation $[\alpha]_D^{20}$: Between -50.0° and -53.0° (0.5 g calculated on the anhydrous basis, water, 25 mL, 100 mm).

pH Dissolve 1.0 g of Protirelin Tartrate Hydrate in 100 mL of water; the pH of this solution is between 3.0 and 4.0.

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Protirelin Tartrate Hydrate in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Protirelin Tartrate Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Weigh 1.0 g of Protirelin Tartrate Hydrate and transfer to a porcelain crucible. Add 10 mL of a solution of magnesium nitrate in ethanol(95) (1 in 10), ignite the ethanol to burn, and then heat gradually to incinerate. If a charred substance still remains by this method, moisten with a small amount of nitric acid, and ignite to incinerate. After cooling, to the residue, add 10 mL of dilute hydrochloric acid, and heat on a steam bath to dissolve. Use this solution as the test solution and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.60 g of Protirelin Tartrate Hydrate in 10 mL of water, and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution onto the plate (1) made of silica gel for thin-layer chromatography, and drop 5 μL of the test solution onto the plate (2) made of silica gel for thin-layer chromatography. Next, develop the plates using a mixture of chloroform, methanol and ammonia water(28) (6 : 4: 1) as the developing solvent to a distance of about 10 cm, and dry the plates at 100 °C for 30 minutes. Spray a mixture of a solution of sulfamic acid in 1 mol/L hydrochloric acid solution (1 in 200) and sodium nitrite solution (1 in 20) (1 : 1) evenly onto the plate (1) and air-dry the plate. Next, spray sodium carbonate solution(1 in 10) evenly onto the plate; the spots other than the principal spot from the test solution are not more intense than the spot from the standard solution. Additionally, spay an solution of ninhydrin in acetone (1 in 50) evenly onto the plate (2) and heat at 80 °C for 5 minutes; no colored spots appear.

Water NMT 4.5% (0.2 g, volume titration, direct titration).

Residue on ignition NMT 0.2% (0.5 g).

Assay Weigh accurately about 0.5 g of Protirelin Tartrate Hydrate, add 80 mL of acetic acid(100), dissolve by warming, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a

blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 51.25 mg of $C_{16}H_{22}N_6O_4 \cdot C_4H_6O_6$

Packaging and storage Preserve in well-closed containers.

Protirelin Tartrate Injection
프로티렐린타르타르산염 주사액

Protirelin Tartrate Injection is an aqueous solution for injection and contains NLT 95.0% and NMT 105.0% of the labeled amount of protirelin tartrate ($C_{16}H_{22}N_6O_4 \cdot C_4H_4O_6$: 510.455).

Method of preparation Prepare as directed under Injections, with Protirelin Tartrate.

Description Protirelin Tartrate Injection is colorless and transparent.

Identification (1) Add 5 mL of water to 0.5 mL of Protirelin Tartrate Injection, add 1 mL of 1 mol/L hydrochloric acid solution of sulfanilic acid (1 in 100) and 1 mL of dilute sodium nitrite TS (1 in 2) while chilling in iced water and shake to mix, allow to stand in the ice bath for 3 minutes, add 3 mL of sodium carbonate TS, and shake to mix; the resulting solution exhibits an orange red color.

(2) Add 5 mL of sodium hydroxide TS to 0.5 mL of Protirelin Tartrate Injection, boil for 5 minutes, cool, and add 5 mL of 1 mol/L hydrochloric acid to neutralize. To 5 mL of this solution, add 1 mL of pyridine, 1 mL of ascorbic acid solution (3 in 2000) and 1 mL of diluted ninhydrin TS (1 in 2), heat for 15 minutes on a steam bath, cool, and shake to mix; the resulting solution exhibits a violet color.

pH Between 5.5 and 6.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 102.74 EU per mg of protirelin tartrate.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets requirements.

Extractable volume of injections Meets the requirements.

Purity ***Related substances***—Spot 50 μL of Protirelin Tartrate Injection on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, methanol and strong ammonia water (6 : 4 : 1) (as the developing solvent) to a distance of about 10 cm, and air-dry the plate. Evenly spray the plate with Pauly's TS; no spots appear other than the spots for protirelin tartrate (orange red) and sorbitol (white to pale yellow).

Assay Pipet an amount of Protirelin Tartrate Injection equivalent to about 7.5 mg of protirelin tartrate ($C_{16}H_{22}N_6O_4 \cdot C_4H_4O_6$), add water to make exactly 200 mL, and use this solution as the test solution. Separately, weigh accurately about 75 mg protirelin tartrate RS and dissolve in water to make exactly 200 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Pipet 4 mL each of the test solution, the standard solution and water, place each in a 25-mL volumetric flask, and cool in iced water. Add 1.0 mL of a 1 mol/L hydrochloric acid solution of sulfanilic acid (1 in 100) and 1.0 mL of diluted sodium nitrite TS (1 in 2), shake to mix, cool in iced water for 5 minutes, add 3.0 mL of sodium carbonate TS, shake to mix, allow to stand for exactly 1 minute, and add methanol to make exactly 25 mL. With the test solution and the standard solution, perform the test as directed under the Ultraviolet-visible Spectroscopy using the blank test solution as a control solution, and determine the absorbances, A_T and A_S, at the absorbance maximum wavelength near 410 nm.

Amount (mg) of protirelin tartrate ($C_{16}H_{22}N_6O_4 \cdot C_4H_4O_6$)
= Amount (mg) of protirelin tartrate × (A_T / A_S) × 0.1

Packaging and storage Preserve in hermetic containers.

Prozyme
프로자임

Prozyme is prepared by the following process: extract enzymes cultured in wheat bran inoculated with *Aspergillus melleus*, purify the extracted enzymes, followed by vacuum-drying at low temperatures. 1 g of Prozyme has a protein digestion activity of NLT 56000 units.

Description Prozyme occurs as a white to pale yellow powder.
It is soluble in water and insoluble in methanol.
It exhibits maximum digestive power at pH between 6.0 and 8.0.

Identification Weigh 10 mg of Prozyme, put into 10 mL of gelatin solution (2 in 10), previously warmed at 40 °C, shake vigorously for 1 minute, and allow it to stand for 5 minutes at 40 °C; the viscosity of the gelatin solution decreases (protein digestion activity).

Loss on drying NMT 10.0% (1 g, 105 °C, 4 hours).

Protein digestion activity assay Weigh accurately about

1.0 g of Prozyme, dilute with pH 8.0 phosphate buffer solution by 200000, and use this solution as the test solution. Take 1.0 mL of 1.5% casein solution into a test tube (15 × 150 mm), place the tube on a steam bath at 37 ± 0.2 ℃, and warm for 5 minutes. Add 1.0 mL of the test solution, shake quickly to mix, react exactly for 60 minutes on a steam bath at 37 ± 0.2 ℃. Add 2.0 mL of 0.4 mol/L trichloroacetic acid, allow it to stand for 25 minutes on a steam bath at 37 ± 0.2 ℃, and filter. Take 1.0 mL of the filtrate, and put into a test tube (18 × 180 mm), add 5 mL of 0.4 mol/L sodium carbonate solution and 1 mL of Folin TS (1 in 5), shake well to mix, and incubate for 20 minutes on a steam bath at 37 ± 0.2 ℃. With this solution, perform the test as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance A around layer thickness of 1 cm and wavelength of 660 nm. Separately, proceed in the same manner with water instead of the test solution, and determine absorbance A_1. One unit of protein digestion activity is defined as the amount when amino acid equivalent to 100 μg of tyrosine is produced in 1 mL of the test solution under the above conditions.

$$\text{Protein digestion activity per g (unit)} = \frac{A - A_1}{100} \times F \times n$$

However, F is the amount of tyrosine obtained from the calibration curve as follows, n is the dilution factor of the test solution.

Drawing a tyrosine calibration curve—Prepare tyrosine solution with 0.1 mol/L hydrochloric acid so that 10 μg, 20 μg, 30 μg, 40 μg, and 50 μg each of tyrosine can be contained per mL. To 1 mL of these solutions, add 5 mL of 0.4 mol/L sodium carbonate solution, then add 1 mL of Folin TS (1 in 5) and mix. Allow the mixtures to stand for 20 minutes at 37 ± 0.2 ℃ to color. Determine the absorbances of these solutions, A_{T10}, A_{T20}, A_{T30}, A_{T40} and A_{T50}. At the same time, determine the absorbance A_{T10} of 0.1 mol/L hydrochloric acid solution of tyrosine without adding the coloring solution. Next, calculate the F value according to the following formula.

$$F = \frac{\frac{10}{A_{T10}-A_{T0}} + \frac{20}{A_{T20}-A_{T0}} + \frac{30}{A_{T30}-A_{T0}} + \frac{40}{A_{T40}-A_{T0}} + \frac{50}{A_{T50}-A_{T0}}}{5}$$

Packaging and storage Preserve in tight containers.

Prozyme and Pancreatin Capsules
프로자임·판크레아틴 캡슐

Prozyme and Pancreatin Capsules contain total protein digestion activity in prozyme and pancreatin NLT 90.0% of the labeled amount.

Method of preparation Prepare as directed under Capsules, with Prozyme and Pancreatin.

Identification (1) Dissolve the contents of 1 capsule of Prozyme and Pancreatin Capsules in 10 mL of 0.1 mol/L phosphate buffer solution (pH 8.0), and heat 2 mL of this solution at 40 ℃. Add 10 mL of gelatin solution (2 in 10) in resulting solution, shake to mix, and allow it to stand for 5 minutes at 40 ℃; the viscosity of the gelatin solution decreases (protein digestion activity).

(2) Perform the test as directed under the Assay; it shows positive.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay ***Total protein digestion activity***—Weigh accurately the contents of NLT 20 capsules of Prozyme and Pancreatin Capsules. Weigh accurately an amount equivalent to 1 capsule of Prozyme and Pancreatin Capsules, dissolve in 0.02 mol/L phosphate buffer solution (pH 8.0) to make 500 mL., Add phosphate buffer solution (pH 8.0) in 10.0 mL of this solution to make 100 mL, and use this solution as the test solution. Pipet 1.0 mL of 1.5% milk casein solution (pH 8.0) into a test tube (15 × 150 mm), put it on a steam bath at 37 ± 0.2 ℃, and warm for 5 minutes. Add 1.0 mL of the test solution, shake quickly to mix, and react exactly for 60 minutes on a steam bath at 37 ± 0.2 ℃. Add 2.0 mL of 0.4 mol/L trichloroacetic acid in the resulting solution, allow it to stand for 25 minutes on a steam bath at 37 ± 0.2 ℃, and filter. Take 1.0 mL of the filtrate and put into a test tube (18 × 180 mm), add 5 mL of 0.4 mol/L sodium carbonate solution and 1 mL of Folin TS (1 in 5), shake well to mix, and incubate for 20 minutes on a steam bath at 37 ± 0.2 ℃. With this solution, perform the test as directed under the Ultraviolet-visible Spectroscopy and determine the absorbance A at the wavelength of 660 nm. Separately, proceed in the same manner with water instead of the test solution, and determine absorbance A_1.

$$\text{Protein digestion activity (unit) in 1 g} = \frac{A - A_1}{1000} \times F \times n$$

Where, F is the amount of tyrosine obtained from the calibration curve as follows, n is the dilution factor of the test solution.

Definition of potency—One unit of protein digestion activity is defined as the amount when amino acid equivalent to 100 μg of tyrosine is produced in 1 mL of the test solution under the above conditions.

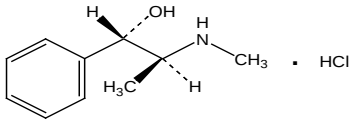
Calibration curve of tyrosine—Prepare tyrosine solution with 0.1 mol/L hydrochloric acid so that 10 μg, 20 μg, 30 μg, 40 μg, and 50 μg each of tyrosine can be contained per mL. To 1 mL of these solutions, add 5 mL of 0.4 mol/L sodium carbonate solution, add 1 mL of Folin TS (1 in 5), and mix. Allow the mixtures to stand for 20 minutes at 37 ± 0.2 ℃ to color. Determine the ab-

sorbances of these solutions, A_{T10}, A_{T20}, A_{T30}, A_{T40}, *and* A_{T50}. At the same time, determine the absorbance A_{T0} of 0.1 mol/L hydrochloric acid solution of tyrosine without adding the Folin TS. Calculate the F value according to the following formula.

$$F = \frac{\frac{10}{A_{T10}-A_{T0}} + \frac{20}{A_{T20}-A_{T0}} + \frac{30}{A_{T30}-A_{T0}} + \frac{40}{A_{T40}-A_{T0}} + \frac{50}{A_{T50}-A_{T0}}}{5}$$

Packaging and storage Preserve in tight containers.

Pseudoephedrine Hydrochloride
슈도에페드린염산염



C10H15NO·HCl : 201.69

(1*S*,2*S*)-2-(Methylamino)-1-phenylpropan-1-ol hydrochloride [*345-78-8*]

Pseudoephedrine Hydrochloride contains NLT 98.0% and NMT 102.0% of pseudoephedrine hydrochloride (C10H15NO·HCl), calculated on the dried basis.

Description Pseudoephedrine Hydrochloride occurs as white fine crystals or a powder. It has a slightly characteristic odor.

It is very soluble in water, freely soluble in ethanol(95), and slightly soluble in chloroform.

Identification (1) Determine the infrared spectra of Pseudoephedrine Hydrochloride and pseudoephedrine hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; it exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Pseudoephedrine Hydrochloride (1 in 50) responds to the Qualitative Analysis (2) for chloride.

Optical rotation $[\alpha]_D^{20}$: Between +61.0° and +62.5° (0.5 g, calculated on the dried basis, water, 10 mL, 100 mm).

Melting point Between 182 and 186 ℃.

pH Dissolve 1.0 g of Pseudoephedrine Hydrochloride in 20 mL of water. The pH of this solution is between 4.6 and 6.0.

Purity ***Related substances***—Dissolve 0.1 g of Pseudoephedrine Hydrochloride in ethanol(95) to make exactly 10 mL and use this solution as the test solution. Separately, dissolve 1.0, 5.0, 10.0 and 20.0 mg each of pseudoephedrine hydrochloride RS in respective ethanol(95) to make exactly 100 mL each, and use these solutions as the standard solutions (1), (2), (3) and (4), respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solutions on the plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethanol(95), acetic acid(100) and water (10 : 3 : 1) as the developing solvent to a distance of about 15 cm, and dry the plate for 2 hours with a hot air blow. Expose the plate to iodine vapor for NLT 30 minutes; the amount of total related substances calculated by comparing the intensities of the spots other than the principal spot obtained from the test solution against spots from the standard solution is NMT 2.0%.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately 100 mg of Pseudoephedrine Hydrochloride, place in a 100-mL volumetric flask, add water to mix, and fill the flask to the gauge line, Use this solution as the test solution. As necessary, the concentration of the test solution can be diluted to 0.1 mg/mL stepwise. Weigh accurately a certain amount of pseudoephedrine hydrochloride RS, dissolve in water to make a solution having a concentration of 0.1 mg/mL per mL, and use this solution as the standard solution (1). Separately, weigh accurately a certain amount each of pseudoephedrine hydrochloride RS and ephedrine sulfate RS, dissolve both in water to make a solution having a concentration of 0.1 mg and 0.002 mg per mL, respectively, and use this solution as the standard solution (2). Perform the test with 10 μL each of the test solution and the standard solution (1) as directed under the Liquid Chromatography, and determine the peak areas, A_T and A_S, of pseudoephedrine hydrochloride, respectively.

$$\text{Amount (mg) of pseudoephedrine hydrochloride } (C_{10}H_{15}NO\cdot HCl) = 100 \times \frac{A_T}{A_S} \times \frac{C_S}{C_T}$$

C_S: Concentration (mg/mL) of pseudoephedrine in the standard solution

C_T: Concentration (mg/mL) of pseudoephedrine in the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 206 nm).

Column: A stainless steel column, about 3.0 mm in internal diameter and about 15 cm in length, packed with phenyl silica gel for liquid chromatography (3.5 μm in particle diameter).

Mobile phase: Mix well 5 mL of triethylamine and 1000 mL of water and adjust the pH to 6.8 with phosphoric acid. To 900 mL of this solution, add 100 mL of water.

Flow rate: 0.6 mL/min

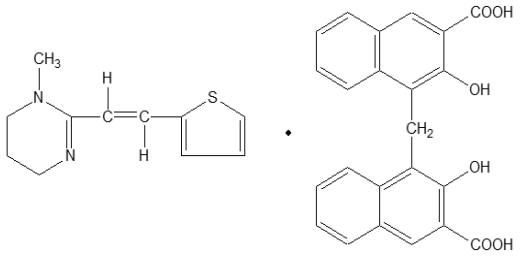
System suitability

System performance: Proceed with 10 μL of the standard solution (2) according to the above conditions; the relative retention times of ephedrine and pseudoephedrine are 0.9 and 1.0, respectively, with the resolution being NMT 2, and the symmetry factor of pseudoephedrine is NMT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution (2) according to the above conditions; the relative standard deviation of the peak area ratio is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Pyrantel Pamoate
피란텔파모산염



$C_{11}H_{14}N_2S \cdot C_{23}H_{16}O_6$: 594.68

4-[(3-Carboxy-2-hydroxynaphthalen-1-yl)methyl]-3-hydroxynaphthalene-2-carboxylic acid [*22204-24-6*]

Pyrantel Pamoate, when dried, contains NLT 98.0% and NMT 101.0% of pyrantel pamoate ($C_{11}H_{14}N_2S \cdot C_{23}H_{16}O_6$).

Description Pyrantel Pamoate occurs as a pale yellow to yellow crystalline powder, and is odorless and tasteless.
It is sparingly soluble in *N*,*N*-dimethylformamide, very slightly soluble in methanol or ethanol(95), and practically insoluble in water, ethyl acetate, ether or chloroform.

Melting point—Between 256 and 264 ℃ (with decomposition).

Identification (1) To 50 mg of Pyrantel Pamoate, add 10 mL of methanol and 1 mL of a mixture of hydrochloric acid and methanol (1 : 1), shake strongly the resulting solution to mix; yellow precipitates is formed. Filter this solution and use the filtrate as the test solution. Use the precipitates for the test of (2). To 0.5 mL of the test solution, add 1 mL of a solution of 2,3-indolinedione in sulfuric acid (1 in 1000); the solution exhibits a red color.

(2) Take the precipitate obtained from (1), wash with methanol, and dry at 105 ℃ for 1 hour. Weigh 10 mg of the dried precipitate, add 10 mL of methanol, shake to mix, and filter. Add one drop of iron(III) chloride TS to 5 mL of the filtrate; the resulting solution exhibits a green color.

(3) Weigh 0.1 g each of Pyrantel Pamoate and pyrantel pamoate RS, dissolve them in 50 mL of *N*,*N*-dimethylformamide, and add methanol to make 200 mL. Pipet 2 mL each of these solutions and add a solution of hydrochloric acid in methanol (9→ 1000) to make 100 mL. Determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared spectra of Pyrantel Pamoate and pyrantel pamoate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Chloride***—Weigh 1.0 g of Pyrantel Pamoate, add 10 mL of dilute nitric acid and 40 mL of water, heat on a steam bath while shaking to mix for 5 minutes. After cooling, add water to make 50 mL, and filter the solution. Pipet 20 mL of the filtrate, add 2 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid solution (NMT 0.036%).

(2) ***Sulfate***—Weigh 0.75 g of Pyrantel Pamoate, add 5 mL of dilute hydrochloric acid and water to make 100 mL, warm on a steam bath while shaking to mix for 5 minutes. After cooling, add water to make 100 mL, and filter the solution. Take 20 mL of the filtrate and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.45 mL of 0.005 mol/L sulfuric acid (NMT 0.144%).

(3) ***Heavy metals***—Proceed with 1.0 g of Pyrantel Pamoate according to Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(4) ***Iron***—Weigh accurately 1.33 g of Pyrantel Pamoate, perform the test directed under the Residue on ignition. To the resulting residue, add 3 mL of hydrochloric acid and 2 mL of nitric acid, and evaporate to dryness on a steam bath. Dissolve the residue in 2 mL of hydrochloric acid on heating gently. Add 18 mL of hydrochloric acid additionally, and add water to make 50 mL. Pipet 5.0 mL of this solution, add water to make 47 mL and use this solution as the test solution. Separately, add water to 1.0 mL of iron standard solution to make 45 mL, add 2 mL of hydrochloric acid, and use this solution as the standard solution. To the test solution and the standard solution, add 50 mg of ammonium peroxydisulfate and 3 mL of 30% ammonium thiocyanate solution, and mix them; the color obtained from the test solution is not more intense than that from the standard solution (NMT 75 ppm).

(5) ***Arsenic***—Proceed with 1.0 g of Pyrantel Pamoate according to Method 3 and perform the test (NMT 2 ppm).

(6) ***Related substances***—Perform the test using a light-resistant container. Dissolve 0.10 g of Pyrantel Pamoate in 10 mL of *N*,*N*-dimethylformamide, and use this solution as the test solution. Pipet 1 mL of this solution, add *N*,*N*-dimethylformamide to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin

Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, acetic acid(100) and water (3 : 1 : 1) to a distance of about 10 cm, and air-dry the plate. Expose to ultraviolet light (principal wavelength: 254 nm); the spots other than pyrantel and pamoate obtained from the test solution are not more intense than the spots (R_f value of about 0.3) of pyrantel from the standard solution.

Loss on drying NMT 1.0% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.3% (1 g).

Assay Weigh accurately about 0.5 g of Pyrantel Pamoate, previously dried, add 25 mL of chloroform and 25 mL of sodium hydroxide TS, shake to mix for 15 minutes, and then extract. Extract again in the same manner twice with 25 mL each of chloroform. Filter the chloroform extracts by using a funnel with 5 g of anhydrous sodium sulfate placed on cotton wool each time. Combine all chloroform extracts, add 30 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of methylosaniline chloride TS). Perform a blank test in the same manner.

Each mL of 1 mol/L perchloric acid VS
= 59.47 mg of $C_{11}H_{14}N_2S \cdot C_{23}H_{16}O_6$

Packaging and storage Preserve in tight containers.

Pyrantel Pamoate Tablets
피란텔파모산염 정

Pyrantel Pamoate Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of pyrantel pamoate ($C_{11}H_{14}N_2S$: 260.31).

Method of preparation Prepare as directed under Tablets, with Pyrantel Pamoate.

Identification (1) Dilute appropriate amounts of Pyrantel Pamoate Tablets and pyrantel pamoate RS with 0.05 mol/L methanolic ammonium hydroxide solution to obtain solutions containing 8 mg of pyrantel pamoate per mL. Shake to mix, centrifuge, take the clear supernatant, and use as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 100 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Shake a mixture of water, formic acid and methyl isobutyl ketone (1 : 1 : 2), and take the supernatant. Next, develop the plate with the supernatant as a developing solvent to a distant of about 18 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 365 nm); the spots from the test solution and the standard solution are the same in R_f value.

(2) The retention times of the major peaks obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tables of Pyrantel Pamoate Tablets, and powder them. Weigh accurately an amount of the powder, equivalent to about 80 mg of pyrantel pamoate ($C_{11}H_{14}N_2S$), add the mobile phase to make exactly 100 mL, and filter. Pipet 1 mL of the filtrate, add the mobile phase to make exactly 10 mL, and use this solution as the test solution. Perform the test with exactly 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of pyrantel pamoate in each solution.

Amount (mg) of pyrantel pamoate ($C_{11}H_{14}N_2S$)
= Amount (mg) of pyrantel pamoate RS × (A_T/ A_S)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 288 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with porous silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile, water, acetic acid and diethylamine (92.8 : 3 : 3 : 1.2). However, adjust the retention time by adjusting the mixing ratio of acetonitrile while maintaining the ratio of acetic acid(100), water and diethylamine (1 : 1 : 0.4).

Flow rate: 1.0 mL/min

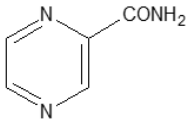
System suitability

System performance: The resolution of pyrantel and pamoate is NLT 10.0. The number of theoretical plates, the symmetry factor, the relative standard deviation of repeated injection, and the retention time of pyrantel are NLT 8000, NMT 0.3 and NMT 1.0% and NLT 2.5 times, respectively. The relative retention times of pyrantel and pamoate are 0.6 and 1.0, respectively.

When preparing a pyrantel pamoate solution, use a light-resistant container or block unnecessary bright light, and conduct the test quickly.

Packaging and storage Preserve in light-resistant, well-closed containers.

Pyrazinamide
피라진아미드



$C_5H_5N_3O$: 123.11

Pyrazine-2-carboxamide [*98-96-4*]

Pyrazinamide, when dried, contains NLT 99.0% and NMT 101.0% of pyrazinamide ($C_5H_5N_3O$).

Description Pyrazinamide occurs as white crystals or a crystalline powder. It is odorless and has a slightly bitter taste.

It is sparingly soluble in water and slightly soluble in ethanol(95) or acetic anhydride.

Identification (1) Determine the absorption spectra of the solutions of Pyrazinamide and pyrazinamide RS in 0.1 mol/L hydrochloric acid TS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Pyrazinamide and pyrazinamide RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 188 and 193 ºC.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Pyrazinamide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Dissolve 0.10 of Pyrazinamide in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 200 mL, and use it as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, water and acetic acid(100) (3 : 1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Observe the plate under ultraviolet light (main wavelength: 254 nm); any spot other than the principal spot obtained from the test solution is not more intense than the spot from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, silica gel, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.1 g of Pyrazinamide, previously dried, dissolve in 50 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 12.31 mg of $C_5H_5N_3O$

Packaging and storage Preserve in well-closed containers.

Pyrazinamide Tablets
피라진아미드 정

Pyrazinamide Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of pyrazinamide ($C_5H_5N_3O$: 123.11).

Method of preparation Prepare as directed under Tablets, with Pyrazinamide.

Identification (1) Powder Pyrazinamide Tablets, weight an amount of the powder, equivalent to about 1 g of pyrazinamide, add about 75 mL of isopropanol, heat on a steam bath, and filter while it's hot. Allow to cool, filter the crystals that form and dry at 105 ºC for 1 hour. Determine the absorption spectra of the aqueous solutions (1 in 100000) of the crystals so obtained and Pyrazinamide RS, respectively, under Ultraviolet-visible Spectrophotometry: both spectra exhibit maximum and minimum at the same wavenumbers. Determine the absorption spectra of the crystal solution and Pyrazinamide RS at the absorbance maximum wavelength at about 268 nm, respectively: the difference is NMT 3.0%.

(2) Take 20 mg of the crystals obtained in Identification (1), add 5 mL of 5 mol/L sodium hydroxide and heat gently: the odor of ammonia is perceptible.

Dissolution Perform the test with 1 tablet of Pyrazinamide Tablets at 50 revolutions per minute according to Method 2, using 900 mL of water as the dissolution medium. Take the dissolved solution after 45 minutes from start of the test, filter, dilute with water, if necessary and use this solution as the test solution. Separately, weigh accurately a portion of Pyrazinamide RS, add water to make constant concentration and use this solution as the standard solution. Determine the absorbances of the test solution and the standard solution at the absorbance maximum wavelength of about 268 nm as directed under Ultraviolet-visible Spectrophotometry using the water as the blank. It meets the requirements if the dissolution rate of Pyrazinamide Tablets in 45 minutes is NLT 75%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tables of Pyrazinamide Tablets, and powder them. Weigh accurately a portion of the powder, equivalent to about 0.1 g of pyrazinamide ($C_5H_5N_3O$) and transfer with the aid of 300 mL of water to a volumetric flask. After sonication for 10 minutes, add water to make exactly 500 mL and mix.

Filter this solution, discard the first portion of the filtrate, take exactly 20 mL of the subsequent filtrate, add water to make 100 mL and use this solution as the test solution. Separately, weigh accurately about 0.1 g of Pyrazinamide RS, add water to make exactly 500 mL, pipet 20 mL of this solution, add water to make exactly 100 mL and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of pyrazinamide in each solution.

$$\text{Amount (mg) of pyrazinamide } (C_5H_5N_3O) = \text{Amount (mg) of pyrazinamide RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: To phosphate buffer solution, pH 8.0, add phosphoric acid to adjust the pH to 3.0. To 1000 mL of this solution, add 10 mL of acetonitrile, mix, and filter.

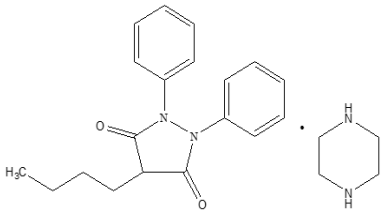
Flow rate: 1 mL/min

System suitability

Selection of column: Proceed with 10 μL of the standard solution according to the above operating conditions; the number of theoretical plates and the symmetry factor of the pyrazinamide peak are NLT 2500 and NMT 1.5, respectively. Then, to 1 mL of hydrochloric acid, add the standard solution to make 5 mL, allow to stand in a boiling water bath for 5 minutes, cool, and proceed according to the above conditions; pyrazinoic acid and pyrazinamide are eluded in this order with the resolution being NLT 6.0.

Packaging and storage Preserve in well-closed containers.

Pyrazinobutazone
피라지노부타존



$C_{19}H_{20}N_2O_2 \cdot C_4H_{10}N_2$: 394.51

Piperazine 4-butyl-1,2-diphenyl-3,5-pyrazolidine dione (1 : 1), [*4985-25-5*]

Pyrazinobutazone contains NLT 74.3% and NMT 82.1% of phenylbutazone ($C_{19}H_{20}N_2O_2$: 308.37) and NLT 20.7% and NMT 22.9% of piperazine ($C_4H_{10}N_2$: 86.14).

Description Pyrazinobutazone occurs as a white to light yellow powder, and has a slight odor and a bitter taste.
It is freely soluble in methanol, soluble in ethanol(95) or tetrahydrofuran, and slightly soluble in water.

Melting point Between 140 and 141 ºC.

Identification Dissolve 50 mg of Pyrazinobutazone in methanol to make 10 mL, and use this solution as the test solution. Separately, weigh 40 mg of phenylbutazone RS and 10 mg of piperazine RS, respectively, dissolve each in methanol to make 10 mL, and use these solutions as the standard solutions. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solutions on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of methanol and ammonia water(28) (20 : 0.3) to a distance of about 15 cm, and air-dry the plate. Examine phenylbutazone under ultraviolet light (main wavelength: 254 nm), and examine piperazine by spraying evenly Dragendorff's TS. The R_f values of spots obtained from the test solution and the standard solutions are the same.

pH Weigh 1.0 g of Pyrazinobutazone, dissolve in 20 mL of neutralized methanol and 100 mL of water; the pH of the resulting solution is between 6.7 and 7.8.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Pyrazinobutazone according to Method 3 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 0.2 g of Pyrazinobutazone according to Method 2 and perform the test (NMT 10 ppm).

(3) ***Blue impurities***—Weigh 2.0 g of Pyrazinobutazone, put into a 50-mL Nessler tube, and add methanol to the gauge line. Put 0.4 mL of the control solution containing 1 mg of azobenzene in 1 mL of methanol into another Nessler tube, add methanol to the gauge line, and compare the colors of the Nessler tubes; the test solution is not more intense than the control solution (NMT 200 ppm as the control solution of azobenzene).

Loss on drying NMT 1.0% (0.2 g, in vacuum, phosphorus pentoxide, 16 hours).

Residue on ignition NMT 0.5% (1 g).

Assay (1) ***Phenylbutazone***—Weigh accurately about 0.3 g of Pyrazinobutazone, dissolve in 30 mL of dimethylformamide, and titrate with 0.1 mol/L potassium hydroxide-ethanol VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L potassium hydroxide-ethanol VS

= 30.84 mg of $C_{19}H_{20}N_2O_2$

(2) ***Piperazine***—Weigh accurately about 0.15 g of Pyrazinobutazone, dissolve in 80 mL of acetic acid(100) for non-aqueous titration and 30 mL of nitromethane, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 4.307 mg of $C_4H_{10}N_2$

Packaging and storage Preserve in tight containers.

Pyrazinobutazone Capsules
피라지노부타존 캡슐

Pyrazinobutazone Capsules contain phenylbutazone ($C_{19}H_{20}N_2O_2$: 308.37) equivalent to NLT 70.3% and NMT 85.7% of the labeled amount of pyrazinobutazone and piperazine ($C_4H_{10}N_2$: 86.14) equivalent to NLT 19.7% and NMT 23.7% of the same.

Method of preparation Prepare as directed under Capsules, with Pyrazinobutazone.

Identification Weigh an amount of Pyrazinobutazone Capsules, equivalent to 0.3 g of pyrazinobutazone according to the labeled amount, add 50 mL of ethanol, shake well to mix, filter, and use the filtrate as the test solution. Weigh 40 mg of phenylbutazone RS, dissolve in methanol to make 10 mL, and use this solution as the standard phenylbutazone solution. Separately, weigh 10 mg of piperazine RS, dissolve in methanol to make 10 mL, and use this solution as the standard piperazine solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each of the test solution and the standard solutions on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of methanol and ammonia water(28) (20 : 0.3) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate for phenylbutazone under ultraviolet light (main wavelength: 254 nm) and spray evenly Dragendorff's TS on the plate to detect piperazine. The R_f values of the spots obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Phenylbutazone***—Weigh accurately the mass of the contents of NLT 20 capsules of Pyrazinobutazone Capsules. Weigh accurately an amount equivalent to about 0.3 g of pyrazinobutazone ($C_{23}H_{30}N_4O_2$), add 30 mL of chloroform and heat for 30 minutes under a reflux condenser. After cooling, add chloroform to make exactly 50 mL, shake to mix, filter and use the filtrate as the test solution. Pipet 20 mL of the test solution, and evaporate chloroform to dryness on a steam bath. To the residue, add 30 mL of dimethylformamide and dissolve by warming. Titrate the solution with 0.1 mol/L potassium hydroxide-ethanol VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L potassium hydroxide-ethanol VS
= 30.84 mg of $C_{19}H_{20}N_2O_2$

(2) ***Piperazine***—Pipet 10 mL of the test solution from (1), and evaporate chloroform to dryness on a steam bath. Dissolve the residue in 30 mL of acetic acid(100) for non-aqueous titration and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 4.307 mg of $C_4H_{10}N_2$

Packaging and storage Preserve in well-closed containers.

Pyrethrin Extract
피레트린 엑스

Pyrethrin Extract is extracted from dried leaves of *Chrysanthemum cinerariaefolium* (Compositae), and contains NLT 90.0% and NMT 110.0% of the labeled amount of total pyrethrin [pyrethrin I($C_{21}H_{28}O_3$: 328.45) and pyrethrin II($C_{22}H_{28}O_5$: 372.45)].

Description Pyrethrin Extract occurs as a yellowish brown to reddish brown liquid and has a characteristic odor.
It is miscible with methanol, ethanol(95), acetone, dichloromethane, chloroform, ether, toluene and kerosene.
It is insoluble in water.

Identification (1) Dissolve an amount of Pyrethrin Extract, equivalent to 50 mg of total pyrethrin, in 100 mL of kerosene. To 2 mL of the solution, add 5 mL of a mixture of phosphoric acid and ethyl acetate (4 : 1), shake to mix for 1 minute, and heat the solution on a steam bath for 3 minutes; the solution turns red.

(2) Dissolve an amount of Pyrethrin Extract, equivalent to 50 mg of total pyrethrin, and about 10 mg of allethrin each in 20 mL of acetone, and use them as the test and control solutions, respectively. Perform the test with these solutions as directed under the Gas chromatograph according to the conditions below; the peaks of pyrethrin I and pyrethrin II from the test solution elute at the relative retention times of about 2.50 and of about 11.0, re-

spectively, to the allethrin peak of the control solution.

Operating conditions

Detector: A flame ionization detector

Column: A glass column about 3 mm in internal diameter and about 1 m in length, packed with silane-treated diatomaceous earth for gas chromatography (150 μm - 180 μm in particle diameter), coated with 50% phenyl-methyl silicon polymer for gas chromatography at a rate of 2%.

Column temperature: A constant temperature of about 205 °C.

Flow rate: Adjust the flow rate so that the retention time of allethrin is about 2.7 minutes.

Selection of column: Proceed with 1 μL of the test solution under the above conditions; select the column where the resolution between the peak of allethrin and the peak with the relative retention time to allethrin of 1.61 is NLT about 3.0.

Purity (1) ***Heavy metals***—Proceed with 0.2 g of Pyrethrin Extract according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 100 ppm).

(2) ***Arsenic***—Proceed with 0.2 g of Pyrethrin Extract according to Method 3 and perform the test (NMT 10 ppm).

Assay The sum of the amounts of pyrethrin I and pyrethrin II is taken as the amount of total pyrethrin.

(1) ***Pyrenthrin I***—Weight accurately the amount of Pyrethrin Extract, equivalent to about 0.1 g of total pyrethrin, add it to 75 mL of ether, shake gently to dissolve, and move to a separatory funnel. Wash the used container with a small amount of ether, add the washing to the separatory funnel, and wash the separatory funnel twice with 50 mL of sodium hydroxide solution (1 in 100) and once with 50 mL of water. Combine the washings, salt out with sodium chloride, then add 50 mL of ether, and shake to mix. Wash the ether layer with 15 mL of water, combine the entire ether solution, and completely evaporate the ether on a steam bath.

Add 15 mL of 0.5 mol/L potassium hydroxide-ethanol solution to the residue, heat on a steam bath under a reflux condenser for 1.5 hours, and then completely evaporate the ether. Add 100 mL of water to the residue and shake well to dissolve. Add 1 g of acid clay, add 17 mL of barium chloride TS, shake to mix, and add water to make exactly 250 mL. Next, pipet 200 mL of the filtrate into a steam distillation flask, neutralize it with dilute sulfuric acid (1 in 20) (indicator: 2 drops of phenolphthalein TS), add 1 mL of dilute sulfuric acid (1 in 20) and carry out steam distillation until about 250 mL of distillate is obtained. Take the distillate in a separatory funnel, add 50 mL of toluene, shake vigorously to mix for 2 - 3 minutes, add a small amount of sodium chloride when turbidity forms, and shake gently to separate. Mix the water layer with 50 mL of toluene on shaking, move the toluene solution to each separatory funnel, and wash each with 10.0 mL of water twice. Combine the entire toluene solution in one separatory funnel, add exactly 10 mL of 0.02 mol/L sodium hydroxide VS, add 5 mL of water, shake vigorously for about 2 minutes. Allow to stand for a while, and titrate the excess sodium hydroxide with 0.01 mol/L sulfuric acid VS (indicator: 2 drops of phenolphthalein TS). Perform a blank test in the same way and make necessary correction.

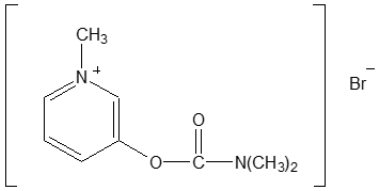
Each mL of 0.02 mol/L sodium hydroxide VS
= 6.569 mg of $C_{21}H_{28}O_3$

(2) ***Pyrenthrin II***—Cool the entire distillate obtained from steam distillation in (1), filter it with suction, and wash the container and the filter paper twice with 10 mL of water each. Combine the washings with the filtrate, saturate with sodium chloride, and transfer to a separatory funnel. Extract three times with 50 mL each of ether, and transfer each ether extract to each separatory funnel. Wash each separatory funnel three times with 10 mL of water, combine the entire ether solution, evaporate the ether on a steam bath. Dry the residue at 100 °C for 10 minutes, dissolve in 2 mL of ethanol(95), add 20 mL of water, and heat to boiling, cool. After filtering if necessary, titrate with 0.02 mol/L sodium hydroxide VS (indicator: 2 drops of phenolphthalein TS). Perform a blank test in the same way and make necessary correction.

Each mL of 0.02 mol/L sodium hydroxide VS
= 3.724 mg of $C_{22}H_{28}O_5$

Packaging and storage Preserve in tight containers.

Pyridostigmine Bromide
피리도스티그민브롬화물



$C_9H_{13}BrN_2O_2$: 261.12

(1-Methylpyridin-1-ium-3-yl) *N*,*N*-dimethylcarbamate bromide [*101-26-8*]

Pyridostigmine Bromide, when dried, contains NLT 98.5% and NMT 101.0% of pyridostigmine bromide ($C_9H_{13}BrN_3O_3$).

Description Pyridostigmine Bromide occurs as a white or almost white, crystalline powder. It is odorless or has a slightly characteristic odor.

It is very soluble in water, freely soluble in acetic acid(100) or ethanol(95), and practically insoluble in ether.

Dissolve 1.0 g of Pyridostigmine Bromide in 10 mL of water; the pH of this solution is between 4.0 and 6.0.

It is deliquescent.

Identification (1) Dissolve 20 mg of Pyridostigmine Bromide in 10 mL of water, and add 5 mL of reinecke salt TS; pale red precipitates are formed.

(2) Add 0.6 mL of sodium hydroxide TS to 0.1 g of Pyridostigmine Bromide; an unpleasant odor of dimethylamine is perceptible.

(3) Determine the absorption spectra of the solutions of Pyridostigmine Bromide and pyridostigmine bromide RS in 0.1 mol/L hydrochloric acid TS (1 in 30000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) An aqueous solution of Pyridostigmine Bromide (1 in 50) responds to the Qualitative Analysis for bromide.

Melting point Between 153 and 157 ºC.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Pyridostigmine Bromide in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Pyridostigmine Bromide according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Pyridostigmine Bromide according to Method 1 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.10 g of Pyridostigmine Bromide in 10 mL of ethanol(95) and use this solution as the test solution. Pipet 2 mL of the test solution, and add ethanol(95) to make exactly 10 mL. Pipet 1 mL of this solution, add ethanol(95) to make exactly 25 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of methanol, chloroform and ammonium chloride TS (5 : 4 : 1) to a distance of about 12 cm, and air-dry the plate. Observe the plate under ultraviolet light (main wavelength: 254 nm); any spot other than the principal spot obtained from the test solution is not more intense than the spot from the standard solutions.

Loss on drying NMT 2.0% (1 g, in vacuum, phosphorus pentoxide, 100 ℃, 5 hours).

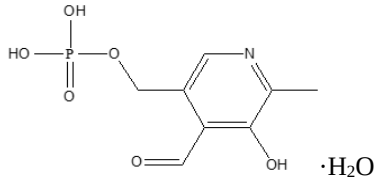
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Pyridostigmine Bromide, previously dried, dissolve in 10 mL of acetic acid(100), add 40 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 26.112 mg of $C_9H_{13}BrN_2O_2$

Packaging and storage Preserve in hermetic containers.

Pyridoxal Phosphate Hydrate
피리독살포스페이트수화물



·H_2O

$C_8H_{10}NO_6P·H_2O$: 265.16
3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridinecarboxaldehyde, [*41468-25-1*]

Pyridoxal Phosphate Hydrate contains NLT 98.0% and NMT 101.0% of pyridoxal phosphate ($C_8H_{10}NO_6P$: 247.14), calculated on the anhydrous basis.

Description Pyridoxal Phosphate Hydrate occurs as a yellowish white to pale yellow crystalline powder. It is odorless.
It is slightly soluble in water, and practically insoluble in ethanol(95), acetone, chloroform or ether.
It dissolves in dilute hydrochloric acid, dilute nitric acid or sodium hydroxide TS. It is affected by light.

Identification (1) To 1 mL of an aqueous solution of Pyridoxal Phosphate Hydrate (1 in 2000), add one drop of iron(III) chloride TS; the resulting solution exhibits an orange color.

(2) To 1 mL of an aqueous solution of Pyridoxal Phosphate Hydrate (1 → 20000), add one drop of a freshly prepared solution of 2,6-dibromoquinonechlorimide in ethanol(95) (1 in 4000); the solution exhibits blue.

(3) Determine the absorption spectrum of the test solution of the Assay as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 386 nm and 390 nm.

(4) Add 10 mL of nitric acid and 10 mL of strong hydrogen peroxide water to 0.3 mg of Pyridoxal Phosphate Hydrate, evaporate to dryness on a steam bath, and heat again. If the residue is colored, add small amounts of nitric acid and strong hydrogen peroxide water, and repeat the procedure in the same manner. Dissolve the residue in 5 mL of water, and filter the solution if necessary. This solution responds to the Qualitative Analysis for phosphate.

pH Between 3.0 and 3.5 (0.05% aqueous solution).

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Pyridoxal Phosphate Hydrate in 10 mL of sodium hydroxide TS; the resulting solution is clear and pale yellow to yellow.

(2) ***Heavy metals***—Proceed with 2.0 g of Pyridoxal Phosphate Hydrate according to Method 2 and perform

the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Dissolve 1.0 g of Pyridoxal Phosphate Hydrate in 5 mL of dilute hydrochloric acid and use this solution as the test solution (NMT 2 ppm).

(4) ***Free phosphoric acid***—Dissolve 0.10 g of Pyridoxal Phosphate Hydrate in 5 mL of dilute nitric acid, and add water to make 30 mL. Next, add 10 mL of ammonium molybdate TS, shake to mix, allow to stand for 10 minutes, add 10 mL of 1-butanol, and shake strongly to mix; the color of 1-butanol layer is not more intense than the following control solution. Prepare the control solution by pipetting 20 mL of standard phosphoric acid and proceeding in the same manner as the test solution (NMT 0.5%).

Water Between 6.0% and 9.0% (0.1 g, volumetric titration, direct titration. However, use a solution of 50 g of imidazole dissolved in 100 mL of the solvent instead of methanol for water determination).

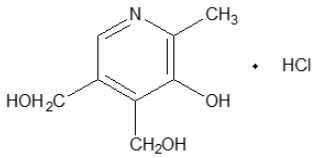
Solvent—1-methoxy-2-propanol of 80%, ethanol(99.5) of 18%, imidazole of 1% and imidazole hydrobromide acid of 1%.

Assay Weigh accurately about 45 mg of Pyridoxal Phosphate Hydrate, and add phosphate buffer solution, pH 6.8, to make exactly 250 mL. Pipet 10 mL of this solution, add phosphate buffer solution, pH 6.8, to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 45 mg of pyridoxal phosphate hydrate RS (water previously measured), proceed in the same manner as the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength around 388 nm as directed under the Ultraviolet-visible Spectroscopy, using phosphate buffer solution, pH 6.8, as the control solution.

Amount (mg) of pyridoxal phosphate hydrate ($C_8H_{10}NO_6P$)
= Amount (mg) of pyridoxal phosphate hydrate RS calculated on the anhydrous basis × (A_T/A_S)

Packaging and storage Preserve in light-resistant, well-closed containers.

Pyridoxine Hydrochloride
피리독신염산염



Vitamin B6 Hydrochloride $C_8H_{11}NO_3 \cdot HCl$: 205.64
4,5-Bis(hydroxymethyl)-2-methylpyridin-3-ol hydrochloride [*58-56-0*]

Pyridoxine Hydrochloride, when dried, contains NLT 98.0% and NMT 101.0% of pyridoxine hydrochloride ($C_8H_{11}NO_3 \cdot HCl$).

Description Pyridoxine Hydrochloride occurs as a white to pale yellow crystalline powder.
It is freely soluble in water, slightly soluble in ethanol(99.5), and practically insoluble in acetic anhydride or acetic acid(100).
It is gradually affected by light.

Melting point—About 206 °C (with decomposition).

Identification (1) Determine the absorption spectra of the solutions of Pyridoxine Hydrochloride and pyridoxine hydrochloride RS in 0.1 mol/L hydrochloric acid TS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectrum of Pyridoxine Hydrochloride and pyridoxine hydrochloride RS, previously dried, as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Pyridoxine Hydrochloride (1 in 10) responds to the Qualitative Analysis for chloride.

pH Dissolve 1.0 g of Pyridoxine Hydrochloride in 50 mL of water; the pH of this solution is between 2.5 and 3.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Pyridoxine Hydrochloride in 20 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Pyridoxine Hydrochloride according to Method 1 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(3) ***Related substances***—Dissolve 1.0 g of Pyridoxine Hydrochloride in 10 mL of water, and use this solution as the test solution. Pipet 2.5 mL of this solution and add water to make exactly 100 mL. Pipet 1 mL of this solution, add water to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the test solution and the

standard solution on a plate of silica gel for thin-layer chromatography. After air-drying, develop the plate with a mixture of acetone, tetrahydrofuran, *n*-hexane and ammonia water(28) (65 : 13 : 13 : 9) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly a solution (1 in 20) of sodium carbonate decahydrate in diluted ethanol(99.5) (3 in 10) on the plate, and air-dry the plate. Spray, again, evenly a solution (1 in 1000) of 2,6-dibromo-*n*-1,4-benzoquinone monoimine in ethanol(99.5), and air-dry the plate; the spots other than the principal spot from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 0.3% (1 g, in vacuum, silica gel, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 40 mg of Pyridoxine Hydrochloride, previously dried, and dissolve in water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 40 mg of pyridoxine hydrochloride RS, previously dried in a desiccator for 4 hours (in vacuum, silica gel), and dissolve in water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Proceed with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of pyridoxine hydrochloride, A_T and A_S.

Amount (mg) of pyridoxine hydrochloride ($C_8H_{11}NO_3$.HCl)
= Amount (mg) of pyridoxine hydrochloride RS × (A_T / A_S)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 1.0 g of sodium 1-hexanesulfonate in 750 mL of water, and add 250 mL of methanol and 10 mL of acetic acid(31).

Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of pyridoxine is NMT 2.0%.

Each mL of 1 mol/L perchloric acid VS
= 20.56 mg of $C_8H_{11}NO_3$·HCl

Packaging and storage Preserve in light-resistant, tight containers.

Pyridoxine Hydrochloride Injection
피리독신염산염 주사액

Vitamin B6 Hydrochloride Injection

Pyridoxine Hydrochloride Injection is an aqueous injection and contains NLT 95.0% and NMT 105.0% of the labeled amount of pyridoxine hydrochloride ($C_8H_{11}NO_3$·HCl : 205.64).

Method of preparation Prepare as directed under Injections, with Pyridoxine Hydrochloride.

Description Pyridoxine Hydrochloride Injection occurs as a clear and colorless to pale yellow liquid.
It is gradually affected by light.

pH—Between 3.0 and 6.0.

Identification The retention times of the major peaks and the ultraviolet absorption spectra at 190 nm to 300 nm obtained from the test solution and the standard solution under the Assay are the same.

Sterility Meets the requirements.

Bacterial endotoxins Less than 3.0 EU per mg of pyridoxine hydrochloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Pyridoxine Hydrochloride Injection equivalent to about 40 mg of pyridoxine hydrochloride ($C_8H_{11}NO_3$·HCl), and add water to make exactly 100 mL. Take exactly 5 mL of this solution, add exactly 5 mL of the internal standard solution, add water to make exactly 100 mL, and use this solution as the standard solution. Separately, weigh accurately about 40 mg of Pyridoxine Hydrochloride RS, previously dried in a desiccator (in vacuum, silica gel) for 4 hours, and dissolve in and water to make exactly 100 mL. Pipet 5 mL of this solution, add exactly 5 mL of the internal standard solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the operating conditions under the Assay of Pyridoxine Hydrochloride Tablets.

Amount (mg) of pyridoxine hydrochloride ($C_8H_{11}NO_3$·HCl)
= Amount (mg) of pyridoxine hydrochloride RS× $\frac{Q_T}{Q_S}$

Internal standard solution—Weigh 50 mg of anhydrous caffeine RS and dissolve in water to make 100 mL.

Packaging and storage Preserve in light-resistant, hermetic containers.

33.3% Pyridoxine Hydrochloride Powder
피리독신염산염 3배산

33.3% Pyridoxine Hydrochloride Powder contains NLT 32.6% of pyridoxine hydrochloride ($C_8H_{11}NO_3$·HCl : 205.64), calculated on the anhydrous basis.

Method of preparation Prepare by finely dispersing Pyridoxine Hydrochloride in edible fatty acid. 33.3% Pyridoxine Hydrochloride Powder is a drug substance.

Description 33.3% Pyridoxine Hydrochloride Powder occurs as a white to pale yellow powder.

Identification (1) Add 1 drop of iron(III) chloride TS to 1 mL of aqueous solution of 33.3% Pyridoxine Hydrochloride Powder (1 in 1000); the solution exhibits a yellowish brown color. Add 1 drop of hydrochloric acid to the solution; the solution turns yellow.

(2) Add 2 mL of freshly prepared ethanol solution of 2,6-dibromquinonchlorimide (1 in 4000) and 1 drop of ammonia TS to 1 mL of aqueous solution of 33.3% Pyridoxine Hydrochloride Powder; the solution exhibits a blue color. Add 1 mL of saturated boric acid solution to 1 mL of aqueous solution of 33.3% Pyridoxine Hydrochloride Powder and proceed in the same manner; the solution does not exhibit a blue color.

(3) A filtrate of aqueous solution of 33.3% Pyridoxine Hydrochloride Powder (1 in 10) responds to the Qualitative Analysis for chloride.

Water NMT 1.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.7 g of 33.3% Pyridoxine Hydrochloride Powder, add 5 mL of acetic acid(100) and 5 mL of acetic anhydride, and dissolve by heating over weak heat. After cooling, add 30 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 20.564 mg of $C_8H_{11}NO_3$·HCl

Packaging and storage Preserve in light-resistant, tight containers.

Pyridoxine Hydrochloride Tablets
피리독신염산염 정

Vitamin B6 Hydrochloride Tablets

Pyridoxine Hydrochloride Tablets contain NLT 95.0% and NMT 115.0% of the labeled amount of pyridoxine hydrochloride ($C_8H_{11}NO_3$·HCl : 205.64).

Method of preparation Prepare as directed under Tablets, with Pyridoxine Hydrochloride.

Identification The retention times of the major peaks and the ultraviolet absorption spectra at 190 nm - 300 nm obtained from the test solution and the standard solution under the Assay are the same, respectively.

Dissolution Perform the test with 1 tablet of Pyridoxine Hydrochloride Tablets at 50 revolutions per minute according to Method 2, using 900 mL of water as the dissolution medium. Take NLT 20 mL of the dissolution medium 45 minutes after starting the test, and filter through a membrane filter with a pore size of NMT 0.8 μm. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Dilute with the dissolution medium suitably, if necessary. Separately, weigh accurately about 10 mg of pyridoxine hydrochloride RS and dissolve it in ethanol(95) to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of pyridoxine, A_T and A_S, in each solution. Meets the requirements if the dissolution rate of Pyridoxine Hydrochloride Tablets in 45 minutes is NLT 75%.

Dissolution rate (%) for the labeled amount of pyridoxine hydrochloride ($C_8H_{11}NO_3$·HCl)

$$= W_S \times \frac{Q_T}{Q_S} \times \frac{90}{C}$$

W_S: Amount (mg) of pyridoxine hydrochloride RS

C: Labeled amount (mg) of pyridoxine hydrochloride ($C_8H_{11}NO_3$·HCl) per tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm, photo-diode array detector (190 nm to 300 nm)).

Column: A stainless steel column about 3.9 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of water, methanol and acetic acid(100) (73 : 27 : 1). Dissolve 0.14 g of sodium 1-hexanesulfonate in 100 mL.

Flow rate: 1 mL/min

System suitability

System performance: Weigh 20 mg of pyridoxine hydrochloride RS and 20 mg of riboflavin RS, put in a mixture of water, acetonitrile and acetic acid(100) (94 : 5 : 1), dissolve at 65 ℃ - 70 ℃ with shaking occasionally, and then cool the resulting solution immediately. Add the mixture of water, acetonitrile and acetic acid(100) (94 : 5 : 1) to make 200 mL. Proceed with 10 μL of this solution according to the above conditions; pyridoxine and riboflavin are eluded in this order.

System repeatability: Repeat the test 5 times with 10 μL each of the above solution according to the above conditions; the relative standard deviation of the peak areas of pyridoxine is NMT 3.0%.

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following procedure.

Transfer 1 tablet of Pyridoxine Hydrochloride Tablets, previously finely powdered, to a 500-mL volumetric flask containing about 300 mL of water, shake for about 30 minutes, and dilute with water to volume. Filter a portion of the mixture, discarding the first 25 mL of the filtrate. Dilute a suitable aliquot of the subsequent filtrate quantitatively and stepwise with diluted hydrochloric acid (1 in 100) so that the concentration of pyridoxine hydrochloride is about 10 μg per mL and use these solutions test solution. Dissolve about 10 mg of Pyridoxine Hydrochloride RS, accurately weighed, in diluted hydrochloric acid (1 in 100) to make exactly 100 mL. Pipet 5.0 mL of this solution and dilute with diluted hydrochloric acid (1 in 100) to make exactly 50 mL and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength at about 290 nm, as directed under Ultraviolet-visible Spectrophotometry.

$$\text{Amount (mg) of pyridoxine hydrochloride } (C_8H_{11}NO_3.HCl) = \frac{T}{D} \times C \times \frac{A_T}{A_S}$$

T: Labeled amount (mg) of pyridoxine hydrochloride per tablet of Pyridoxine Hydrochloride Tablets

D: Dilution factor

C: Concentration (μg/mL) of the standard solution

Assay Weigh accurately the mass of NLT 20 tablets of Pyridoxine Hydrochloride Tablets, and powder them. Weigh accurately a portion of the powder, equivalent to about 40 mg of pyridoxine hydrochloride ($C_8H_{11}NO_3$·HCl), add water and shake to mix for 15 minutes. Extract with water to make the volume exactly 100 mL. Discard the first 10 mL of the filtrate, take exactly 5 mL of the subsequent filtrate and 5 mL of internal standard solution, add water to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 40 mg of pyridoxine hydrochloride RS, previously dried in a desiccator for 4 hours (in vacuum, silica gel), and dissolve in water to make exactly 100 mL. Pipet 5 mL of the solution, add exactly 5 mL of the internal standard solution, dilute with water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios of pyridoxine, Q_T and Q_S, to those of the internal standard in each solution, respectively.

$$\text{Amount (mg) of pyridoxine hydrochloride } (C_8H_{11}NO_3.HCl) = \text{Amount (mg) of pyridoxine hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh accurately about 50 mg of Anhydrous Caffeine RS, and dissolve in with water to make 100mL.

Operating conditions

Detector: An ultraviolet absorbance photometer (wavelength: 280 nm). However, a photo-diode array detector (190 nm to 300 nm) is used when the Identification is performed.

Column: A stainless steel column about 4 mm in internal diameter and 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Dissolve 1.0 g of sodium 1-hexanesulfonate in 750 mL of water, and add 250 mL of methanol and 10 mL of acetic acid(31).

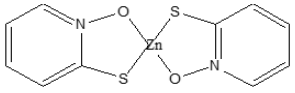
Flow rate: Adjust the flow rate so that the retention time of pyridoxine is about 5 minutes.

System suitability

Selection of column: Proceed with 20 μL of the standard solution under the above conditions; pyridoxine and the internal standard are eluted in this order with the resolution being NLT 3.0.

Packaging and storage Preserve in light-resistant, tight containers.

Pyrithione Zinc
피리티온아연



$(C_5H_4ONS)_2Zn$: 317.70

(T-4)-Bis[1-hydroxy-*O*)-2(1*H*)-pyridinethionato-S2]-zinc, [*13463-41-7*]

Pyrithione Zinc, when dried, contains NLT 90.0% and NMT 101.0% of pyrithione zinc [$(C_5H_4ONS)_2Zn$: 317.70].

Description Pyrithione Zinc occurs as a yellowish, grayish white powder and is odorless.

It is soluble in dimethlyl sulfoxide, sparingly soluble in dimethylformamide or chloroform, and practically insoluble in water or ethanol.
It dissolves in sodium hydroxide TS.

Melting point Between 225 and 235 ℃ (with decomposition).

Identification (1) Incinerate 1 g of Pyrithione Zinc, and dissolve the residue in dilute hydrochloric acid; the solution responds to the Qualitative Analysis for zinc salt.

(2) Put 10 mg of Pyrithione Zinc in a test tube, add a small piece of sodium metal, melt it by heating over low heat while stirring with a glass rod, dissolve in 5 mL of water, and filter. Add 1 mL of lead TS to the filtrate; black precipitates are formed.

(3) Put 5 mg of Pyrithione Zinc in a test tube, add 10 mg of 2,4-dinitrochlorobenzene, and heat over low heat for about 1 hour. Add 4 mL of potassium hydroxide-ethanol TS; the solution exhibits a dark reddish brown color.

(4) Dissolve 0.1 g of Pyrithione Zinc in 5 mL of sodium hydroxide TS, add 1 mL of copper sulfate TS; a dark green precipitate develops.

Purity (1) ***Chloride***—Weigh and incinerate 2.5 g of Pyrithione Zinc, add 10 mL of water, boil for 5 minutes, cool, add water to make 100 mL, and filter. Proceed with 25 mL of the filtrate as the test solution and perform the test as directed under the Chloride. Prepare the control solution with 0.4 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.025%).

(2) ***Arsenic***—Add 0.5 g of potassium nitrate and 0.5 g of anhydrous sodium carbonate to 0.2 g of Pyrithione Zinc, ignite to melt. After cooling, add 15 mL of dilute sulfuric acid, heat until white smoke does not appear, add water to make the test solution 5 mL, proceed as directed under the Arsenic, and perform the test (NMT 10 ppm).

(3) ***Lead***—Weigh 1.0 g of Pyrithione Zinc, add 20 mL of concentrated nitric acid, shake to mix, and heat to dissolve. Heat again and concentrate the solution to make 7 mL. Cool quickly to room temperature, add water to make 100 mL, and use this solution as the test solution. Proceed with 20 mL of this solution, and perform the test as directed under the Heavy Metals (NMT 25 ppm).

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

Residue on ignition Between 45.6% and 52.2% (1 g).

Assay Weigh accurately about 0.3 g of Pyrithione Zinc, previously dried, put in a 500 mL iodine flask, and dissolve with 20 mL of hydrochloric acid. Dissolve again in 200 mL of water, and titrate with 0.1 mol/L iodine VS (indicator: 3 mL of starch TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L iodine VS
= 15.885 mg of $(C_5H_4ONS)_2Zn$

Packaging and storage Preserve in light-resistant, tight containers.

Pyrithione Zinc Solution
피리티온아연 액

Pyrithione Zinc Solution is an aqueous suspension and contains NLT 47.0% and NMT 53.0% of pyrithione zinc [$(C_5H_4ONS)_2Zn$: 317.70].

Method of preparation Prepare as directed under Solutions with Pyrithione Zinc.

Description Pyrithione Zinc Solution occurs as a white aqueous suspension and has a slightly characteristic odor.

Identification (1) Put 1 g of Pyrithione Zinc Solution into a porcelain crucible, heat the crucible over lower heat, charr, and incinerate by ignition. After cooling, dissolve With 20 mL of 2 mol/L hydrochloric acid. Neutralize the portion of the resulting solution with sodium hydroxide TS; precipitates are formed. Add again excess sodium hydroxide TS, and add sodium sulfide TS; white precipitates are formed. Take the precipitates separately and add dilute acetic acid; the precipitates do not dissolve, but dissolves on adding dilute hydrochloric acid.

(2) Dissolve 10 mg of Pyrithione Zinc Solution in 0.5 mol/L sodium hydroxide TS to make 1000 mL, and determine the absorption spectrum of the resulting solution as directed under the Ultraviolet-visible Spectroscopy using 0.5 mol/L sodium hydroxide solution as the control solution; it exhibits maxima around 244 nm and 283 nm.

pH Between 5.0 and 8.0.

Assay Take exactly an amount of Pyrithione Zinc Solution, equivalent to about 50 mg of pyrithione zinc ($(C_5H_4ONS)_2Zn$) according to the labeled amount, add dimethlyl sulfoxide to make exactly 200 mL. Pipet 4 mL of the resulting solution, dissolve in 6 mL of the saturated solution of ethylenediaminetetraacetic acid disodium salt and 4 mL of 0.1% 2,2-dipyridyl disulfide solution, and add water to make exactly 100 mL, and warm on a steam bath (about 70 ℃). After cooling, use this solution as the test solution. Separately, weigh accurately about 50 mg of pyrithione zinc RS, proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Proceed with 20 mL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of pyrithione zinc, A_T and A_S, from the test solution and the standard solution, respectively.

Amount (mg) of pyrithione zinc ($(C_5H_4ONS)_2Zn$)

$$= Amount\ (mg)\ of\ \text{pyrithione zinc RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 235 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B in stages or gradient elution as follows.

Mobile phase A: Acetonitrile

Mobile phase B: Water

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 10	30 → 90	70 → 10
10 - 15	90 → 30	10 → 70
15 - 20	30	70

Flow rate: 0.8 mL/min

Packaging and storage Preserve in light-resistant, tight containers.

Pyrithione Zinc Suspension
피리티온아연 현탁액

Pyrithione Zinc Suspension contains NLT 90.0% and NMT 110.0% of the labeled amount of pyrithione zinc [$(C_5H_4ONS)_2Zn$: 317.70].

Method of preparation Prepare as directed under Suspensions, with Pyrithione Zinc and Pyrithione Zinc solution.

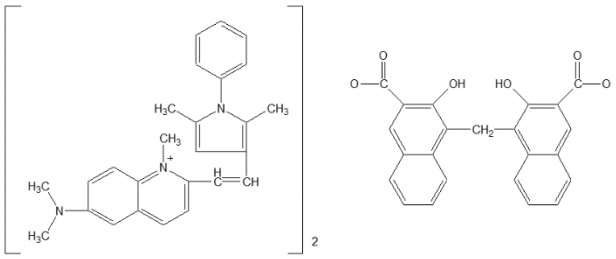
Identification Shake Pyrithione Zinc Suspension well to mix, take an amount of Pyrithione Zinc Suspension, equivalent to 10 mg of pyrithione zinc, and add 1 mL of 1 mol/L sodium hydroxide TS and 9 mL of acetonitrile. Warm to dissolve, cool, filter, and use the filtrate as the test solution. Separately, weigh 10 mg of pyrithione zinc RS, add 1 mL of 1 mol/L sodium hydroxide TS and 9 mL of acetonitrile, warm to dissolve, and use as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of aluminum oxide with fluorescence indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, methanol and acetic acid(100) (20 : 1 : 1) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

Assay Pipet an amount of Pyrithione Zinc Suspension, equivalent to 20 mg of pyrithione zinc [$(C_5H_4ONS)_2Zn$], and put it in a 100-mL beaker. Add 50 mL of dimethylformamide, stir using a stirrer, completely separate (using a glass rod, if necessary), and then filter into a 200-mL volumetric flask. Wash the beaker and filter paper three times with 40 mL each of dimethylformamide to filter, combine the filtrate and washings, add dimethylformamide to make exactly 200 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of pyrithione zinc RS, dissolve in dimethylformamide to make exactly 200 mL, and use this solution as the standard solution. Take exactly 10.0 mL each of the test solution and the standard solution, and add 0.2 mL of 4.5% iron(III) chloride solution to develop color. After 5 minutes, perform the test with the solution, using dimethylformamide as a control solution, under the Ultraviolet-visible Spectroscopy, and determine the absorbances A_T and A_S at the wavelength of 596 nm.

$$\text{Amount (mg) of pyrithione zinc } [(C_5H_4ONS)_2Zn] = \text{Amount (mg) of pyrithione zinc RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in light-resistant, tight containers.

Pyrvinium Pamoate
피르비늄파모산염



$C_{75}H_{70}N_6O_6$: 1151.40

3-Carboxy-1-[(3-carboxy-2-oxidonaphthalen-1-yl)methyl]naphthalen-2-olate [*3546-41-6*]

Pyrvinium Pamoate contains NLT 96.0% and NMT 104.0% of pyrvinium pamoate ($C_{75}H_{70}N_6O_6$), calculated on the anhydrous basis.

Description Pyrvinium Pamoate occurs as a bright orange or blackish orange crystalline powder.
It is very soluble in acetic acid(100), slightly soluble in chloroform or methoxyethanol, very slightly soluble in ethanol(95), and practically insoluble in water or ether.

Identification (1) Determine the absorption spectrum of a solution of acetic acid of Pyrvinium Pamoate in methanol (1 in 200), prepared according to the Assay, as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima at about 358 nm and 505 nm, and the absorbance ratio, A_{505}/A_{358}, is between 1.93 and 2.07.

(2) Determine the infrared spectra of Pyrvinium

Pamoate and pyrvinium pamoate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Water NMT 6.0% (0.2 g, volumetric titration, direct titration, use a mixture of methanol and chloroform (1 : 1) instead of methanol for water determination).

Residue on ignition NMT 0.5% (1 g)

Assay Weigh accurately 0.25 g each of Pyrvinium Pamoate and pyrvinium pamoate RS (water previously measured), dissolve each in 125 mL of acetic acid(100), and add methanol exactly to make exactly 250 mL. Pipet 5 mL each of these solutions, add the methanol to make exactly 500 mL, and use them as the test solution and the standard solution, respectively. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength of about 505 nm as directed under the Ultraviolet-visible Spectroscopy, using methanol as the control solution.

$$\text{Amount (mg) Pyrvinium Pamoate } (C_{75}H_{70}N_6O_6) = \text{Amount (mg) of pyrvinium pamoate RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in light-resistant, tight containers.

Pyrvinium Pamoate Syrup
피르비늄파모산염 시럽

Pyrvinium pamoate syrup contains NLT 0.90 w/v% and NMT 1.10 w/v% of pyrvinium ($C_{26}H_{28}N_3^+$: 382.52).

Method of preparation Prepare as directed under Syrups, with Pyrvinium Pamoate.

Description Pyrvinium pamoate syrup occurs as a dark red, opaque suspensions.

Identification Determine the absorption spectra, between 300nm and 600 nm, of the test solution and the standard solution obtained in the Assay as directed under the Ultraviolet-visible Spectroscopy; both solutions exhibit similar intensities of absorption at the same wavenumbers.

pH Between 6.0 and 8.0.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Shake Pyrvinium Pamoate Syrup well to remove any air bubbles, transfer an amount equivalent to 50 mg (about 5 mL) of pyrvinium ($C_{26}H_{28}N_3^+$) to a 250-mL volumetric flask, and then rinse the pipet with 10 mL of methanol. Dissolve in 100 mL of acetic acid(100) and fill up methanol to the gauge line to mix. Take 3.0 mL of this solution in a 100-mL volumetric flask, fill up methanol to the gauge line to mix, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of pyrvinium pamoate RS (water content is previously measured), dissolve in acetic acid(100) at a ratio of 4 mL per 3 mg of pyrvinium pamoate, dilute with methanol to obtain a solution containing 9 μg per mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the maximum wavelength of absorbance of about 505 nm as directed under the Ultraviolet-visible Spectroscopy, using methanol as the control solution.

$$\text{Amount (w.v\%) of pyrvinium } (C_{26}H_{28}N_3^+) = 0.1677 \times C \times \frac{A_T}{A_S} \times 0.6644$$

C: Concentration of the standard solution (μg/mL)

Packaging and storage Preserve in light-resistant, tight containers.

Pyrvinium Pamoate Tablets
피르비늄파모산염 정

Pyrvinium Pamoate Tablets contain NLT 92.0% and NMT 108.0% of the labeled amount of pyrvinium ($C_{26}H_{28}N_3^+$: 382.52).

Method of preparation Prepare as directed under Tablets, with Pyrvinium Pamoate.

Identification Perform the test according to the Identification of Pyrvinium Pamoate Syrup.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Perform the test by using a light-resistant container. Take a number of tablets of Pyrvinium Pamoate Tablets, equivalent to about 0.5 g of pyrvinium ($C_{26}H_{28}N_3^+$), put in a 500-mL volumetric flask, add 25 mL of water and 25 mL of acetone, and heat on a steam bath while shaking to mix for 10 minutes. Add 250 mL of acetone (100) to the warmed liquid, heat again for 5 minutes, cool the solution, and add methanol to make exactly 500 mL. Centrifuge a portion of the resulting solution until the supernatant becomes transparent, pipet 3 mL of the clear supernatant, add methanol to make exactly 500 mL, and use this solution as the test solution. Separately, weight accurately an appreciate amount of the pyrvinium pamoate RS (water content is previously measured), dis-

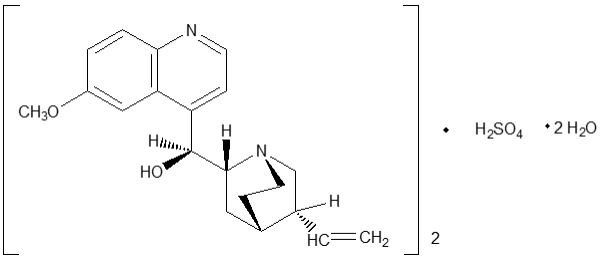
solve in acetic acid(100) at a ratio of 1 mL of acetic acid to 3 mg of pyrvinium pamoate, dilute with methanol to make a solution containing about 9 μg per mL, and use this solution as the standard solution. Determine the absorbances, AT and AS, a control solution and the standard solution, respectively, at the absorbance maximum wavelength of about 505 nm as directed under Ultraviolet-visible Spectrophotometry, using methanol as the blank.

$$\text{Content (w/v\%) of pyrvinium } (C_{26}H_{28}N_3^+) = 83.3\times C \times \frac{A_T}{A_S} \times 0.6644$$

C: Concentration of the standard solution (μg/mL)

Packaging and storage Preserve in light-resistant, tight containers.

Quinidine Sulfate Hydrate
퀴니딘황산염수화물



Quinidine Sulfate $(C_{20}H_{24}N_2O_2)_2\cdot H_2SO_4\cdot 2H_2O$: 782.94
(*S*)-[(2*R*,5*R*)-5-Ethenyl-1-azabicyclo[2.2.2]octan-2-yl]-(6-methoxyquinolin-4-yl) methanol; sulfuric acid; dihydrate [*6591-63-5*]

Quindine Sulfate Hydrate, when dried, contains NLT 98.5% and NMT 101.0% of quinidine sulfate $[(C_{20}H_{24}N_2O_2)_2\cdot H_2SO_4$: 746.91].

Description Quindine Sulfate Hydrate occurs as a white crystal, is odorless and has a very bitter taste.
It is freely soluble in ethanol(95) or hot water, sparingly soluble in water, and practically insoluble in ether.
It, previously dried, is freely soluble in chloroform.
It is gradually changed to dark brown by light.

Optical rotation $[\alpha]_D^{20}$: Between +275° and +287° (0.5 g after drying, 0.1 mol/L sodium hydroxide, 25 mL, 100 mm).

Identification (1) Dissolve 10 mg of Quindine Sulfate Hydrate in 10 mL of water and add 2 to 3 drops of dilute hydrochloric acid; the solution exhibits a blue fluorescence.

(2) Add 1 to 2 drops of bromine TS and 1 mL of ammonia TS to 5 mL of the aqueous solution of Quindine Sulfate Hydrate (1 in 1000); the solution exhibits a green color.

(3) Add 1 mL of silver nitrate TS to 5 mL of aqueous solution of Quindine Sulfate Hydrate (1 in 100) and dissolve by stirring with a glass rod and allow to stand; a white precipitate forms. Add nitric acid in drops to the solution; the precipitate dissolves.

(4) Dissolve 0.4 g of Quindine Sulfate Hydrate in 20 mL of water and 1 mL of dilute hydrochloric acid; the solution responds to the Qualitative Analysis for sulfate.

pH Dissolve 1.0 g of Quindine Sulfate Hydrate in 100 mL of freshly boiled and cooled water. The pH of this solution is between 6.0 and 7.0.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Quindine Sulfate Hydrate according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Chloroform and ethanol-insoluble components***—Add 15 mL of a mixture of chloroform and ethanol(99.5) (2 : 1) to 2.0 g of Quindine Sulfate Hydrate, heat for 10 minutes at 50 ℃ and cool, and filter under weak suction using a glass filter weighed beforehand; wash the residue 5 times using 10 mL each of a mixture of chloroform and ethanol(99.5) (2 : 1), and dry for 1 hour at 105 ℃; the amount is NMT 2.0 mg.

(3) ***Related substances***—Dissolve about 20 mg of Quindine Sulfate Hydrate in the mobile phase to make exactly 100 mL and use this solution as the test solution. Separately, weigh 25 mg of cinchonine RS and dissolve in the mobile phase to make exactly 100 mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method and calculate the amount corresponding to each peak by the percentage peak area method; the amount of dihydroquinidine sulfate is NMT 15.0%, and Quinidine Sulfate and dihydroquinine sulfate are NMT 1.0%, respectively. The total area of the peaks other than the major peak is not greater than the peak area of cinchonine from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 235 nm).

Column: A stainless steel column about 4 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: A mixture of water, acetonitrile, methanesulfonic acid TS and dimethylamine solution (1 in 10) (43 : 5 : 1 : 1).

Flow rate: Adjust the flow rate so that the retention time of quinine is about 10 minutes.

System suitability

Detection sensitivity: Adjust the sensitivity so that the peak height of cinchonidine obtained from 50 μL of the standard solution is between 5 mm and 10 mm.

System performance: Dissolve 10 mg each of Quindine Sulfate Hydrate and quinine sulfate in 5 mL of methanol, and add the mobile phase to make 50 mL. Proceed with 50 μL of this solution according to the above conditions; quinidine, quinine, dihydroquinidine and dihydroquinine are eluted in this order with the resolution between quindine and quinine and between quinine and dihydroquinidine being NLT 1.2, respectively.

Time span of measurement: About 2 times the retention time of quinine after the solvent peak.

(4) ***Readily carbonizable substances***—Weigh 0.2 of Quindine Sulfate Hydrate and perform the test. The color of this solution is not more intense than that of the Matching Fluid for Color M.

Loss on drying NMT 5.0% (1 g, 130 ℃, 3 hours).

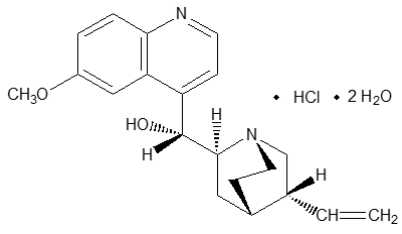
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Quindine Sulfate Hydrate, previously dried, dissolve in 20 mL of acetic acid(100), add 80 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (indicator: 3 drops of methylrosaniline chloride TS). However, the endpoint of the titration is when the violet color of this solution turns to blue and then finally to bluish green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 24.897 mg of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4$

Packaging and storage Preserve in light-resistant, well-closed containers.

Quinine Hydrochloride Hydrate
퀴닌염산염수화물



Quinine Hydrochloride

$C_{20}H_{24}N_2O_2 \cdot HCl \cdot 2H_2O$: 396.91

(*R*)-[(2*S*,4*S*,5*R*)-5-Ethenyl-1-azabicyclo[2.2.2]octan-2-yl]-(6-methoxyquinolin-4-yl) methanol dihydrate hydrochloride [*6119-47-7*]

Quinine Hydrochloride Hydrate, when dried, contains NLT 98.5% and NMT 101.0% of Quinine Hydrochloride ($C_{20}H_{24}N_2O_2 \cdot$ HCl: 360.88).

Description Quinine Hydrochloride Hydrate occurs as a white crystal, is odorless and has a very bitter taste. It is very soluble in ethanol(99.5), freely soluble in ethanol(95), acetic acid(100) or acetic anhydride, sparingly soluble in water, and practically insoluble in ether. It, previously dried, is freely soluble in chloroform.
The color of Quinine Hydrochloride Hydrate is gradually changed to brown by light.

Identification (1) An aqueous solution (1 in 50) of Quinine Hydrochloride Hydrate does not exhibit fluorescence. Add 100 mL of water and 1 drop of dilute sulfuric acid to 1 mL of this solution; a blue fluorescence is exhibited.

(2) Add 1 to 2 drops of bromine TS and 1 mL of ammonia TS to 5 mL of the aqueous solution of Quinine Hydrochloride Hydrate (1 in 1000); the solution exhibits a green color.

(3) Add 1 mL of dilute nitric acid and 1 mL of silver nitrate TS to 5 mL of the aqueous solution of Quinine Hydrochloride Hydrate (1 in 50); a white precipitate is formed. Isolate the precipitate and add a surplus amount of ammonia TS; the precipitate dissolves.

Optical rotation $[\alpha]_D^{20}$: Between -245° and -255° (0.5 g after drying, 0.1 mol/L sodium hydroxide TS, 25 mL, 100 mm).

pH Dissolve 1.0 g of Quinine Hydrochloride Hydrate in 100 mL of freshly boiled and cooled water. The pH of this solution is between 6.0 and 7.0.

Purity (1) ***Sulfate***—Weigh 1.0 g of Quinine Hydrochloride Hydrate and perform the test. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.048%).

(2) ***Barium salt***—Add 10 mL of water to 0.5 g of Quinine Hydrochloride Hydrate, heat to dissolve, and add 1 mL of dilute hydrochloric acid; no turbidity is produced.

(3) ***Chloroform and ether-insoluble components***—Add 15 mL of a mixture of chloroform and ethanol(99.5) (2 : 1) to 2.0 g of Quinine Hydrochloride Hydrate, heat for 10 minutes at 50 ℃ and cool, and filter under weak suction using a glass filter (G4) weighed beforehand. Wash the residue 5 times with 10 mL of a mixture of chloroform and ethanol(99.5) (2 : 1) each time, and dry for 1 hour at 105 ℃; the amount is NMT 2.0 mg.

(4) ***Related substances***—Weigh 20 mg of Quinine Hydrochloride Hydrate, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh 25 mg of cinchonidine and dissolve in the mobile phase to make exactly 100 mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method, and calculate the amount corresponding to each peak by the percentage peak area method; the amount of dihydroquinine hydrochloride is

NMT 10.0%, and the total area of the peaks other than the major peak is not greater than the peak area of cinchonidine from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 235 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: A mixture of water, acetonitrile, methanesulfonic acid TS and diethylamine solution (1 in 10) (43 : 5 : 1 : 1).

Flow rate: Adjust the flow rate so that the retention time of quinine is about 10 minutes.

System suitability

Detection sensitivity: Adjust the sensitivity so that the peak height of cinchonidine obtained from 50 μL of the standard solution is between 5 mm and 10 mm.

System performance: Dissolve 10 mg each of Quinine Hydrochloride Hydrate and quinidine sulfate in 5 mL of methanol, and add the mobile phase to make 50 mL. Proceed with 50 μL of this solution according to the above conditions; quinidine, quinine, dihydroquinidine and dihydroquinine are eluted in this order with the resolution between quinidine and quinine and between quinine and dihydroquinidine being NLT 1.2, respectively.

Time span of measurement: About 2 times the retention time of quinine after the solvent peak.

(5) ***Readily carbonizable substances***—Proceed with 0.25 g of Quinine Hydrochloride Hydrate and perform the test. The color of this solution is not more intense than that of the Matching Fluid for Color M.

Loss on drying NMT 10.0% (1 g, 105 ℃, 5 hours).

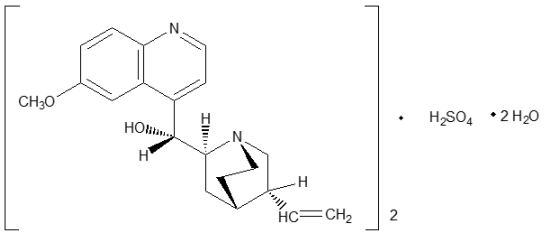
Residue on ignition NMT 0.1% (1 g).

Assay Weigh exactly about 0.4 g of Quinine Hydrochloride Hydrate, previously dried, dissolve in 100 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 18.044 mg of $C_{20}H_{24}N_2O_2 \cdot HCl$

Packaging and storage Preserve in light-resistant, well-closed containers.

Quinine Sulfate Hydrate
퀴닌황산염수화물



Quinine Sulfate

$(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$: 782.94

(*R*)-[(2*S*,5*R*)-5-Ethenyl-1-azabicyclo[2.2.2] octan-2-yl]-(6-methoxyquinolin-4-yl) methanol; sulfuric acid; dihydrate [*6119-70-6*]

Quinine Sulfate Hydrate, contains NLT 98.5% and NMT 101.0% of quinine sulfate [$(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4$: 746.91] on the dried basis.

Description Quinine Sulfate Hydrate occurs as white crystals or a crystalline powder, which is odorless and has a very bitter taste.

It is freely soluble in acetic acid(100), soluble in hot ethanol, sparingly soluble in hot water, slightly soluble in water, ethanol(95), ethanol(99.5) or chloroform, and practically insoluble in ether.

It is gradually changed to brown slowly by light.

Identification (1) Determine the absorption spectra of aqueous solutions of Quinine Sulfate Hydrate and quinine sulfate hydrate RS (1 in 2000) as directed under the Ultraviolet-visible spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectrum of Quinine Sulfate Hydrate and quinine sulfate hydrate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 0.4 g of Quinine Sulfate Hydrate in 20 mL of water and 1 mL of dilute hydrochloric acid; the solution responds to the Qualitative Analysis for sulfate.

Optical rotation $[\alpha]_D^{20}$: Between -235° and -245° (0.75 g after drying, 0.1 mol/L sodium hydroxide TS, 25 mL, 100 mm).

pH Add 2.0 g of Quinine Sulfate Hydrate to 20 mL of freshly boiled and cooled water, shake to mix, and filter; the pH of this solution is between 5.5 and 7.0.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Quinine Sulfate Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Chloroform and ethanol-insoluble components***—Add 15 mL of a mixture of chloroform and ethanol(99.5) (2 : 1) to 2.0 g of Quinine Sulfate Hydrate, heat for 10 minutes at 50 ℃ and cool, and filter under weak suction using a glass filter weighed beforehand; wash the residue 5 times using 10 mL each of a mixture of chloroform and ethanol(99.5) (2 : 1), and dry for 1 hour at

105 ℃; the amount is NMT 2.0 mg.

(3) ***Related substances***—Dissolve about 20 mg of Quinine Sulfate Hydrate, accurately weighed, in the mobile phase to make exactly 100 mL and use this solution as the test solution. Separately, weigh 25 mg of cinchonidine RS and dissolve in the mobile phase to make exactly 100 mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method, and calculate the amount of dihydroquinidine hydrochloride by the percentage peak area method; it is NMT 5%. The total area of the peaks other than the major peak and the above peaks is not greater than the peak area of cinchonidine from the standard solution.

Operating conditions

Detector: An ultraviolet photometer (wavelength: 235 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: A mixture of water, acetonitrile, methanesulfonic acid TS and diethylamine solution (1in 10) (43 : 5 : 1 : 1).

Flow rate: Adjust the flow rate so that the retention time of quinine is about 10 minutes.

System suitability

Detection sensitivity: Adjust the sensitivity so that the peak height of cinchonidine obtained from 50 μL of the standard solution is between 5 mm and 10 mm.

System performance: Dissolve 10 mg of each of Quinine Sulfate Hydrate and quinidine sulfate in 5 mL of methanol, and add the mobile phase to make 50 mL. Proceed with 50 μL of this solution according to the above conditions; quinidine, quinine, dihydroquinidine and dihydroquinine are eluted in this order with the resolution between quinidine and quinine and between quinine and dihydroquinidine being NLT 1.2, respectively.

Time span of measurement: About 2 times the retention time of quinidine after the solvent peak.

Loss on drying NMT 5.0% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

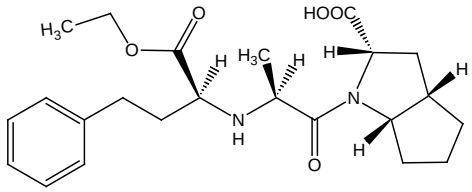
Assay Weigh accurately about 0.5 g of Quinine Sulfate Hydrate, dissolve in 20 mL of acetic acid(100), add 80 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of methylrosaniline chloride TS). However, the endpoint of the titration is when the violet color of this solution turns to blue and then finally to bluish green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS

= 24.90 mg of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4$

Packaging and storage Preserve in light-resistant, well-closed containers.

Ramipril
라미프릴



$C_{23}H_{32}N_2O_5$: 416.51

(2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(2*S*)-1-Ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]-3,3a,4,5,6,6a-hexahydro-2*H*-cyclopenta[b]pyrrole-2-carboxylic acid [*87333-19-5*]

Ramipril, when dried, contains NLT 98.0% and NMT 101.0% ramipril ($C_{23}H_{32}N_2O_5$).

Description Ramipril occurs as a white or almost white, crystalline powder.
It is freely soluble in methanol and sparingly soluble in water.

Identification Determine the infrared spectra of Ramipril and Ramipril RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 105 and 112 ℃.

Optical rotation $[\alpha]_D^{20}$: Between +32° and +38° (after drying, 0.25 g, 0.1 mol/L methanol hydrochloric acid TS, 25 mL, 100 mm).

Purity (1) ***Palladium*** —Weigh accurately about 0.2 g of Ramipril, dissolve in a mixture of water and nitric acid (997 : 3) to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of palladium, dissolve in 9 mL of hydrochloric acid, and add water to be exactly 100 mL. Take an appropriate amount of this solution, add a mixture of water and nitric acid (997 : 3) so that the solution contains 0.02, 0.03 and 0.05 μg per mL, and use this solution as the standard solution. Weigh accurately 0.15 g of magnesium nitrate, add a mixture of water and nitric acid (997 : 3) to make exactly 100 mL, and use this solution as the blank test. Perform the test with 20 μL of the test solution, 20 μL of the standard solution and 10 μL of the blank test solution according to the following conditions as directed under the calibration curve under the Atomic Absorption Spectroscopy and determine the concentration of palladium; it is NMT 0.002%.

$$\text{Content (\%) of palladium} = 0.1 \times \frac{\text{Concentration of palladium in test solution from eqalign calibration curve (μg/mL)}}{\text{Concentration of ramipril in test solution (mg/mL)}}$$

Gas: Air–acetylene or hydrogen
Lamp: Palladium hollow cathode lamp
Wavelength: 247.6 nm

(2) ***Related substances***—Weigh accurately about 125 mg of Ramipril, dissolve in the mobile phase B to make exactly 5 mL, and use this solution as the test solution. Pipet 1 mL of this solution and add the mobile phase to make exactly 100 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions. Determine the peak area of each solution as directed in the automatic integration method and calculate the amount of each related substance; as for the Ramipril related substance I with 0.77 of the relative retention time for ramipril from the test solution, ramipril related substance II with 1.28 of the relative retention time and ramipril related substances III with 1.56 of the relative retention time and ramipril related substances IV with 1.65 of the relative retention time, the total amount is NMT 0.5%. Any other individual unidentified related substances are NMT 0.1%, and the total related substances is NMT 1.0%. However, it is excluded in cases where the peak is smaller than 0.05%.

$$\text{Content (\%) of each related substance} = \frac{A_T}{A_S} \times rf \times \frac{1}{2}$$

A_T: Peak area of each related substances from the test solution
A_S: Peak area of ramipril from the standard solution
rf: Correction factor of each peak of related substances to that of the ramipril peak
Ramipril related substance I: 1.04
Ramipril related substance II: 1.14
Ramipril related substance III: 2.13
Ramipril related substance IV: 1.21
Other related substances: 1.00

Operating conditions
Detector: An ultraviolet absorption photometer (wavelength: 210 nm).
Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).
Column temperature: A constant temperature of about 65 °C.
Mobile phase: Use mobile phases A and B to control stepwise or based on the gradient elution as follows.
Mobile phase A: Dissolve 2.0 g of sodium perchlorate in a mixture of 800 mL of water and 0.5 mL of triethylamine, adjust the pH to 3.6 ± 0.1 with phosphoric acid, and mix after adding 200 mL of acetonitrile.
Mobile B: Dissolve 2.0 g of sodium perchlorate in a mixture of 300 mL of water and 0.5 mL of triethylamine, adjust the pH to 2.6 ± 0.1 with phosphoric acid, and mix after adding 700 mL of acetonitrile.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 6	90	10
6 - 7	90 → 75	10 → 25
7 - 20	75 → 65	25 → 35
20 - 30	65 → 25	35 → 75
30 - 40	25	75
40 - 45	25 → 90	75 → 10
45 - 55	90	10

Flow rate: 1.3 mL/minute
System suitability
Test for required detectability: Take exactly 1 mL of the standard solution and add the mobile phase to make exactly 10 mL. Proceed with 20 μL of this solution according to the above conditions and confirm that the signal-to-noise ratio of the ramipril peak is NLT 10.
System performance: Proceed with 20 μL of the standard solution, perform the test according to the above conditions and adjust so that the retention time of ramipril is between 16 and 19 minutes in the stage where the capacity ratio is 75 : 25.
System repeatability: Repeat the test 6 times with 20 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of ramipril is NMT 2.0%.

Loss on drying NMT 0.2% (1 g, in vacuum, 60 ℃, 6 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Ramipril, dissolve in 25 mL of methanol, add 25 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 41.651 mg of $C_{23}H_{32}N_2O_5$

Packaging and storage Preserve in tight containers.

Ramipril Tablets
라미프릴 정

Ramipril Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of ramipril ($C_{23}H_{32}N_2O_5$:

416.51).

Method of preparation Prepare as directed under Tablets, with Ramipril.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Dissolution Perform the test with 1 tablet of Ramipril Tablets at 75 revolutions per minute according to Method 2 under the Dissolution, using 500 mL of 0.1 mol/L hydrochloric acid solution as the dissolution medium. Filter the solution 30 minutes after starting the dissolution and use this solution as the test solution. Separately, weigh accurately an appropriate amount of ramipril RS, add the dissolution medium to make the same concentration as the test solution, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Assay under Ramipril Tablets. Meets the requirements if the dissolution rate of Ramipril Tablets in 30 minutes is NLT 75%.

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed as directed under the Assay.

Assay Weigh accurately the mass of NLT 20 tables of Ramipril Tablets and powder. Weigh accurately an amount equivalent to about 10 mg of ramipril ($C_{23}H_{32}N_2O_5$), add 0.1 mol/L hydrochloric acid TS, and shake for about 10 minutes to make 50 mL. Use this solution as the test solution Separately, weigh accurately about 10 mg of ramipril RS and dissolve in 0.1 mol/L hydrochloric acid to make 50 mL. Use the resulting solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of ramipril for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of ramipril } (C_{23}H_{32}N_2O_5) = \text{Amount (mg) of ramipril RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μL in particle diameter).

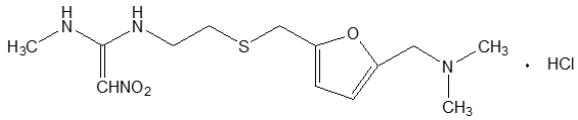
Mobile phase: A mixture of the buffer solution and acetonitrile (60 : 40), adjusted the pH to 2.1 ± 0.1 with 85% phosphoric acid.

Flow rate: 1.0 mL/min

Buffer solution: Dissolve 14 g of sodium perchlorate monohydrate and 5.8 g of 85% phosphoric acid in 1000 mL of water and adjust the pH to 2.5 ± 0.1 with triethylamine.

Packaging and storage Preserve in tight containers.

Ranitidine Hydrochloride
라니티딘염산염



$C_{13}H_{22}N_4O_3S \cdot HCl$: 350.86

(*E*)-*N*-(2-(((5-((Dimethylamino)methyl)furan-2-yl)methyl)thio)ethyl)-*N*-methyl-2-nitroethene-1,1-diamine hydrochloride [*66357-59-3*]

Ranitidine Hydrochloride contains NLT 97.5% and NMT 102.0% of ranitidine hydrochloride ($C_{13}H_{22}N_4O_3S \cdot HCl$), calculated on the dried basis.

Description Ranitidine Hydrochloride occurs as a white to pale yellow, crystalline powder and is odorless.
It is very soluble in water, freely soluble in methanol and practically insoluble in ethanol(99.5).
It is hygroscopic.
It is gradually colored by light.

Melting point—About 160 ℃ (with decomposition).

Identification (1) Determine the absorption spectra of Ranitidine Hydrochloride and Ranitidine Hydrochloride RS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Ranitidine Hydrochloride and Ranitidine Hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Ranitidine Hydrochloride (1 in 50) responds to the Qualitative Analysis for chloride.

pH Dissolve 1.0 g of Ranitidine Hydrochloride in 100 mL of water; the pH of this solution is between 4.5 and 6.0.

Purity (1) ***Clarity and color of solution***—An aqueous solution of Ranitidine Hydrochloride (1 in 10) is pale yellow to light yellow and is clear.

(2) ***Heavy metals***—Proceed with about 2.0 g of Ranitidine Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Weigh about 1.0 g of Ranitidine Hydrochloride and perform the test according to Method 4 (NMT 2 ppm).

(4) ***Related substances***—Dissolve about 0.2 g of

Ranitidine Hydrochloride in 10 mL of methanol and use this solution as the test solution. Weigh accurately about 20 mg of Ranitidine Hydrochloride, dissolve in 10 mL of methanol, pipet1 mL of this solution, and add methanol to make 10 mL. Use this solution as the standard solution (1). Dilute the standard solution (1) with methanol and make the standard solution (2) containing 0.1 mg in 1 mL, the standard solution (3) containing 60 μg in 1 mL, and the standard solution (4) containing 10 μg in 1 mL. Separately, weigh accurately and dissolve ranitidine related substances I {5-[[(2-aminoethyl)thio]methyl]-N,N,-dimethyl-2-furanmethylamine,hemifumarate} in methanol, make a solution containing 1.3 mg of ranitidine related substances I RS in 1 mL, and use it as the resolution solution. Also, weigh accurately ranitidine related substances II [[N,N'-bis{2-[({5-[dimethylamino)methyl]-2-furanyl}methyl)thio]ethyl}-2-nitro-1,1-ethenediamine] RS, dissolve in methanol, make a solution containing about 1 mg in 1 mL, and use this solution as the identification solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution, the standard solution (1), the standard solution (2), the standard solution (3), the standard solution (4) and the identification solution on the plate made of silica gel with fluorescent indicator for thin-layer chromatography. Separately, drop 10 μL of the test solution in the same plate and drop 10 μL of the resolution solution on the top. Develop the plate with a mixture of ethyl acetate, 2-propanol, ammonia water(28) and water (25 : 15 : 5 : 1) as a developing solvent to a distance of about 15 cm, and air-dry the plate. Expose the plate to iodine steam; none of the spot from the test solution equivalent to the R_f value of the principal spot from the identification solution is larger or more intense than the principal spot from the standard solution (2) (NMT 0.5%). Also, another spot from the test solution is not larger or not more intense than the principal spot from the standard solution (3) (NMT 0.3%). The sum of all the spots other than the principal spot from the test solution is NMT 1.0%. One spot appears in the chromatogram of the standard solution (4), and the principal spot is completely separated from the mixed chromatogram of the test solution and the separation solution.

Loss on drying NMT 0.75% (1 g, 60 ℃, in vacuum, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.1 g of Ranitidine Hydrochloride, transfer to a 100-mL volumetric flask, and dissolve by adding the mobile phase, and fill the flask up to the gauge line. Pipet 1.0 mL of this solution, transfer to a 10-mL volumetric flask, add the mobile phase up to the gauge line, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of Ranitidine Hydrochloride RS, dissolve in mobile phase so that 1 mL contains 0.1 μg, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas, A_T and A_S, for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of ranitidine hydrochloride } (C_{13}H_{22}N_4O_3S\cdot HCl) = C \times \frac{A_T}{A_S} \times 1000$$

C: Concentration (mg/mL) of the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 322 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and between 20 and 30 cm in length, packed with octadecylsilanized silica gel (3 μm to 10 μm in particle diameter).

Mobile phase: A deaerated and filtered mixture of methanol and 0.1 mol/L ammonium acetate TS (85 : 15).

Flow rate: 2 mL/minute

System suitability

System performance: Weigh accurately an appropriate amount of Ranitidine Hydrochloride RS and ranitidine related substances III [N-{2[({5-[dimethylamino)methyl]-2-furanyl}methyl)sulfinyl]ethyl}-N'-methyl-2-nitro-1,1-ethyldiamine] RS and dissolve in the mobile phase so that 1 mL each of the solution contains 0.1 mg of Ranitidine Hydrochloride RS and 0.01 mg of Ranitidine Hydrochloride related substances III. Proceed with 10 μL each of these solutions according to the above operating conditions; the resolution between the two components is NLT 1.5, the symmetry factor is NMT 2.0, and the plate number is NLT 700.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of ranitidine is NMT 2.0%

Packaging and storage Preserve in light-resistant, tight containers.

Ranitidine Hydrochloride Tablets
라니티딘염산염 정

Ranitidine Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of ranitidine ($C_{13}H_{22}N_4O_3S$: 314.40).

Method of preparation Prepare Ranitidine Hydrochloride Tablets as directed under Tablets, with Ranitidine Hydrochloride.

Identification (1) The R_f values of the principal spots from the test solution and standard solution of the related substance test are the same.

(2) The retention time of the major peak of the test

solution corresponds to that of the standard solution, as obtained in the Assay.

(3) Weigh an amount of Ranitidine Hydrochloride Tablets, previously powdered, equivalent to 0.1 g of Ranitidine Hydrochloride according to the labeled amount, add 2 mL of water, shake to mix, and filter. The filtrate responds to the Qualitative Analysis for chloride.

Purity ***Related substances***—Take a suitable quantity of tablets and put them to methanol, shake and mix to have complete crumbling of tablets, and filter. Take a suitable amount of the filtrate and make a methanol solution having known concentration of 20 mg of ranitidine (corresponds to 22.3 mg of ranitidine hydrochloride) per mL. Use this solution as the test solution. Weigh accurately a suitable amount of ranitidine hydrochloride RS and dissolve it in methanol. Make a solution containing 0.22 mg per mL and use this solution as the standard stock solution. Take a suitable amount of this standard stock solution and dilute it with methanol to make standard solution (1) containing 110 μg per mL, standard solution (2) containing 66 μg per mL, standard solution (3) containing 22 μg per mL, and standard solution (4) containing 11 μg per mL. Weigh accurately and dissolve ranitidine related substances I {5-[[(2-aminoethyl)thio]methyl]-N,N,-dimethyl-2-furanmethylamine,hemifumarate} in methanol, make a solution containing 1.27 mg of ranitidine related substances per mL, and use it as the resolution solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution, standard stock solution, and standard solutions (1), (2), (3) and (4) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Separately, drop 10 μL of the test solution on the same plate and drop 10 μL of the resolution solution on the top. After drying, develop the plate with a mixture of ethyl acetate, 2-propanol, ammonia water(28) and water (25 : 15 : 5 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Allow the plate to stand in iodine vapor; the spots other than the principal spot obtained from the test solution are not more intense than the principal spot from the standard solution (1). Spot 1 other than the principal spot is also not more intense than that from the standard solution (1) (NMT 0.5%). Also, it is not more intense than the spots other than the principal spot obtained from the standard solution (2) (NMT 0.3%) The sum of all the spots other than the principal spot obtained from the test solution is NMT 2.0%. The system is suitable if the principal spots obtained from the test solution and resolution solution are completely separated, and one spot is observed in the standard solution (4).

Dissolution Perform the test with 1 tablet of Ranitidine Hydrochloride Tablets at 50 revolutions per minute according to Method 2 under the Dissolution Test, using 900 mL of water as the dissolution solution. Take 20 mL of the dissolved solution 45 minutes after starting the dissolution test and filter by a membrane filter with a pore size of not exceeding 0.8 μm. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 0.22 g of Ranitidine Hydrochloride RS and dissolve in water to make exactly 100 mL. Pipet 1 mL of this solution and add water to make 100 mL. Pipet 1 mL of this solution, add water to make 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength of about 314 nm as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as the control solution.

It meets the requirements if the dissolution rate of Ranitidine Hydrochloride Tablets in 45 minutes is NLT 80%.

Uniformity of Dosage Units It meets the requirements when the procedure for content uniformity is performed as directed under the Assay.

Assay Weigh accurately NLT 20 Ranitidine Hydrochloride Tablets and powder. Weigh accurately an amount equivalent to about 10 Ranitidine Hydrochloride Tablets and add more than 250 mL of the mobile phase, shake and mix until completely dispersed, and then filter. Take a suitable amount of the filtrate and dilute it with the mobile phase to have the same concentration as that of the standard solution. Use this solution as the test solution. Separately, weigh accurately an appropriate amount of Ranitidine Hydrochloride RS, and dissolve in the mobile phase to make a solution of exact concentration containing about 0.12 mg per mL. Use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the operating conditions in the Assay. Determine the peak areas, A_T and A_S, of ranitidine for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of Ranitidine } (C_{13}H_{22}N_4O_3S) = C \times \frac{A_T}{A_S} \times \frac{314.40}{350.87} \times \frac{L}{D}$$

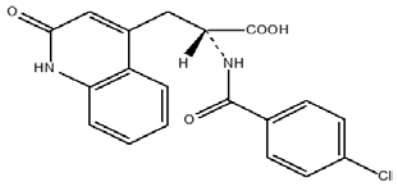
C: Concentration (mg/mL) of standard solution

L: Labeled amount (mg) of Ranitidine in 1 tablet

D: Concentration (mg/mL) of Ranitidine in the test solution according to the labeled amount of ranitidine in 1 tablet

Packaging and storage Preserve in light-resistant, tight containers.

Rebamipide
레바미피드



and enantiomer

$C_{19}H_{15}ClN_2O_4$: 370.79

(2*RS*)-2-(4-Chlorobenzoylamino)-3-(3-oxo-1,2-dihydroquinolin-4-yl)propanoic acid, [*90098-04-7*]

Rebamipide, when dried, contains NLT 99.0% and NMT 101.0% of rebamipide ($C_{19}H_{15}ClN_2O_4$: 370.79).

Description Rebamipide occurs as a white to pale yellow crystalline powder. It is odorless and has a bitter taste.

It is freely soluble in *N*,*N*-dimethylformamide, very slightly soluble in methanol or ethanol and practically insoluble in water or ether.

A solution of Rebamipide in *N*,*N*-dimethylformamide (1 in 20) shows no optical rotation.

Melting point—Between 288 and 294 ℃ (with decomposition).

Identification (1) Perform the Flame Coloration (2) with Rebamipide; the resulting solution exhibits a green color.

(2) Determine the absorption spectrum of a solution of Rebamipide in methanol (7 in 1000000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits absorption maxima at the wavelengths between 228 nm and 232 nm and between 327 nm and 331 nm.

(3) Determine the infrared absorption spectrum of Rebamipide as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; it exhibits absorption at the wavenumbers of about 3280 cm^{-1}, 1730 cm^{-1}, 1644 cm^{-1}, 1602 cm^{-1}, 1540 cm^{-1} and 760 cm^{-1}.

Purity (1) ***Clarity and color of solution***—Weigh 1.0 g of Rebamipide, and dissolve in 20 mL of *N*,*N*-dimethylformamide acid TS; the resulting solution is clear and colorless.

(2) ***Chloride***—Weigh about 0.5 g of Rebamipide, dissolve in 40 mL of *N*,*N*-dimethylformamide, and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.028%).

(3) ***Heavy metals***—Proceed with about 2.0 g of Rebamipide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Prepare the test solution with about 1.0 g of Rebamipide according to Method 3 under the Arsenic (NMT 2 ppm).

(5) ***m-Chloro isomer***—Weigh accurately about 20 mg of Rebamipide, dissolve in 5 mL of *N*,*N*-dimethylformamide, add 50% *N*,*N*-dimethylformamide solution to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of *m*-chloro isomer, dissolve in 5 mL of *N*,*N*-dimethylformamide, and add 50% *N*,*N*-dimethylformamide solution to make exactly 100 mL (standard solution 1). Pipet 2.0 mL of this solution and add 50% *N*,*N*-dimethylformamide solution to make exactly 100 mL. Pipet 5 mL of this solution, add 50% *N*,*N*-dimethylformamide solution to make exactly 20 mL, and use this solution as the standard solution (standard solution 2). Perform the test with 20 μL each of the test solution and the standard solution 2 according to the following conditions as directed under the Liquid Chromatography. Determine the peak areas of m-chloro isomer in each solutions, AT and AS according to the automatic integration method; A_T is not larger than A_S (NMT 0.5%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel (5 μm in particle diameter).

Column temperature: Room temperature

Mobile phase: Dissolve 0.58 g of anhydrous sodium monohydrogen phosphate and 2.0 g of potassium dihydrogen phosphate in 1000 mL of water, and filter through a membrane filter with a pore size of NMT 0.45 μm. Take 830 mL of the filtrate and add 170 mL of acetonitile.

Flow rate: Adjust the flow rate so that the retention time of rebamipide is about 20 minutes.

Selection of column: Take 10 mL of the test solution and add 50 μL of the standard solution (1). Proceed with 20 μL of this solution according to the above operating conditions; *m*-chloro isomer and rebamipide are eluted in this order, and the ratio of height between rebamipide peak and *m*-chloro isomer on the peak height of m-chloro isomer is NMT 0.6.

Detection sensitivity: Adjust so that the peak height of *m*-chloro obtained from 20 μL of the standard solution (2) is 5 mm to 10 mm.

Time span of measurement: The range until the termination of peak Elution of Rebamipide.

m-chloro iomer—2-(3-Chlorobenzoylamino)-3-[2(1*H*)-quinolinon-4-yl]propionic acid

(6) ***Debenzoylated isomer*** —Use the test solution in (5) as the test solution. Weigh accurately 12 mg of *debenzoylated isomer* as free base, calculated on the dehydrated basis, dissolve in 10 mL of 0.05 mol/L potassium hydroxide TS, and add 50% *N*,*N*-dimethylformamide solution to make exactly 100 mL. Pipet 2 mL of this solution and add 50% *N*,*N*-dimethylformamide solution to make exactly 100 mL. Pipet 5 mL of this solution, add 50% dimethylformamide solution to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution according to the following conditions as directed under the Liquid Chromatography Determine the peak areas of debenzoylated isomer A_T and A_S, for each solu-

tion according to the automatic integration method; A_T is not greater than A_S (NMT 0.3%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with Aminopropylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Dissolve 0.58 g of anhydrous sodium monohydrogen phosphate and 2.0 g of potassium dihydrogen phosphate in 1000 mL of water, and filter through a membrane filter with a pore size of NMT 0.45 μm. Take 200 mL of the filtrate and add 800 mL of acetonitile.

Flow rate: Adjust the flow rate so that the retention time of debenzoylated isomer is about 10 minutes.

Selection of column: Adjust so that the peak height of debenzoylated isomer obtained from 20 μL of the standard solution is 5 mm to 10 mm.

Debenzoyl—2-Amino-3-[2(1*H*)-quinolinone-4-yl]propionate·2HCl

(7) ***Related substances***—Use the test solution in (5) as the test solution. Pipet 2 mL of this solution and add 50% *N*,*N*-dimethylformamide solution to make exactly 100 mL. Pipet 5.0 mL of this solution, add 50% *N*,*N*-dimethylformamide solution to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution according to the following conditions as directed under the Liquid Chromatography. Determine the peak area of each solution according to automatic integration method; the total area of the peak other than rebamipide from the test solution is not greater than the peak area of rebamipide from the standard solution (NMT 0.5%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel (5 μm in particle diameter).

Mobile phase: A mixture of water, acetonitrile and acetic acid(100) (70 : 30 : 1).

Flow rate: Adjust the flow rate so that the retention time of rebamipide is about 8 minutes.

Selection of column: Weigh accurately 20 mg of *p*-chlorobenzoic acid, dissolve in exactly 5 mL of *N*,*N*-dimethylformamide, and add 50% dimethylformamide solution to make exactly 100 mL. Pipet 5 mL each of this solution and the test solution, add 50% *N*,*N*-dimethylformamide solution to make exactly 100 mL. Proceed with 20 μL of this solution according to the above operating conditions; use a column from which rebamipide and *p*-chlorobenzoic acid are eluted in this order with the resolution between their peaks being NLT 8.

Detection sensitivity: Adjust so that the peak height of rebamipide obtained from 20 μL of the standard solution is 5 mm to 10 mm.

Time span of area measurement: About 3 times the retention time of rebamipide from the solvent peak.

Loss on drying NMT 3.0% (1 g, 105 °C, 2 hours).

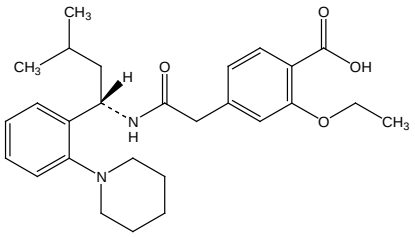
Residue on ignition NMT 0.10% (1 g).

Assay Weigh accurately about 0.6 g of Rebamipide, previously dried, dissolve in 60 mL of *N*,*N*-dimethylformamide, and titrate with 0.1 mol/L potassium hydroxide VS. (indicator: 2 drops of phenol red TS) The endpoint of titration is when the pale yellow color of the solution turns purple. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L potassium hydroxide VS
= 37.08mg of $C_{19}H_{15}ClN_2O_4$

Packaging and storage Preserve in well-closed containers.

Repaglinide
레파글리니드



$C_{27}H_{36}N_2O_4$: 452.59

(*S*)-2-Ethoxy-4-[2-(3-methyl-1-[2-(piperidin-1-yl)phenyl]butylamino)-2-oxoethyl]benzoic acid [*135062-02-1*]

Repaglinide contains NLT 98.0% and not more 101.0% of repaglinide ($C_{27}H_{36}N_2O_4$), calculated on the dried basis.

Description Repaglinide occurs as a white solid.
It is soluble in methanol.

Melting point—Between 132 and 136 ℃.

Identification (1) Determine the absorption spectra of solutions of Repaglinide and Repaglinide RS in methanol (1 in 40000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Repaglinide and Repaglinide RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Repaglinide according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Weigh accurately about 100 mg of Repaglinide, dissolve in methanol to make exactly 10 mL, and use this solution as the test solution. Pipet 1 mL of this solution and add methanol to make exactly 100 mL. Pipet 1 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 3 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution according to the automatic integration method and determine the amount of related substances; repaglinide related substances I with 1.2 of the relative retention time for repaglinide from the test solution, repaglinide related substances II with 0.2 of the relative retention time or repaglinide related substances III with 0.9 of the relative retention time is NMT 0.1%, and the total related substances is NMT 0.5%. However, exclude any peaks smaller than 0.05%.

$$\text{Content (\%) of related substances} = \frac{A_T}{A_S} \times rf \times \frac{1}{10}$$

A_T: Peak area of each related substance from the test solution

A_S: Peak area of repaglinide from the standard solution

rf: The correction factor for each related substance for repaglinide peak

Repaglinide related substances I: 3.36
Repaglinide related substances II: 0.68
Repaglinide related substances III: 0.93
Other related substances: 1.00

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in inside diameter and about 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 45 ℃.

Mobile phase: Use mobile phases A and B to control stepwise or based on the gradient elution as follows.

Mobile phase A: Dissolve 3 g of potassium dihydrogen phosphate in 1000 mL of water, and adjust pH to 7.0 with 1 mol/L sodium hydroxide TS.

Mobile phase B: Methanol

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0	40	60
0 - 2	40 → 30	60 → 70
2 - 8	30	70
8 - 12	30 → 10	70 → 90
12 - 15	10	90

Flow rate: 1.0 mL/min

System suitability

Test for required detectability: Pipet 5 mL of the standard solution and add the mobile phase to make exactly 10 mL. Proceed with 3 μL of this solution according to the above conditions; confirm that the signal-to-noise ratio of repaglinide peak is NLT 10.

System performance: Proceed with 3 μL of the standard solution according to the above conditions; the symmetry factor for repaglinide peak is NLT 0.8 and NMT 2.0.

System repeatability: Repeat the test 6 times with 3 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of repaglinide is NMT 10%.

Isomer Perform the test without exposure to light, using light-resistant containers. Weigh exactly 10 mg of Repaglinide, add methanol to make exactly 10 mL, and use this solution as the test solution. Dissolve an appropriate amount of repaglinide enantiomer {2-ethoxy-4-[2-({(1R)-3-methyl-1-[2-(piperidin-1-yl)phenyl]butyl}amino)-2-oxoethyl]benzoic acid} RS in methanol to make a concentration of 2.0 μg/mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions; the amount of repaglinide enantiomer is NMT 0.2%.

$$\text{Content (\%) of repaglinide enantiomer} = (C_S/C_T) \times (A_i/A_S) \times 100$$

C_S: Concentration (mg/mL) of repaglinide enantiomer in the standard solution

C_T: Concentration (mg/mL) of repaglinide in the test solution

A_i: Peak area of repaglinide enantiomer obtained from the test solution

A_S: Peak area of repaglinide enantiomer obtained from the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 10 cm in length, packed with silica gel for liquid chromatography (5 μm in particle diameter, α1-acid glycoprotein).

Use mobile phases A and B to control stepwise or based on the gradient elution as follows.

Mobile phase A: Dissolve 1 g of potassium dihydrogen phosphate in 1000 mL of water and adjust pH to 4.7 with 2N sodium hydroxide TS or phosphoric acid.

Mobile phase B: Acetonitrile

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 4	80 → 60	20 → 40
4 - 6	60	40

Flow rate: 1.0 mL/min
Injection volume: 10 μL
System suitability

Test for required detectability: Proceed with solutions of 1.0 mg/mL of repaglinide RS and 0.02 mg/mL of repaglinide enantiomer RS in methanol as the system suitability solution according to the above conditions; the resolution between repaglinide and repaglinide enantiomer is NLT 1.5.

Loss on drying NMT 0.5% (30 mg, 105 ℃, constant mass).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 25 mg each of Repaglinide and Repaglinide RS, dissolve in methanol to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas A_T and A_S of repaglinide.

$$\text{Amount (mg) of repaglinide } (C_{27}H_{36}N_2O_4) = \text{Amount (mg) of repaglinide RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in inside diameter and about 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 45 ℃.

Mobile phase: A mixture of phosphate buffer solution and methanol (200 : 800).

Flow rate: 1.0 mL/min

System suitability

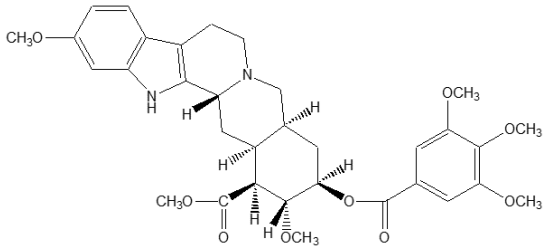
System performance: Dissolve 25 mg of repaglinide RS and 2 mg of repaglinide related substance II RS in methanol to make 50 mL and proceed with 10 μL of this solution according to the above conditions; the relative retention time is 1.0 and 0.4, respectively.

System repeatability: Repeat the test 5 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of repaglinide is NMT 2.0%.

Phosphate buffer solution—Add phosphoric acid in potassium dihydrogen phosphate solution (1 in 1000) and adjust pH to 2.5.

Packaging and storage Preserve in tight containers.

Reserpine
레세르핀



$C_{33}H_{40}N_2O_9$: 608.68

Methyl(1*R*,15*S*,17*R*,18*R*,19*S*,20*S*)-6,18-dimethoxy-17-(3,4,5-trimethoxybenzoyl)oxy-1,3,11,12,14,15,16,17,18,19,20,21-dodecahydroyohimban-19-carboxylate [*50-55-5*]

Reserpine, when dried, contains NLT 96.0% and NMT 101.0% of reserpine ($C_{33}H_{40}N_2O_9$).

Description Reserpine occurs as white to pale yellow crystals or a crystalline powder.
It is freely soluble in acetic acid(100) or chloroform, slightly soluble in acetonitrile, very slightly soluble in ethanol(95), and practically insoluble in water or ether.
It is affected by light.

Identification (1) To 1 mg of Reserpine, add 1 mL of vanillin-hydrochloric acid TS and warm; the resulting solution exhibits a vivid purple color.

(2) Determine the absorption spectra of solutions of Reserpine and reserpine RS in acetonitrile (1 in 50,000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Reserpine and Reserpine RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -114° and -127° (0.25 g after drying, chloroform, 25 mL, 100 mm).

Purity ***Related substances***—Perform this procedure without exposure to daylight, using a light-resistant container. Dissolve 50 mg of Reserpine in 50 mL of acetonitrile, and use this solution as the test solution. Pipet 3 mL of this solution, add acetonitrile to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution as directed in the automatic integration method; the sum of peak areas other than reserpine from the test solution is not greater than the peak area of

reserpine from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 268 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of pH 3.0 0.05 mol/L potassium dihydrogen phosphate and acetonitrile (13 : 7).

Flow rate: Adjust the flow rate so that the retention time of reserpine is about 20 minutes.

System suitability

Detection sensitivity: Adjust the sensitivity so that the peak height of reserpine obtained from 10 μL of the standard solution is about 20 mm.

System performance: Dissolve 10 mg of Reserpine and 4 mg of butyl p-hydroxybenzoate in 100 mL of acetonitrile. To 5 mL of this solution, add acetonitrile to make 50 mL. Proceed with 20 μL of this solution according to the operating conditions in the Assay; reserpine and butyl p-hydroxybenzoate are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of reserpine is NMT 2.0%.

Time span of measurement: About 2 times the retention time of reserpine.

Loss on drying NMT 0.5% (0.2 g, in vacuum, 60 ℃, 3 hours).

Residue on ignition NMT 0.2% (0.2 g).

Assay Perform this procedure without exposure to daylight, using a light-resistant container. Weigh accurately about 10 mg each of Reserpine and Reserpine RS, previously dried, and dissolve each in acetonitrile to make exactly 100 mL. Pipet 5 mL each of the solution, add 10 mL of internal standard solution, 5 mL of acetonitrile and water to make 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of reserpine to the internal standard, respectively.

$$\text{Amount (mg) of reserpine } (C_{33}H_{40}N_2O_9) = \text{Amount (mg) of reserpine RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of butyl p-hydroxybenzoate in acetonitrile (1 in 50,000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 268 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of pH 3.0 0.05 mol/L potassium dihydrogen phosphate and acetonitrile (11 : 9).

Flow rate: Adjust the flow rate so that the retention time of reserpine is about 10 minutes.

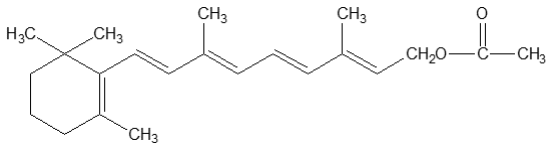
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; reserpine and the internal standard are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the ratios of the peak area of reserpine to that of the internal standard is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Retinol Acetate
레티놀아세테이트



Vitamin A Acetate $C_{22}H_{32}O_2$: 328.49

(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,4,6,8-tetraenylacetate [*127-47-9*]

Retinol Acetate is synthetic retinol acetate or a combination of synthetic retinol acetate and vegetable oil, containing NLT 2,500,000 vitamin A units per gram. A suitable antioxidant may be added.

Retinol Acetate contains NLT 95.0% and NMT 105.0% of the labeling unit.

Description Retinol Acetate occurs as pale yellow to yellowish red crystals or a ointment-like material. It has a non-rancid, slightly characteristic odor.

It, when powdered, is very soluble in chloroform or ether, freely soluble in petroleum ether, soluble in ethanol(95) or 2-propanol, and is practically insoluble in water.

It is affected by air or light.

Identification Weigh an amount equivalent to 15,000 units of Retinol Acetate and Retinol Acetate RS, dissolve each in 5 mL of petroleum ether, and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-

layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of cyclohexane and ether (12 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly antimony(III) chloride TS on the plate; the colors and R_f values of the principal spot obtained from the test solution and the blue spot from the standard solution are the same.

Purity (1) ***Acid value***—NMT 2.0. Weigh accurately 5.0 g of Retinol Acetate and perform the test.

(2) ***Peroxide***—Weigh accurately 5 g of Retinol Acetate, place in a 250 mL stoppered Erlenmeyer flask, add 50 mL of a mixture of Acetic acid(100) and isooctane (3 : 2), and dissolve by shaking gently to mix. Pass gently about 600 mL of nitrogen through this solution to replace the air in the flask. While passing the nitrogen again, add 0.1 mL of saturated potassium iodide TS, immediately stopper the flask, and mix by shaking in a constant circular motion for 1 minute. Add 30 mL of water, stopper the flask, and mix by shaking vigorously for 5 to 10 seconds. Titrate this solution with 0.01 mol/L sodium thiosulfate VS. However, the endpoint of the titration is when the blue color obtained by adding 0.5 mL of starch TS becomes decolorized as the solution near the endpoint turns pale yellow. Calculate the amount of peroxide according to the following equation; the value is NMT 10 meq/kg.

$$\text{Amount (meq/kg) of peroxide} = (V / W)\times 10$$

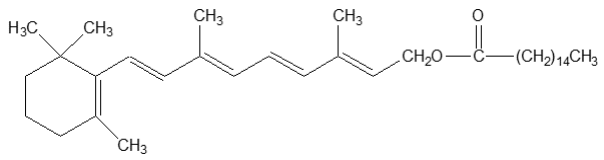
V: Volume (mL) of 0.01 mol/L sodium thiosulfate VS consumed

W: Amount (g) of Retinol Acetate taken

Assay Perform the test according to Method 1 under the Vitamin A Assay.

Packaging and storage Preserve in light-resistant, tight containers, by almost fully filling the container or replacing the air of an empty space with nitrogen, in a cold place.

Retinol Palmitate
레티놀팔미테이트



Vitamin A Palmitate $C_{36}H_{60}O_2$: 524.86

(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-tri-methylcyclohexen-1-yl)nona-2,4,6,8-tetraenyl hexadecanoate

[*79-81-2*]

Retinol Palmitate is synthetic retinol palmitate or a combination of synthetic retinol palmitate and vegetable oil, containing NLT 1,500,000 vitamin A units per gram.

A suitable antioxidant may be added.

Retinol Palmitate contains NLT 95.0% and NMT 105.0% of the labeling unit.

Description Retinol Palmitate occurs as a pale yellow to yellowish red, solid oil phase or oil phase material. It has a non-rancid, slightly characteristic odor.
It is very soluble in petroleum ether, slightly soluble in ethanol(95), and practically insoluble in water.
It is decomposed by air or light.

Identification Take an amount equivalent to 15,000 units each of Retinol Palmitate and Retinol Palmitate RS, dissolve each in 5 mL of petroleum ether, and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of cyclohexane and ether (12 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly antimony(III) chloride TS on the plate; the colors and R_f values of the principal spot obtained from the test solution and the blue spot from the standard solution are the same.

Purity (1) ***Acid value***—NMT 2.0. Weigh accurately 5.0 g of Retinol Palmitate and perform the test.

(2) ***Peroxide***—Weigh accurately 5 g of Retinol Palmitate, place in a 250 mL stoppered Erlenmeyer flask, add 50 mL of a mixture of Acetic acid(100) and isooctane (3 : 2), and dissolve by shaking gently to mix. Pass gently about 600 mL of nitrogen through this solution to replace the air in the flask. While passing the nitrogen again, add 0.1 mL of saturated potassium iodide TS, immediately stopper the flask, and shake to mix in a constant circular motion for 1 minute. Add 30 mL of water, stopper the flask, and mix by shaking vigorously for 5 to 10 seconds. Titrate this solution with 0.01 mol/L sodium thiosulfate VS. However, the endpoint of the titration is when the blue color obtained by adding 0.5 mL of starch TS is decolorized as the solution near the endpoint turns pale yellow. Calculate the amount of peroxide according to the following equation; the value is NMT 10 meq/kg.

$$\text{Amount (meq/kg) of peroxide} = (V / W)\times 10\ \text{mol/L}$$

V: Volume (mL) of 0.01 mol/L sodium thiosulfate VS consumed

W: Amount (g) of Retinol Palmitate taken

Assay Perform the test according to Method 1 under the Vitamin A Assay.

Packaging and storage Preserve in light-resistant, tight containers, as almost well-filled or under nitrogen atmos-

phere, and in a cold place.

Retinol Palmitate Oil
레티놀팔미테이트유

Vitamin A Palmitate Oil

Retinol Palmitate Oil contains NLT 1000,000 IU of retinol palmitate ($C_{36}H_{60}O_2$: 524.87) (vitamin A) per g.

Method of preparation Prepare Retinol Palmitate Oil by adding tocopherol, antioxidant and vegetable oil to retinol palmitate.

Description Retinol Palmitate Oil occurs as a greenish yellow to yellow oily liquid.

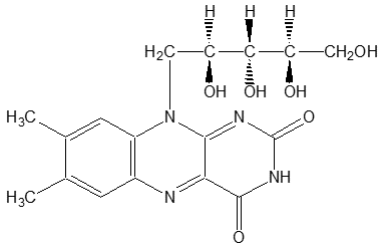
Identification Perform the test with Retinol Palmitate Oil as directed under the Identification of Retinol Palmitate under the Analysis for Vitamins.

Acid value NMT 2.0.

Assay Perform the test with Retinol Palmitate Oil as directed under the Assay of Retinol Palmitate under the Analysis for Vitamins.

Packaging and storage Preserve in light-resistant, tight containers.

Riboflavin
리보플라빈



Vitamin B_2 $C_{17}H_{20}N_4O_6$: 376.36

7,8-Dimethyl-10-[(2*S*,3*S*,4*R*)-2,3,4,5-tetrahydroxypentyl]benzo[g]pteridine-2,4-dione [*83-88-5*]

Riboflavin, when dried, contains NLT 98.0% and NMT 101.0% of Riboflavin ($C_{17}H_{20}N_4O_6$).

Description Riboflavin occurs as yellow to orange crystals and has a slight odor.
It is very slightly soluble in water and practically insoluble in ethanol(95), acetic acid(100) or ether.
It dissolves in sodium hydroxide TS.
A saturated solution of Riboflavin is neutral.
It is decomposed by light.

Melting point—About 290 °C (with decomposition).

Identification (1) An aqueous solution of Riboflavin (1 in 100000) is pale yellowish green and has an intense yellowish green fluorescence. To 5 mL of this solution, add 20 mg of sodium hydrosulfite; the color and fluorescence of the solution disappear, but reappear slowly on shaking the mixture in air. This fluorescence disappears upon the addition of dilute hydrochloric acid or sodium hydroxide TS.

(2) Transfer 10 mL of a solution of Riboflavin (1 in 100000) into a glass-stoppered test tube, add 1 mL of sodium hydroxide TS, and illuminate with a fluorescence lamp of 10 to 30 watts at 20 cm distance for 30 minutes at 20 to 40 ℃. Acidify with 0.5 mL of acetic acid(31), add 5 mL of chloroform, and shake well to mix; the chloroform layer shows a yellowish green fluorescence.

(3) Determine the absorption spectra of solutions of Riboflavin and Riboflavin RS in phosphate buffer solution, pH 7.0 (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Optical rotation $[\alpha]_D^{20}$: Between -128° and -142°. Weigh accurately about 0.1 g of Riboflavin, previously dried, dissolve in exactly 4 mL of dilute sodium hydroxide TS, add 10 mL of freshly boiled and cooled water, and add exactly 4.0 mL of aldehyde-free alcohol while shaking well to mix. Add freshly boiled and cooled water to make exactly 20 mL, and determine the optical rotation in a 100 mm cell within 30 minutes after preparing the solution.

Purity ***Lumiflavin***—To 25 mg of Riboflavin, add 10 mL of ethanol-free chloroform, shake to mix for 5 minutes, and filter. The color of the filtrate is not more intense than that of the following control solution.

Control solution—Take 2.0 mL of $\frac{1}{60}$ mol/L potassium dichromate, and add water to make exactly 1000 mL.

Loss on drying NMT 1.5% (0.5 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Perform the test without exposure to daylight, using light-resistant vessels. Weigh accurately about 15 mg of Riboflavin, previously dried, dissolve in 800 mL of diluted acetic acid(100) (1 in 400) by warming, cool, add water to make exactly 1000 mL, and use this solution as the test solution. Separately, weigh accurately about 15 mg of Riboflavin RS, previously dried at 105 ℃ for 2 hours, dissolve in 800 mL of diluted acetic acid(100) (1 in 400) by warming, cool, and add water to make exactly 1000 mL. Use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy using water as the control solution, and determine the absorbances, A_T and A_S, at a wavelength of 445 nm. Add 20 mg of sodium hydrosulfite to 5 mL of each solution, shake until it decolorized, and immediately measure the

absorbances, A_T and A_S of these solutions.

$$\text{Amount (mg) of Riboflavin } (C_{17}H_{20}N_4O_6) = \text{Amount (mg) of Riboflavin RS} \times \frac{A_T - A_{T'}}{A_S - A_{S'}}$$

Packaging and storage Preserve in light-resistant, tight containers.

33.3% Riboflavin Powder
리보플라빈 3배산

33.3% riboflavin powder contains NLT 32.6% of riboflavin ($C_{17}H_{20}N_4O_6$: 376.36), calculated on the anhydrous basis.

Method of preparation Prepare by finely dispersing Riboflavin in edible fatty acid. A corn starch may be added. 33.3% Riboflavin Powder is a drug substance.

Description 33.3% Riboflavin Powder occurs a yellow to orangey yellow powder.

Identification Perform the test with 33.3% Riboflavin Powder as directed under the Identification for Riboflavin in the Pharmacopoeia.

Water NMT 1.0% (0.5 g, volumetric titration, direct titration).

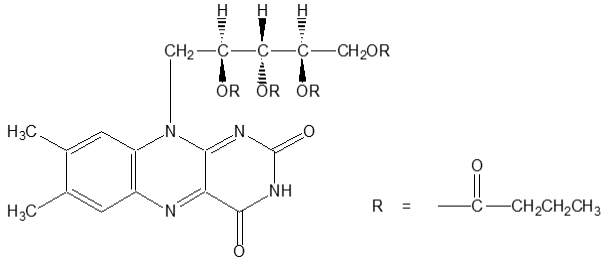
Residue on ignition NMT 0.1% (1 g).

Assay Perform the test using light-resistant containers. Weigh accurately an amount of 33.3% Riboflavin Powder, equivalent to about 15 mg of riboflavin, add 800 mL of diluted acetic acid(100) (1 in 400), and warm to dissolve. After cooling, add water to make 1000 mL, and use this solution as the test solution. Separately, dry riboflavin RS at 105 ℃ for 2 hours. Weigh accurately about 15 mg, add 800 mL of diluted acetic acid(1 in 400), warm to dissolve, cool, add water to make 1000 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy using water as a control solution, and determine the absorbances, A_T and A_S, at a wavelength of 445 nm. Add sodium hydrosulfite in an amount of 20 mg per 5 mL of each solution, shake to mix until decolorized, and immediately measure the absorbances, A_T and A_S of these solutions.

$$\text{Amount (mg) of riboflavin } (C_{27}H_{20}N_4O_6) = \text{Amount (mg) of riboflavin RS} \times \frac{A_T - A_{T'}}{A_S - A_{S'}}$$

Packaging and storage Preserve in light-resistant, tight containers.

Riboflavin Butyrate
리보플라빈부티레이트



$C_{33}H_{44}N_4O_{10}$: 656.72

[(2*R*,3*S*,4*S*)-2,3,4-Tri(butanoyloxy)-5-(7,8-dimethyl-2,4-dioxobenzo[g]pteridin-10-yl)pentyl] butanoate [*752-56-7*]

Riboflavin Butyrate, when dried, contains NLT 98.5% and NMT 101.0% of Riboflavin Butyrate ($C_{33}H_{44}N_4O_{10}$).

Description Riboflavin Butyrate occurs as orange crystals or a crystalline powder and has a characteristic odor and a slightly bitter taste.
It is freely soluble in methanol, ethanol(95) or chloroform, slightly soluble in ether, and practically insoluble in water.
It is decomposed by light.

Identification (1) A solution of Riboflavin Butyrate in ethanol(95) (1 in 100000) shows a pale yellow color with intense yellowish green fluorescence. To this solution, add dilute hydrochloric acid or sodium hydroxide TS; the fluorescence disappears.

(2) Dissolve 10 mg of Riboflavin Butyrate in 5 mL of ethanol(95), and add 2 mL of a mixture of sodium hydroxide (3 in 20) and hydroxylamine hydrochloride (3 in 20) (1 : 1), and shake well to mix. Add 0.8 mL of hydrochloric acid and 0.5 mL of iron(III) chloride TS, and add 8 mL of ethanol(95); the resulting solution exhibits a deep reddish brown color.

(3) Determine the absorption spectra of solutions of Riboflavin Butyrate and Riboflavin Butyrate RS in ethanol (4 in 250000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Melting point Between 146 and 150 ºC.

Purity (1) ***Chloride***—Dissolve 2.0 g of Riboflavin Butyrate in 10 mL of methanol, add 24 mL of dilute nitric acid and water to make exactly 100 mL, shake well to mix, and allow to stand for 10 minutes. Filter, discard the first 10 mL of the filtrate, and use the subsequent filtrate as the test solution. To 25 mL of the test solution, add water to make exactly 50 mL, add 1 mL of silver nitrate TS, and allow to stand for 5 minutes; the turbidity of the solution is not more intense than that of the following control solution.

Control solution—To 25 mL of the test solution, add 1 mL of silver nitrate TS, allow to stand for 10 minutes, and filter. Wash the precipitate with 5 mL of water 4 times, combine the washings with the filtrate, add 0.30 mL of 0.01 mol/L hydrochloric acid and water to make exactly 50 mL, add again 1 mL of water, and mix (NMT 0.021%).

(2) ***Heavy metals***—Proceed with about 2.0 g of Riboflavin Butyrate as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Free acid***—Take 1.0 g of Riboflavin Butyrate, add 50 mL of freshly boiled and cooled water, shake to mix, and filter. Take 25 mL of the filtrate, add 0.50 mL of 0.01 mol/L sodium hydroxide TS and 2 drops of phenolphthalein TS; the color of the solution is red.

(4) ***Related substances***—Dissolve 0.10 g of Riboflavin Butyrate in 10 mL of chloroform, and use this solution as the test solution. Pipet 1.0 mL of the test solution and add chloroform to make exactly 50 mL. Pipet 5 mL of this solution, add chloroform to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform and 2-propanol (9 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, silica gel, 4 hours).

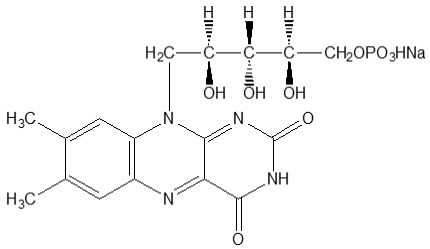
Residue on ignition NMT 0.1% (1 g).

Assay Perform the test in a light-resistant container away from direct sunlight. Weigh accurately about 40 mg of Riboflavin Butyrate, previously dried, and dissolve in ethanol(95) to make exactly 500 mL. Pipet 10 mL of this solution, add ethanol(95) to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of Riboflavin RS, previously dried at 105 ℃ for 2 hours, dissolve in 150 mL of diluted acetic acid(100) (2 in 75) by warming, cool, and add water to make exactly 500 mL. Pipet 5 mL of this solution, add ethanol(95) to make exactly 50 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S of the test solution and the standard solution, respectively, at a wavelength of 445 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of Riboflavin Butyrate ($C_{33}H_{44}N_4O_{10}$)
= Amount (mg) of riboflavin RS $\times \frac{A_T}{A_S} \times 1.7449 \times \frac{1}{2}$

Packaging and storage Preserve in light-resistant, tight containers.

Riboflavin Sodium Phosphate
리보플라빈포스페이트나트륨



Vitamin B2 Phosphate
Riboflavin Phosphate $C_{17}H_{20}N_4NaO_9P$: 478.33
Sodium[(2*S*,3*R*,4*R*)-5-(7,8-dimethyl-2,4-dioxobenzo[g]pteridin-10-yl)-2,3,4-trihydroxypentyl] hydrogen phosphate [*130-40-5*]

Riboflavin Sodium Phosphate contains NLT 92.0% and NMT 101.0% of Riboflavin Sodium Phosphate ($C_{17}H_{20}N_4NaO_9P$), calculated on the anhydrous basis.

Description Riboflavin Sodium Phosphate occurs as a yellow to orange crystalline powder. It is odorless and has a slightly bitter taste.
It is soluble in water and practically insoluble in ethanol(95), chloroform or ether.
It is decomposed by light.
It is very hygroscopic.

Identification (1) A solution of Riboflavin Sodium Phosphate (1 in 100000) is pale yellowish green and has an intense yellowish green fluorescence. To 5 mL of the solution, add 20 mg of sodium hydrosulfite; the color and fluorescence of the solution disappear, but reappear slowly on shaking the mixture in air. This fluorescence disappears upon the addition of dilute hydrochloric acid or sodium hydroxide TS.

(2) Transfer 10 mL of a solution of Riboflavin Sodium Phosphate (1 in 100000) into a glass-stoppered test tube, add 1 mL of sodium hydroxide TS, illuminate with a fluorescence lamp of 10 to 30 watts at 20 cm distance for 30 minutes between 20 and 40 ℃, acidify with 0.5 mL of acetic acid(31), and shake with 5 mL of chloroform; the chloroform layer shows a yellowish green fluorescence.

(3) Determine the absorption spectra of solutions of Riboflavin Sodium Phosphate and riboflavin sodium phosphate RS in phosphate buffer solution, pH 7.0 (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Take 50mg of Riboflavin Sodium Phosphate, add 10 mL of nitric acid, evaporate on a steam bath to dryness, and ignite. Boil the residue with 10 mL of diluted nitric acid (1 in 50) for 5 minutes, After cooling, neutralize with ammonia TS, and filter, if necessary; the fil-

trate responds to the Qualitative Analysis for sodium salt and phosphate.

Optical rotation $[\alpha]_D^{20}$: Between + 38° and +43° (0.3 g calculated on the anhydrous basis, 5 mol/L hydrochloric acid TS, 20 mL, 100 mm).

pH Dissolve 0.20 g of Riboflavin Sodium Phosphate in 20 mL of water; the pH of the resulting solution is between 5.0 and 6.5.

Purity (1) ***Clarity and color of solution***—Dissolve 0.20 g of Riboflavin Sodium Phosphate in 10 mL of water; the solution is clear and yellow to orange.

(2) ***Heavy metal***—Proceed with 2.0 g of Riboflavin Sodium Phosphate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Lumiflavin***—To 35 mg of Riboflavin Sodium Phosphate, add 10 mL of ethanol-free chloroform, shake to mix for 5 minutes, and filter. The color of the filtrate is not more intense than that of the following control solution.

Control solution—To 3.0 mL of 1/60 mol/L potassium dichromate, add water to make 1000 mL.

(4) ***Free phosphoric acid***—Weigh accurately about 0.4 g of Riboflavin Sodium Phosphate, dissolve in water to make exactly 100 mL, and use this solution as the test solution. Pipet 5 mL each of the test solution and phosphoric acid standard solution, transfer to 25 mL volumetric flasks, add 2.5 mL of ammonium molybdate-sulfuric acid TS and 1 mL of 1-amino-2-naphthol-4-sulfonic acid TS, respectively. Shake to mix, add water to make exactly 25 mL, and allow to stand for 30 minutes at 20 ± 1 ℃. Perform the test with these solutions as directed under the Ultraviolet-visible Spectrophotometry, using a solution prepared with 5 mL of water in the same manner as the blank, and determine the absorbances, A_T and A_S, of the test solution and the phosphoric acid standard solution at a wavelength of 740 nm; the free phosphoric acid content is NMT 1.5%.

$$\text{Content (\%) of free phosphoric acid } (H_3PO_4) = \frac{A_T}{A_S} \times \frac{1}{W} \times 257.8$$

W: Amount (mg) of Riboflavin Sodium Phosphate calculated on the anhydrous basis

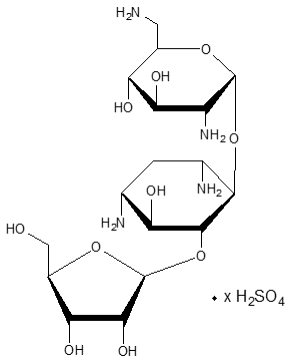
Water Transfer 25 mL of a mixture of methanol for water determination and ethylene glycol for water determination (1 : 1) to a dry flask for titration, and titrate with a test solution for water determination to the endpoint. Weigh accurately about 0.1 g of Riboflavin Sodium Phosphate, and quickly transfer to the titration flask, add a certain amount of the excess test solution for water determination, stir to mix for 10 minutes, and perform the test; the water content is NMT 10.0%.

Assay Perform the test without exposure to daylight, using light-resistant vessels. Weigh accurately about 0.1 g of Riboflavin Sodium Phosphate, and dissolve in diluted acetic acid(100) (1 in 500) to make exactly 1000 mL. Pipet 10 mL of this solution, add diluted acetic acid(100) (1 in 500) to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 15 mg of Riboflavin RS, previously dried at 105 ℃ for 2 hours, dissolve in 800 mL of diluted acetic acid(100) (1 in 400) by warming, cool, add water to make exactly 1000 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectrophotometry, using water as the blank. Determine the absorbances, A_T and A_S, at 445 nm. Add 20 mg of sodium hydrosulfite to 5 mL of each solution, shake until decolorized, and immediately measure the absorbances, A_T' and A_S', of the solutions.

$$\text{Amount (mg) of riboflavin sodium phosphate } (C_{17}H_{20}N_4NaO_9P) = \text{Potency (mg) of riboflavin RS} \times \frac{A_T - A_{T'}}{A_S - A_{S'}} \times 1.2709 \times 5$$

Packaging and storage Preserve in light-resistant, tight containers.

Ribostamycin Sulfate
리보스타마이신황산염



$C_{17}H_{34}N_4O_{10}\cdot xH_2SO_4$

5-Amino-2-(aminomethyl)-6-[4,6-diamino-2-[(2*S*,4*R*,5*R*)-3,4-dihydroxy-5-(hydroxy-methyl)oxolan-2-yl]oxy-3-hydroxycyclohexyl]oxyoxane-3,4-diol; sulfuric acid [*53797-35-6*]

Ribostamycin Sulfate is a peptide compound with antibacterial activity produced by the growth *Streptomyces ribosidificus*.

Ribostamycin Sulfate contains NLT 680 μg and NMT 780 μg (potency) of ribostamycin ($C_{17}H_{34}N_4O_{10}$: 454.47) per mg, calculated on the dried basis.

Description Ribostamycin Sulfate occurs as a white to pale yellow powder.

It is very soluble in water and practically insoluble in ethanol(95).

Identification (1) Dissolve 0.12 g each of Ribostamycin Sulfate and ribostamycin sulfate RS in 20 mL of water and use these solutions as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solutions and the standard solutions on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with potassium dihydrogen phosphate (3 in 40) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly 0.2% ninhydrin-water saturated 1-butanol TS on the plate, and heat the plate at 100 ℃ for 10 minutes; the principal spot obtained from the test solution and the spots from the standard solution exhibit a purplish brown color, and their R_f values are identical.

(2) An aqueous solution of Ribostamycin Sulfate (1 in 5) responds to the Qualitative Analysis (1) for sulfate.

Optical rotation $[\alpha]_D^{20}$: Between +42° and +49° (0.25 g, after drying, 25 mL of water, 100 mm).

pH Dissolve 1.0 g (potency) of Ribostamycin Sulfate in 20 mL of water; the pH of this solution is between 6.0 and 8.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Ribostamycin Sulfate in 5 mL of water; the resulting solution is clear and colorless to pale yellow.

(2) ***Heavy metals***—Proceed with 1.0 g of Ribostamycin Sulfate according to Method 1 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Ribostamycin Sulfate according to Method 1 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.12 g of Ribostamycin Sulfate in water to make 20 mL, and use this solution as the test solution. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with potassium dihydrogen phosphate (3 in 40) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly 0.2% ninhydrin-water saturated 1-butanol TS on the plate and heat the plate at 100 ℃ for 10 minutes; the spots other than the principal spot obtained from the test solution are not more intense than those from the standard solution.

Loss on drying NMT 5.0% (0.5 g, NMT 0.67 kPa, 60 ℃, 3 hours).

Residue on ignition NMT 1.0% (1 g).

Sterility It meets the requirements when Ribostamycin Sulfate is used in sterile preparations. However it is exempt from the requirements when there is a final sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins Less than 0.50 EU per mg (potency) of ribostamycin when used for the manufacturing of sterile preparations.

Assay ***Cylinder plate method*** (1) Medium: Agar media for seed and base layer Use the medium of the Microbial Assays for Antibiotics (A) (2) (a) ① ⓐ.

(2) Test organism: Use *Bacillus subtilis* ATCC 6633 as the test organism.

(3) Weigh accurately an amount of Ribostamycin Sulfate, equivalent to about 20 mg (potency), and dissolve in water to make exactly 50 mL. Take exactly an appropriate amount of this solution, dilute with 0.1 mol/L phosphate buffer solution, pH 8.0, to make solutions containing 20 μg (potency) and 5 μg (potency) per mL, and use these solutions as the high concentration test solution and the low concentration test solution, respectively. Separately, weigh accurately an amount of ribostamycin sulfate RS, previously dried, equivalent to about 20 mg (potency), and dissolve in diluted phosphate buffer solution, pH 6.0, (1 in 2) to make exactly 50 mL, and use this solution as the standard stock solution. Preserve the standard stock solution below 5 to 15 ℃, and use it within 20 days. Pipet an appropriate amount of the standard stock solution, dilute with 0.1 mol/L phosphate buffer solution, pH 8.0, to make solutions containing 20 μg (potency) and 5 μg (potency) per mL, and use these solutions as the high concentration standard solution and the low concentration standard solution, respectively. With these solutions, perform the test as directed under the Microbial Assays for Antibiotics (A) (8).

Packaging and storage Preserve in tight containers.

Ribostamycin Sulfate for Injection
주사용 리보스타마이신황산염

Ribostamycin Sulfate for Injection is an injection, which is dissolved before use. Ribostamycin Sulfate for Injection contains NLT 90.0% and NMT 120.0% of the labeled amount of ribostamycin ($C_{17}H_{34}N_4O_{10}$: 454.48).

Method of preparation Prepare Ribostamycin Sulfate for Injection as directed under Injections, with Ribostamycin Sulfate.

Description Ribostamycin Sulfate for Injection occurs as a white to yellowish white powder.

Identification (1) Dissolve an amount of Ribostamycin Sulfate for Injection, equivalent to 10 mg (potency) of ribostamycin sulfate, in 2 mL of water, add 3 mL of an-

throne TS; the resulting solution exhibits a blue to greenish blue color.

(2) Dissolve an amount of Ribostamycin Sulfate for Injection, equivalent to 20 mg (potency) of ribostamycin sulfate in 2 mL of 1/15 mol/L phosphate buffer solution (pH 5.6), add 1 mL of ninhydrin TS, and heat to boiling; the resulting solution exhibits a bluish purple color.

pH Dissolve Ribostamycin Sulfate for Injection in water to make 50 mg (potency) per mL; the pH of the solution is between 6.0 and 8.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.50 EU per mg (potency) of ribostamycin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Loss on drying NMT 5.0% (0.1 g, 0.7 kPa, 60 ºC, 3 hours).

Assay ***Cylinder plate method*** (1) Medium: Use the medium of the Microbial Assays for Antibiotics (A) (2) (a) ① ⓐ.

(2) Test organism: Use *Bacillus subtilis* ATCC 6633 as the test organism.

(3) Weigh accurately an amount of Ribostamycin Sulfate for Injection equivalent to about 0.1 g (potency) of ribostamycin sulfate according to the labeled potency, add sterile purified water, and shake well to mix to make exactly 200 mL. Take an appropriate amount of this solution and dilute with 0.1 mol/L phosphate buffer solution (pH 8.0) to obtain a solution having known concentrations of 20.0 μg and 5.0 μg (potency) per mL, and use them as the high-concentration test solution and the low-concentration test solution, respectively. Separately, weigh accurately an amount of ribostamycin RS equivalent to about 20 mg (potency), and dissolve in 0.05 mol/L phosphate buffer (pH 6.0) to obtain the standard stock solution having known concentrations of 400 μg (potency) per mL. Store the standard stock solution at 5 to 15 °C and use within 20 days. Pipet an appropriate amount of this standard stock solution and dilute with 0.1 mol/L phosphate buffer (pH 8.0) to obtain a solution having concentrations of 20.0 μg and 5.0 μg (potency) per mL, and use them as the high concentration standard solution and the low concentration standard solution, respectively. With these solutions, perform the test according (A) (8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in hermetic containers.

Ribostamycin Sulfate Injection
리보스타마이신황산염 주사액

Ribostamycin Sulfate Injection contains NLT 90.0% and NMT 120.0% the labeled amount of ribostamycin ($C_{17}H_{34}N_4O_{10}$: 454.48).

Method of preparation Prepare Ribostamycin Sulfate Injection as directed under Injections, with Ribostamycin Sulfate.

Description Ribostamycin Sulfate Injection occurs as a clear, pale yellow liquid.

Identification (1) Dissolve an amount of Ribostamycin Sulfate Injection, equivalent to 10 mg(potency) of ribostamycin sulfate in 2 mL of water, add 3 mL of anthrone TS; the resulting solution exhibits a blue to greenish blue color.

(2) When dissolve an amount of Ribostamycin Sulfate Injection, equivalent to 20 mg(potency) of ribostamycin sulfate in 2 mL of 1/15 mol/L phosphate buffer solution (pH 5.6), add 1 mL of ninhydrin TS, and삽입 heat to boiling; the resulting solution exhibits a bluish purple color.

pH Between 4.5 and 6.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.50 EU per mg (potency) of ribostamycin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay ***Cylinder plate method*** (1) Medium: Use the medium of the Microbial Assays for Antibiotics (A) (2) (a) ① ⓐ.

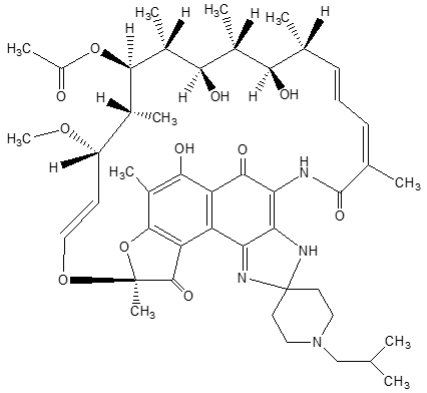
(2) Test organism: Use *Bacillus subtilis* ATCC 6633 as the test organism.

(3) Weigh accurately an amount of Ribostamycin Sulfate Injection, equivalent to 0.1 g (potency) of ribostamycin sulfate according to the labeled potency, add sterile purified water to make exactly 200mL. Take an appropriate amount of this solution and dilute with 0.1 mol/L phosphate buffer solution (pH 8.0) to obtain a solution having known concentrations of 20.0 μg and 5.0 μg (potency) per mL, and use them as the high-concentration test solution and the low-concentration test solution, respectively. Separately, weigh accurately an amount of ribostamycin RS equivalent to about 20 mg (potency) of

ribostamycin, add 0.05 mol/L phosphate buffer (pH 6.0), dissolve to make the standard stock solution containing 400 μg (potency) per mL. Store the standard stock solution at 5 to 15 °C and use within 20 days. Pipet an appropriate amount of this standard stock solution and dilute with 0.1 mol/L phosphate buffer (pH 8.0) to obtain a solution having known concentrations of 20.0 μg and 5.0 μg (potency) per mL, and use them as the high concentration standard solution and the low concentration standard solution, respectively. With these solutions, perform the test as directed under the Microbial Assays for Antibiotics (A) (8).

Packaging and storage Preserve in hermetic containers.

Rifabutin
리파부틴



$C_{46}H_{62}N_4O_{11}$: 847.01

(9*S*,12*E*,14*S*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*S*,22*E*,24*Z*)-6,16,18,20-Tetrahydroxy-1‘-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethylspiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo[2‘,3‘:7,8]naphth[1,2-*d*]imidazole-2,4‘-piperidine]-5,10,26-(3*H*,9*H*)-trione-16-acetate [*72559-06-9*]

Rifabutin contains 950 μg to 1020 μg (potency) per mg of rifabutin ($C_{46}H_{62}N_4O_{11}$: 847.01), calculated on the anhydrous basis.

Description Rifabutin occurs as a purple powder.
It is soluble in methanol or chloroform, sparingly soluble in ethanol(95) and slightly soluble in water.

Identification (1) Determine the infrared spectra of Rifabutin and rifabutin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Purity (1) ***Heavy metals*—**Proceed with 1.0 g of Rifabutin according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances*—**Perform the test according to the Assay, measure each peak area of the test solution by automatic integration method, and calculate each value in accordance with the percentage peak area method; the percentage of each related substance, other individual substances and all related substances is NMT 1.0%, 0.5% and 3.0%, respectively, with relative retention times to Rifabutin being 0.5, 0.6, 0.8 and 1.4.

(3) ***Isobutylpiperidone*—**Weigh accurately about 0.1 g (potency) of Rifabutin, dissolve in a mixture of chloroform and methanol (1 : 1) to make 10 mg (potency), and use this solution as the test solution. Separately, weigh accurately about 0.1 g of isobutylpiperidone RS, dissolve in a mixture of chloroform and methanol (1 : 1) to make 1 mg per mL, take 0.5, 1.0, 2.0, 5.0 and 10.0 mL respectively, and dissolve in a mixture of chloroform and methanol (1 : 1) to make 100 mL. Use these solutions as the standard solutions (S_1, S_2, S_3, S_4 and S_5). Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solutions and the standard solutions (S_1, S_2, S_3, S_4 and S_5) onto the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator) and develop the plate with a mixture of petroleum ether (60 - 80℃) and acetone (10 : 3) to a distance of about 10 cm. Air-dry the thin-layer chromatographic plate, expose it to iodine vapor for 5 minutes, and evenly spray 5% starch TS; The violet spots of Isobutylpiperidone from the test solution are not darker than those of the S_4 standard solution (NMT 0.5%).

Water NMT 2.5% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.3% (1 g).

Assay Weigh accurately about 50 mg (potency) each of Rifabutin and rifabutin RS, dissolve in the mobile phase to make exactly 50 mL, respectively. Take 2 mL of each solution, add the mobile phase to make exactly 20 mL, and use these solutions as the test and standard solutions. Measure the peak area of Rifabutin in the test and standard solution, A_T and *As*, respectively, by testing 10 μL each of the test and standard solutions as directed under Liquid Chromatography according to the following conditions.

$$\text{Potency (μg) of Rifabutin } (C_{46}H_{62}N_4O_{11}) = \text{Potency (μg) of rifabutin RS} \times \frac{A_T}{A_S} \times \frac{100}{100-m}$$

m: water (%)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column of about 4.7 mm in internal diameter and 11 cm in length is filled with 5

μm octadecylsilanized silica gel for liquid chromatography.

Mobile phase: Add 2 mol/L sodium hydroxide TS to a mixture of 2 mol/L of 0.1 mol/L potassium dihydrogen phosphate TS and acetonitrile (1 : 2), and adjust the pH to 6.5.

Flow rate: 1.0 mL/min

Packaging and storage Preserve in light-resistant, tight containers.

Rifabutin Capsules
리파부틴 캡슐

Rifabutin Capsules contain NLT 90.0% and NMT 120.0% the labeled amount of rifabutin ($C_{46}H_{62}N_4O_{11}$: 847.01).

Method of preparation Prepare as directed under Capsules, with Rifabutin.

Identification (1) Weigh 0.2 g each of Rifabutin Capsules and rifabutin RS (potency), dissolve in 200 mL of methanol, filter, and take 2 mL of the filtrate each. Add methanol to make 100 mL and use these solutions as the test solution and the standard solution, respectively. Determine the absorption spectra of the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy; both the test solution and the standard solution exhibit an absorption maximum at the same wavelengths.

(2) The retention times of the major peaks from the test solution and the standard solution obtained under the Assay are the same.

Purity ***Related substances***—Weigh accurately an amount of NLT 20 capsules of Rifabutin Capsules equivalent to 25 mg (potency) of rifabutin, dissolve in 5 mL of acetonitrile, add the mobile phase to make 50 mL, and filter with a filter (pore size: 0.5 μm). Use this solution as the test solution. Perform the test with 10 μL of the test solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of the test solution by the automatic integration method and calculate each amount in accordance with the percentage peak area method; the percentage of each related substance, other individual substances and all related substances is NMT 1.0%, 0.5% and 4.5%, respectively, with relative retention times to rifabutin being 0.5, 0.6, 0.8 and 1.4.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless-steel column about 4.6 mm in internal diameter and about 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: To a mixture of acetonitrile and 0.1 mol/L of potassium dihydrogen phosphate TS (1 : 1), add 2 mol/L sodium hydroxide TS to adjust the pH 6.5.

Flow rate: about 1.0 mL/min

System suitability

System performance: Dissolve 10 mg of rifabutin in 2 mL of methanol, add 1 mL of 2 mol/L sodium hydroxide, allow to stand for 4 minutes, and add 1 mL of 2 mol/L hydrochloric acid. Dilute with the mobile phase to make 50 mL. Perform the test with these solutions according to the above conditions; 1 major peak and 2 sub peaks appear at the relative retention time of 0.5, 0.6, 0.8 and 1.0 for the peak area of rifabutin, and the resolution of rifabutin and the relative retention time of the peak area of rifabutin for about 0.8 peak is NLT 1.3. Proceed with the system suitability solution according to the above conditions; the number of theoretical plates is NLT 2000.

System repeatability: Weigh accurately 25 mg of rifabutin RS, dissolve in 5 mL of acetonitrile, add acetonitrile to make exactly 50 mL, and use this solution as the system suitability solution. Repeat the test 6 times with this solution each of these solutions under the above operating conditions; the relative standard deviation of the peak areas is NMT 2.0%.

Dissolution Perform the test with 1 capsule of Rifabutin Capsules at 100 revolutions per minute according to Method 1, using 900 mL of 0.01 mol/L hydrochloric acid TS as the test solution. After 45 minutes from the start of the test, take NLT 20 mL of the dissolved solution and filter. Take *V* mL of the filtrate, add the dissolution medium to make exactly *V'* mL of a solution having a known concentration of about 13.0 μg (potency) of rifabutin per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 13 mg of rifabutin RS and dissolve it in 100 mL of the test solution. Pipet 10 mL of this solution, add the test solution to make exactly 100 mL, and use this solution as the standard solution. With the test solution and the standard solution, perform the test as directed under the Ultraviolet-visible Spectroscopy using the blank test solution as a control solution, and determine the absorbances, A_T and A_S, at 280 nm. Meets the requirements if the dissolution rate in 45 minutes is NLT 75.0%.

Dissolution rate (%) with respect to the labeled amount of rifabutin ($C_{46}H_{62}N_4O_{11}$)

$$= \text{Potency (mg) of rifabutin RS} \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 90$$

C: Labeled amount [mg (potency)] of rifabutin ($C_{46}H_{62}N_4O_{11}$) in 1 capsule

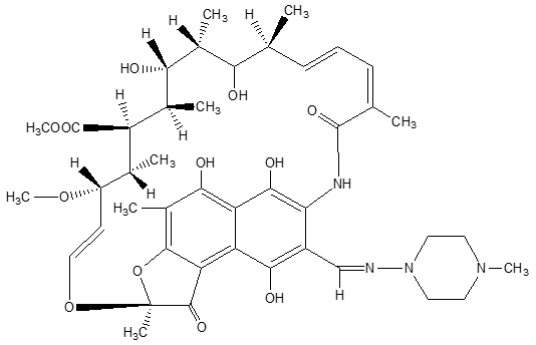
Uniformity of dosage units Meets the requirements.

Assay Proceed as directed under the Assay under Rifabutin. Weigh accurately the contents of NLT 20 capsules of Rifabutin Capsules, powder if necessary, weigh

accurately an amount equivalent to about 50 mg (potency) of rifabutin, and add the mobile phase to make exactly 50 mL. Take 2 mL of this solution, add the mobile phase to make exactly 20 mL, filter, and use this solution as the test solution.

Packaging and storage Preserve in light-resistant, tight containers.

Rifampicin
리팜피신



$C_{43}H_{58}N_4O_{12}$: 822.94

(2*S*,12*Z*,14*E*,16*S*,17*S*,18*R*,19*R*,20*R*,21*S*,22*S*,23*R*,24*E*)-5,6,9,17,19-Pentahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-(4-methyl-piperazin-1-yliminomethyl)-1,11-dioxo-1,2-dihydro-2,7-(Epoxy-pentadeca[1,11,13]trien-imino)naphtho[2,1-*b*]furan-21-yl acetate [*13292-46-1*]

Rifampicin is a derivative of a substance having antibacterial activity produced by the growth of *Streptomyces mediterranei*.

Rifampicin contains NLT 970 μg and NMT 1020 μg (potency) of rifampicin ($C_{43}H_{58}N_4O_{12}$) per mg.

Description Rifampicin occurs as orange to reddish brown crystals or a crystalline powder.
It is slightly soluble in water, methanol, ethanol(95) or acetonitrile.

Identification (1) To 5 mL of solutions of Rifampicin and rifampicin RS in methanol (1 in 5000), add 0.05 mol/L phosphate buffer solution (pH 7.0) to make 100 mL. Determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Rifampicin and rifampicin RS as directed in the potassium bromide disk under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

pH Suspend 0.1 g of Rifampicin in 10 mL of water; the pH of a suspension is between 4.0 and 6.0.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Rifampicin according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Rifampicin according to Method 3 and perform the test (NMT 2 ppm).

(3) ***Related substances***—Weigh accurately about 0.10 g of Rifampicin, add in acetonitrile to make exactly 50 mL, and use this solution as the test stock solution. Pipet 5 mL of this solution, add diluent to make exactly 50 mL, and use this solution as the test solution. Separately, pipet 1 mL of the test stock solution, and add acetonitrile to make exactly 100 mL. Pipet 5.0 mL of this solution, add diluent to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area by the automatic integration method; the peak area of the related substances with a relative retention time of about 0.7 with respect to the rifampicin peak obtained from the test solution is not larger than 1.5 times the peak area of rifampicin from the standard solution (1.5%), the peak area of related substances other than rifampicin and the ones eluted at the relative retention time of about 0.7 obtained from the test solution is not larger than the rifampicin peak area from the standard solution (1%), and the sum of these peak areas is not larger than 3.5 times the rifampicin peak area from the standard solution (3.5%).

Diluent—Weigh accurately 2.1 g of citric acid monohydrate, 13.4 g of dibasic potassium phosphate and 3.1 g of potassium dihydrogen phosphate, dissolve in water to make 1000 mL, and mix this solution and acetonitrile (3 : 1).

Operating conditions

Proceed as directed under the operating conditions under the Assay.

System suitability

Test for required detectability: Pipet 2 mL of the standard solution and add diluent to make exactly 20 mL. Confirm that the peak area of rifampicin obtained from 50 μL of this solution is equivalent to 7% to 13% of the peak area of rifampicin obtained from 50 μL of the standard solution.

System performance: To 5 mL of a solution of rifampicin in acetonitrile (1 in 5000), add 1 mL of a solution of butyl p-hydroxybenzoate in acetonitrile (1 in 5000), and add diluent to make exactly 50 mL. Proceed with 50 μL of this solution under the above conditions; butyl p-hydroxybenzoate and rifampicin are eluted in this order with the resolution being NLT 1.5.

System repeatability: Repeat the test 6 times with 50 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of rifampicin is NMT 2.0%.

Time span of measurement: About 3 times the retention time of rifampicin.

Loss on drying NMT 2.0% (1.0 g, NMT 0.67 kPa, 60 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 40 mg (potency) of Rifampicin and rifampicin RS, and dissolve in acetonitrile to make exactly 200 mL. Pipet 10 mL each of these solutions, add citric acid-phosphate-acetonitrile TS to make 50 mL, and use these solutions as the test solution and standard solution. Prepare the test solution and the standard solution before use. With 50 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas A_T and A_S of rifampicin.

$$\text{Potency (μg) of rifampicin } (C_{43}H_{58}N_4O_{12}) = \text{Potency (μg) of rifampicin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 10 cm in length, packed with octylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Take 4.2 g of citric acid monohydrate and 1.4 g of sodium perchlorate, dissolve in a mixture of water, acetonitrile, and pH 3.1 phosphate buffer (11 : 7 : 2) to make exactly 1000 mL, and use this solution as the mobile phase.

pH 3.1 phosphate buffer—Dissolve 136.1 g of potassium dihydrogen phosphate in 500 mL of water, add 6.3 mL of phosphoric acid, and add water to make exactly 1000 mL.

Flow rate: 2.0 mL/min

System suitability

System performance: To 5 mL of a solution of rifampicin in acetonitrile (1 in 5000), add 1 mL of a solution of butyl p-hydroxybenzoate in acetonitrile (1 in 5000), add citric acid-phosphate-acetonitrile TS to make 50 mL. Proceed with 50 μL of this solution under the above conditions; butyl p-hydroxybenzoate and rifampicin are eluted in this order with the resolution being NLT 1.5.

System repeatability: Repeat the test 5 times with 50 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of rifampicin is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Rifampicin Capsules
리팜피신 캡슐

Rifampicin Capsules contain NLT 93.0% and NMT 105.0% the labeled amount of rifampicin ($C_{43}H_{58}N_4O_{12}$: 822.94).

Method of preparation Prepare as directed under Capsules, with Rifampicin.

Identification (1) Take out the content of Rifampicin Capsules, mix well, and powder, if necessary. Dissolve an amount equivalent to 20 mg (potency) according to the labeled potency in 100 mL of methanol and filter. Add 0.05 mol/L phosphate (pH 7.0) to 5 mL of the filtrate to make 100 mL and determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 234 and 238 nm, 252 and 256 nm, 331 and 335 nm and 472 and 476 nm.

(2) Weigh about 0.1 g (potency) of Rifampicin Capsules according to the labeled potency, transfer to a glass-stoppered flask, and add 10 mL of methanol. Mix by shaking vigorously for several minutes, filter, and use this solution as the test solution. Separately, weigh an appropriate amount of rifampicin RS, dissolve in methanol to obtain a solution having known concentration of 5 mg per mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solutions and the standard solution to the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of chloroform and ethanol (2 : 1) as the developing solvent, and air-dry the plate. The R_f values of the red spots obtained from the test solution and the standard solution are the same.

Purity ***Related substances***—Perform this test immediately after the test solution and the standard solution are prepared. Weigh accurately the mass of the content from NLT 20 capsules of Rifampicin Capsules, and power. Weigh accurately an amount of Rifampicin Capsules equivalent to about 20 mg (potency) according to the labeled potency and dissolve in acetonitrile to make exactly 10 mL. Pipet 2 mL of this solution, add a mixture of methanol and acetonitrile (1 : 1) to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg (potency) of rifampicin RS and dissolve in acetonitrile to make exactly 10 mL. Pipet 2 mL of this solution and add a mixture of methanol and acetonitrile (1 : 1) to make exactly 20 mL. Pipet 1 mL of this solution, add a mixture of methanol and acetonitrile (1 : 1) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak area of each solution by calculating the peak area of each solution with auto-

matic integration method; the amount of quinone of the relative retention time of 0.5 of rifampicin from the test solution is NMT 4.0% and of N-oxide of the relative retention time of 1.2 is NMT 1.5%. The amount of each related substance other than the above peaks is NMT 1.5% and the sum of related substances is 2.0%. However, the peak area of quinone and N-oxide is the area calculated by the automatic integration method with the correction factor of 1.24 and 1.16 each.

$$\text{Content (\%) of related substances} = \frac{W_S}{W_T} \times \frac{A_i}{A_S} \times 2$$

W_S: Amount [mg (potency)] of rifampicin RS

W_T: Amount [mg (potency)] of Rifampicin Capsules taken

A_S: Peak area from the standard solution

A_i: Peak area of each related substance

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 25 cm in length, packed with octylsilane silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 2.1 g of sodium perchlorate, 6.5 g of citric acid monohydrate and 2.3 g of potassium dihydrogen phosphate in 1100 mL of water and add 900 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of rifampicin is about 12 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution, and add a mixture of methanol and acetonitrile (1 : 1) to make exactly 20 mL. Confirm that the peak area of rifampicin obtained with 20 μL of this solution is equivalent to 3.5% to 6.5% peak area of rifampicin in the standard solution.

System performance: Proceed with 20 μL of the standard solution according to the above operating conditions; the number of theoretical plates of rifampicin peak are NLT 2500 plates with the symmetry factor being NMT 4.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of rifampicin is NMT 2.0%.

Time span of measurement: About 2.5 times the retention time of rifampicin.

Loss on drying NMT 3.0% (0.1 g, in vacuum, 60 °C, 3 hours).

Dissolution Perform the test with 1 capsule of Doxycycline Capsules at 100 revolutions per minute according to Method 1 under the Dissolution, using 900 mL of 0.1 mol/L hydrochloric acid TS as the dissolution medium. Take the dissolved solution after 45 minutes from the start of the test and filter. Discard the first 10 mL of the filtrate, pipet V mL of the subsequent filtrate, add the dissolution medium to make exactly V' mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of rifampicin RS, previously dried, dissolve it in the dissolution medium to make it the same concentration as the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength of about 475 nm as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as a control solution. It meets the requirements when the dissolution rate in 45 minutes is NLT 75% (Q).

$$\text{Dissolution rate (\%) with respect to the labeled amount of rifampicin } (C_{43}H_{58}N_4O_{12}) = C_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 90000$$

Cs: Concentration [mg (potency)/mL] of the standard solution

C: Labeled amount [mg (potency)] of rifampicin ($C_{43}H_{58}N_4O_{12}$) in 1 capsule

Uniformity of dosage units It meets the requirements when performing the mass variation test.

Assay Weigh accurately the contents of NLT about 20 capsules of Rifampicin Capsules. Weigh accurately an amount equivalent to about 75 mg (potency) of Rifampicin Capsules according to the labeled potency and dissolve in a mixture of methanol and acetonitrile (1 : 1) to make exactly 50 mL. Pipet 10 mL of this solution and add acetonitrile to make exactly 50 mL. Pipet 5 mL of this solution, dissolve 2.1 g of citric acid monohydrate, 27.6 g of disodium hydrogen phosphate dodecahydrate solution and 3.1 g of Potassium dihydrogen phosphate in 1000 mL of a mixture of water and acetonitrile (3 : 1), add this solution to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 30 mg (potency) of rifampicin RS, dissolve it in 20 mL of a mixture of methanol and acetonitrile (1 : 1), add acetonitrile to make exactly 100 mL. Pipet 5 mL of this solution, dissolve 2.1 g of citric acid monohydrate, 27.6 g of dibasic sodium phosphate and 3.1 g of potassium dihydrogen phosphate in 1000 mL of a mixture of water and acetonitrile (3 : 1), add this solution to make exactly 50 mL, and use this solution as the standard solution. Pipet 50 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas A_T and A_S of rifampicin for each solution.

$$\text{Potency (μg) of rifampicin } (C_{43}H_{58}N_4O_{12}) = \text{Potency (μg) of rifampicin RS} \times \frac{A_T}{A_S} \times \frac{5}{2}$$

Operating conditions

Proceed as directed under the operating conditions in the Assay under Rifampicin.

System suitability

System performance: Dissolve about 30 mg (potency) of rifampicin RS in 20 mL of methanol and acetonitrile (1 : 1), and add acetonitrile to make 100 mL. Take 5 mL of this solution, add 2 mL of butyl p-hydroxybenzoate and acetonitrile (1 : 1) (1 in 5000) dissolved in a solution of 2.1 g of citric acid monohydrate, 27.6 g of dibasic sodium phosphate and 3.1 g of potassium dihydrogen phosphate dissolved in 1000 mL of a mixture of water and acetonitrile (3 : 1) to make 50 mL. Proceed with 50 μL of this solution under the above conditions; butyl p-hydroxybenzoate and rifampicin are eluted in this order with the resolution being NLT 1.5.

System repeatability: Repeat the test 5 times with 50 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of rifampicin is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Rifampicin Tablets
리팜피신 정

Rifampicin Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of rifampicin tablets ($C_{43}H_{58}N_4O_{12}$: 822.95).

Method of preparation Prepare as directed under Tablets, with Rifampicin.

Identification Weigh an amount of Rifampicin Tablets, previously powdered, equivalent to 0.1 g (potency) according to the labeled potency, place it in a glass-stoppered flask, add 10 mL of methanol, shake vigorously to mix, filter the resulting solution, and test the filtrate in accordance with (2) of the Identification for Rifampicin Tablets.

Dissolution Proceed with 1 tablet of Rifampicin Tablets at 100 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of Solution 2 as the test solution. Take the dissolved solution after 45 minutes from the start of the test and filter. Discard the first 10 mL of the filtrate, pipet V mL of the subsequent filtrate, add the test solution to obtain a solution having known concentration of 100 μg of rifampicin per mL according to the labeled amount. Make it exactly V′ mL and use this solution as the test solution. Separately, weigh accurately about 40 mg of rifampicin RS and add the test solution to make 200 mL. Pipet 25 mL of this solution, add the test solution to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of rifampicin ($C_{43}H_{58}N_4O_{12}$) in each solution, respectively. Meets the requirements if the dissolution rate of Rifampicin Tablets in 45 minutes is NLT 75%.

Dissolution rate (%) with respect to the labeled amount of rifampicin ($C_{43}H_{58}N_4O_{12}$)

$$Ws \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 225$$

*W*s: Amount (mg) of rifampicin RS

C: Labeled amount (mg) of rifampicin ($C_{43}H_{58}N_4O_{12}$) in 1 tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of 0.05 mol/L potassium dihydrogen phosphate TS (pH 3.5) and acetonitrile (40 : 60).

Flow rate: 0.5 mL/min

0.05 mol/L potassium dihydrogen phosphate TS (pH 3.5)—Add phosphoric acid to 0.05 mol/L potassium dihydrogen phosphate TS to adjust the pH to 3.5.

Uniformity of dosage units Meets the requirements.

Loss on drying NMT 3.0% (0.1 g, 0.7 kPa, 60 ºC, 3 hours).

Assay Weight NLT 20 tablets of Rifampicin Tablets, and powder. Weigh accurately an amount of the powder equivalent to about 0.1 g (potency) according to the labeled potency, and dissolve in methanol to make exactly 100 mL. Pipet 5 mL of this solution, add phosphate buffer solution TS (pH 7.0) to make exactly 50 mL, and use this solution as the test solution. Separately, weigh exactly about 0.1 g (potency) of rifampicin RS, dissolve in methanol to make exactly 100 mL. Pipet 5 mL of this solution, add phosphate buffer solution (pH 7.0) to make exactly 50 mL, and use this solution as the standard solution. Proceed with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of rifampicin in each solution, A_T and A_S, respectively.

$$\text{Potency (μg) of rifampicin } (C_{43}H_{58}N_4O_{12}) = \text{Potency (μg) of rifampicin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer

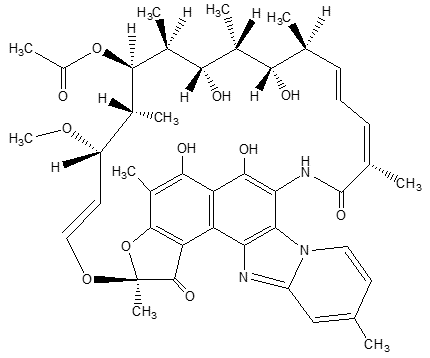
(wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Mobile phase: Adjust the pH of 0.05 mol/L potassium dihydrogen phosphate solution to 3.5 with phosphoric acid. To 400 mL of the resulting solution, add 600 mL of acetonitrile to mix.

Packaging and storage Preserve in light-resistant, tight containers.

Rifaximin
리팍시민



$C_{43}H_{51}N_3O_{11}$: 785.88

(2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*R*,27*S*,28*E*)-5,6,21,23-Tetrahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-1,15-dioxo-1,2-dihydro-2,7-(Epoxypentadeca[1,11,13]trienimino)benzofuro[4,5-*e*]pyrido[1,2-*a*]benzimidazol-25-yl acetate [*80621-81-4*]

Rifaximin contains NLT 980 μg (potency) of rifaximin ($C_{43}H_{51}N_3O_{11}$: 785.88) per mg, calculated on the anhydrous and solvent-free basis.

Description Rifaximin occurs as an orange powder.
It is soluble in methanol, acetone, chloroform or ethyl acetate, and practically insoluble in water.

Identification (1) Dissolve 15 mg (potency) of Rifaximin in methanol to make 10 mL. Take 1 mL of this solution, add methanol to make 100 mL, and determine the absorption spectrum as directed under the Ultraviolet-visible Spectroscopy; it exhibits absorption maxima at wavelengths of between 453 nm and 457 nm, between 370 nm and 374 nm, between 291 nm 295 nm and between 233 nm and 237 nm.

(2) Determine the infrared spectra of Rifaximin and rifaximin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Weigh about 50 mg (potency) each of Rifaximin and rifaximin RS, dissolve in 5 mL of methanol, and use these solutions as the test solution and the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator), develop the plate with a mixture of chloroform and methanol (95 : 5) as a developing solvent. Air-dry the plate, and examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f value and the color of the spots obtained from the test solution and the standard solutions are identical.

Crystal polymorphism Homogenize Rifaximin and rifaximin RS by pressing with a glass rod, mold the powder onto the packing part of the X-ray powder diffraction device holder, and perform the test according to the Characterization of Crystalline and Partially Crystalline Solids by X-ray Powder Diffraction; the angles in the range of 6.6°±0.2 ; 7.4°±0.2 ; 7.9°±0.2 ; 8.8°±0.2 ; 10.5°±0.2 ; 11.1°±0.2 ; 11.8°±0.2 ; 12.9°±0.2 ; 17.6°±0.2 ; 18.5°±0.2 ; 19.7°±0.2 ; 21.0°±0.2 ; 21.4°±0.2 ; 22.1°±0.2 represent the characteristic diffraction angles (2θ) of rifaximin α-form crystals.

Operating conditions

X-ray tube: Copper anode

Wavelength: Kα1 (1.540562 Å), Kα2 (1.544398 Å) (use nickel filter to suppress Kβ (1.392218 Å))

Detector: Sodium iodide scintillation counter

Tube current and voltage: 15 mA, 30 kV

Counting time: 1.3 seconds per step / 0.02°

Scanning range of diffraction angle (2θ): Between 2.0° and 35.0°.

Sample holder: Amorphous glass (isotropic 9200/2G, depth of 0.2 mm).

Purity (1) ***Ethanol***—Weigh accurately about 50 mg of Rifaximin, add 1 mL of the internal standard solution and *N*,*N*-dimethylformamide to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately 0.25 g of ethanol(95) and add *N*,*N*-dimethylformamide to make exactly 50 mL. Pipet 1 mL of this solution, add 1 mL of the internal standard solution and *N*,*N*-dimethylformamide to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of ethanol to that of the internal standard, respectively (NMT 0.5%).

$$\text{Ethanol content (\%)} = \frac{Q_T}{Q_S} \times \frac{\text{Amount (mg) of ethanol taken}}{\text{Amount (mg) of Rifaximin taken}} \times \frac{100}{50}$$

Internal standard solution—Weigh 1.5 g of 2-propanol and add *N*,*N*-dimethylformamide to make 100 mL.

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A column about 0.53 mm in internal diameter and about 30 m in length, packed with diatomaceous earth for gas chromatography coated 100.0% with dimethyl polysiloxane.

Column temperature: Initially maintain at 60 ℃ for 2 minutes, raise the temperature at a rate of 25 ℃ per minute until it reaches 200 ℃, and maintain at 200 ℃ for 5 minutes.

Sample injection port and detector temperature: 220 ℃.

Carrier gas: Nitrogen

Flow rate: About 10 mL/min.

(2) ***Heavy metal***—Proceed with 1.0 g of Rifaximin according to Method 3 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Weigh accurately about 0.1 g (potency) of Rifaximin, dissolve in 10 mL of acetonitrile, add water to make exactly 25 mL, and use this solution as the test solution. With 20 μL of the test solution, perform the test as directed under the Liquid Chromatography according to the following conditions. Measure each peak area by the automatic integration method and calculate the amount by the area percentage (rifampicin Y: NMT 0.5%, individual related substances: NMT 0.2%, total related substances: NMT 2.0%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 276 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: 40 °C

Mobile phase: A mixture of mobile phase A and mobile phase B (63 : 37).

Mobile phase A: A mixture of methanol and acetonitrile (1 : 1).

Mobile phase B: 0.05 mol/L ammonium formate TS (adjust the pH to 7.2 with ammonia TS).

Flow rate: About 1.4 mL/min.

Relative retention time: Rifaximin Y 0.67

Time span of measurement: About 3 times the retention time of rifaximin after the solvent peak.

Water NMT 2.5% (0.2 g, volumetric titration, direct titration).

Assay Weigh accurately about 40 mg (potency) each of Rifaximin and rifaximin RS and dissolve each in methanol to make exactly 100 mL. Pipet 10 mL each of these solutions, add 10 mL of internal standard solution, add the mobile phase to make exactly 100 mL, and use these solutions as the test solution and the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of rifaximin to that of the internal standard for the test solution and the standard solution.

$$\text{Potency (μg) of rifaximin } (C_{43}H_{51}N_3O_{11}) = \text{Potency of rifaximin RS (μg)} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh 45 mg of naproxen and dissolve in methanol to make 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 276 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of mobile phase A and mobile phase B (65 : 35).

Mobile phase A: A mixture of methanol and acetonitrile (60 : 40).

Mobile phase B: To 1000 mL of 0.01 mol/L ammonium dihydrogen phosphate, add 1 g of sodium 1-heptanesulfonate, and adjust the pH to 3.0 with acetic acid.

Flow rate: About 1.5 mL/min.

Packaging and storage Preserve in light-resistant, tight containers.

Rifaximin Tablets
리팍시민 정

Roxithromycin Tablets contains NLT 90.0% and NMT 120.0% of rifaximin ($C_{43}H_{51}N_3O_{11}$: 785.88) of the labeled amount.

Method of preparation Rifaximin Tablets as directed under Tablets, with Rifaximin.

Identification Powder Rifaximin Tablets, dissolve an amount equivalent to about 50 mg (potency) of Rifaximin Tablets in 5 mL of methanol, and use this solution as the test solution. Separately, dissolve 50 mg (potency) of rifaximin RS in 5 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator), develop the plate with a mixture of chloroform and methanol (95 : 5) as a developing solvent. Air-dry the plate, and examine the plate under ultraviolet light (main wavelength: 254 nm); the *Rf* values of the spots obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 tablet of Rifaximin

Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water containing 0.5% sodium lauryl sulfate as the dissolution medium.
Filter the medium 60 minutes after starting the test and use this solution as the test solution.
Separately, weigh accurately about 22.2 mg of rifaximin RS, dissolve in the fresh medium to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution according to the Liquid Chromatography under the following conditions, and determine the peak areas A_T and A_S of rifaximin ($C_{43}H_{51}N_3O_{11}$) in each solution.
The dissolution rate in 60 minutes of Rifaximin Tablets is NLT 80%.

Dissolution rate (%) with respect to the labeled amount of rifaximin ($C_{43}H_{51}N_3O_{11}$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 900$$

*W*s: Amount (mg) of rifaximin RS
C: Labeled amount (mg) of rifaximin ($C_{43}H_{51}N_3O_{11}$) in 1 tablet

Operating conditions
Detector: An ultraviolet absorption photometer (wavelength: 370 nm).
Column: A stainless-steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).
Column temperature: A constant temperature of about 40 °C.
Mobile phase: A mixture of mobile phase A and mobile phase B (13 : 7).
Mobile phase A: A mixture of methanol and acetonitrile (3 : 2).
Mobile phase B: Add 1 g of sodium 1-heptanesulfonate to 1000 mL of 0.01 mol/L ammonium dihydrogen phosphate, and adjust the pH to 3.0 with acetic acid.
Flow rate: 1.0 mL/min
System suitability
System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of rifaximin is NMT 2.0%.

Uniformity of dosage units Meets the requirements.

Water NMT 8.0% (0.1 g, volumetric titration, direct titration).

Assay Weigh accurately the mass of NLT 20 tablets of Rifaxamin Tablets, and powder. Then, weigh accurately an appropriate amount, equivalent to about 400 mg (potency), according to the labeled potency, and dissolve in methanol to make exactly 100 mL. Take 10.0 mL of this solution, add 10.0mL each of the internal standard solution, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 40 mg of rifaximin RS, and dissolve in methanol to make exactly 100 mL. Take 10.0 mL of this solution, put 10.0mL of the internal standard solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak area ratios, Q_T and Q_S, of rifaximin to the peak area of the internal standard in each solution.

Potency (μg) of rifaximin ($C_{43}H_{51}N_3O_{11}$)
= Potency (μg) of rifaximin RS

$$\times \frac{Q_T}{Q_S} \times \frac{100}{(100 - m)}$$

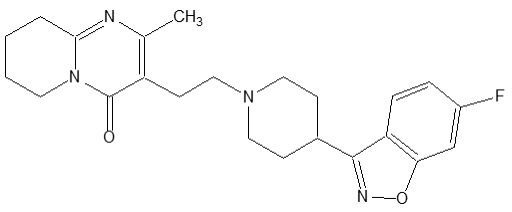
m: The sum of water (%) and ethanol (%) in Rifaximin Tablets

Internal standard solution—Weigh 45 mg of naproxen, and dissolve in methanol to make 100 mL.

Operating conditions
Detector: An ultraviolet absorption photometer (wavelength: 276 nm).
Column: A stainless-steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).
Mobile phase: A mixture of mobile phase A and mobile phase B (65 : 35).
Mobile phase A: A mixture of methanol and acetonitrile (60 : 40).
Mobile phase B: Add 1 g of sodium 1-heptanesulfonate to 1000 mL of 0.01 mol/L ammonium dihydrogen phosphate TS, and adjust the pH to 3.0 with acetic acid.
Flow rate: About 1.5 mL/min.

Packaging and storage Preserve in light-resistant, tight containers.

Risperidone
리스페리돈



$C_{23}H_{27}FN_4O_2$: 410.48
3-[2-[4-(6-Fluoro-1,2-benzoxazol-3-yl) piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetra-

hydropyrido[1,2-a]pyrimidin-4-one [*106266-06-2*]

Risperidone contains NLT 99.0% and NMT 101.0% of risperidone ($C_{23}H_{27}FN_4O_2$), calculated on the dried basis.

Description Risperidone occurs as a white to pale yellow powder.
It is freely soluble in dichloromethane, sparingly soluble in alcohol and practically insoluble in water.
It dissolves in dilute hydrochloric acid.
It shows crystalline polymorphism.

Identification (1) Determine the absorption spectra of solutions of Risperidone and Risperidone RS in 2-propanol (1 in 40000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Risperidone and Risperidone RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If any difference appears between the spectra, dissolve each in the minimum possible volume of acetone, evaporate to dryness, and perform the test with the residue in the same manner.

Melting point Between 169 and 173 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g of Risperidone in 0.75 w/v% of L-tartaric acid solution to make 100 mL; the resulting solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 2.0 g of Risperidone according to Method 2 under the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Weigh accurately 0.10 g of Risperidone, add methanol to make exactly 100 mL, and use this solution as the test solution. To 1.0 mL of the test solution, add methanol to make exactly 100 mL. To 5.0 mL of this solution, add methanol to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 10 μL each of methanol (blank test solution), the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions; each area of the peaks other than the major peak obtained from the test solution is not greater than that of the major peak obtained from the standard solution. In addition, the sum of the peak areas other than the major peak from the test solution is not greater than 1.5 times the area of the major peak from the standard solution. Exclude any peaks obtained from the blank test solution and any peaks having an area NMT 0.25 times the area of the major peak from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 260 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 10 cm in length, packed with base-deactivated octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Mobile phase: Control the stepwise or gradient elution by mixing the mobile phases A and B as follows.

Mobile phase A: 0.5 w/v% ammonium acetate solution

Mobile phase B: Methanol

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 2	70	30
2 - 17	70 → 30	30 → 70
17 - 22	30	70

Flow rate: 1.5 mL/min

System suitability

Test for required detectability: Pipet 2 mL of the standard solution and add methanol to make exactly 20 mL. Confirm that the peak area of Risperidone obtained from 10 μL of this solution is equivalent to 7% to 13% of the peak area of Risperidone obtained from the standard solution.

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the number of theoretical plates of Risperidone is NLT 1000 with the symmetry factor being NMT 2.0.

System repeatability: Repeat the test 6 times according to the above conditions with 10 μL each of the standard solution; the relative standard deviation of the peak area of Risperidone is NMT 2.0%.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

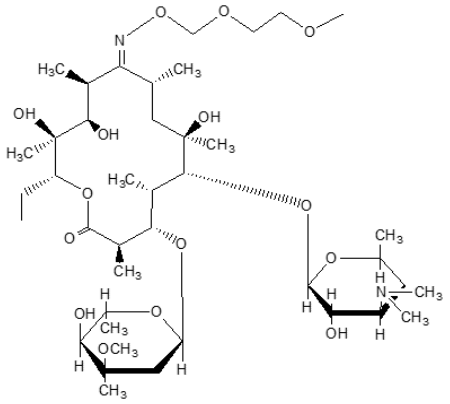
Residue on ignition NMT 0.1% (1 g, platinum crucible).

Assay Weigh accurately about 0.16 g of Risperidone, dissolve in 70 mL of a mixture of 2-butanone and acetic acid(100) (7 : 1), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 20.53 mg of $C_{23}H_{27}FN_4O_2$

Packaging and storage Preserve in tight containers.

Roxithromycin
록시트로마이신



$C_{41}H_{76}N_2O_{15}$: 837.05

(3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,10*Z*,11*S*,12*R*,13*S*,14*R*)-6-[(2*S*,3*R*,4*S*,6*R*)-4-(Dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy-14-ethyl-7,12,13-trihydroxy-4-[(2*R*,4*R*,5*S*,6*S*)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-10-(2-methoxyethoxymethoxyimino)-3,5,7,9,11,13-hexamethyl-oxacyclotetradecan-2-one [*80214-83-1*]

Roxithromycin is a derivative of erythromycin.

Roxithromycin contains NLT 970 μg and NMT 1020 μg (potency) of roxithromycin ($C_{41}H_{76}N_2O_{15}$) per mg, calculated on the anhydrous basis.

Description Roxithromycin occurs as a white, crystalline powder.
It is freely soluble in ethanol(95) or acetone, soluble in methanol, sparingly soluble in acetonitrile and practically insoluble in water.

Identification Determine the infrared spectra of Roxithromycin and roxithromycin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -93° and -96° (0.5 g, calculated on the anhydrous basis, acetone, 50 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 2 g of Roxithromycin and perform the test according to Method 2. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Erythromycin and erythromycinoxime***—Weigh about 0.2 g (potency) of Roxithromycin, dissolve in methanol to make exactly 10 mL, and use this solution as the test solution. Separately, weigh 40 mg (potency) of erythromycin RS, dissolve in methanol to make exactly 100 mL, and use this solution as the erythromycin standard solution. Weigh 40 mg of erythromycinoxime RS, dissolve in methanol to make exactly 100 mL, and use this solution as the erythromycinoxime standard solution. With these tests and standard solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solutions, the erythromycin standard solution and the erythromycinoxime standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of toluene, chloroform and diethylamine (50 : 40 : 7) as the developing solvent. Take the plate out and dry the plate at 100 ℃ to 105 ℃ for 5 minutes. Prepare a color agent by dissolving 2.5 g of phosphomolybdic acid n-hydrate in 2.5 mL of sulfuric acid and 50 mL of acetic acid(100), spray evenly the agent on the plate, and heat the plate at 100 ℃ to 105 ℃; the spots obtained from the test solution are not greater or more intense than the spots from the erythromycin standard solution (R_f value: about 0.35) and the erythromycinoxime standard solution (R_f value: about 0.28) (NMT 2.0%, respectively).

(3) ***Related substances***—Weigh accurately 40 mg of Roxithromycin, dissolve in the mobile phase A to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of roxithromycin RS, and dissolve in the mobile phase A to make exactly 10 mL. Pipet 1.0 mL of this solution, add the mobile phase A to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the above operating conditions, and determine the peak area of each solution with the automatic integration method; the area of the peak having the relative retention time of about 1.05 for roxithromycin in the test solution is NMT 2 times the peak area of roxithromycin in the standard solution. Each peak area other than the peak having the relative retention time of 1.05 for roxithromycin is not greater than the peak area of roxithromycin in the standard solution, and the total area of peaks other than roxithromycin from the test solution is not greater than 6 times the peak area of roxithromycin from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C

Mobile phase: Control the gradient elution by mixing the mobile phases A and B as directed under the following table.

Mobile phase A: To 200 mL of ammonium dihydrogen phosphate solution (17 in 100), add 510 mL of water, and adjust the pH to 5.3 with 2 mol/L sodium hydroxide TS. To this solution, add 315 mL of acetonitrile.

Mobile phase B: A mixture of acetonitrile and water (7 : 3).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 38	100	0
38 - 39	100 → 90	0 → 10
39 - 80	90	10

Flow rate: Adjust so that the retention time of roxithromycin is about 21 minutes.

System suitability

Test for required detectability: Pipet 2 mL of the standard solution and add the mobile phase A to make exactly 10 mL. Confirm that the peak area of roxithromycin obtained from 20 μL of this solution is 15% to 25% of the peak area of roxithromycin from the standard solution.

System performance: Weigh 5 mg each of roxithromycin RS and *N*-demethylroxithromycin and dissolve in the mobile phase A to make 100 mL. Proceed with 20 μL of this solution according to the above conditions, *N*-demethylroxithromycin and roxithromycin are eluted in this order with the resolution being NLT 6.

System repeatability: Repeat the test five times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of roxithromycin is NMT 2.0%

Water NMT 3.0% (0.3 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 20 mg (potency) each of Roxithromycin and roxithromycin RS, dissolve in the mobile phase to make exactly 10 mL, pipet 5 mL of these solutions, and add the mobile phase to make exactly 20 mL. Use these solutions as the test solution and the standard solution. Perform the test with exactly 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of roxithromycin.

$$\text{Potency (μg) of roxithromycin } (C_{41}H_{76}N_2O_{15}) = \text{Potency (μg) of roxithromycin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silicagel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Dissolve 2.876 g of ammonium dihydrogen phosphate in 800 mL of water, add 30 mL of 10% tetrabutylammonium hydroxide, adjust the pH to 6.0 with phosphoric acid, and add water to make 1000 mL. To 999 mL of this solution, add 1701 mL of methanol.

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the symmetry factor of the roxithromycin peak is NMT 1.5.

System repeatability: Repeat the test six times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of roxithromycin is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Roxithromycin Granules
록시트로마이신 과립

Roxithromycin Granules contain NLT 90.0% and NMT 120.0% of the labeled amount of roxithromycin ($C_{41}H_{76}N_2O_{15}$: 837.05).

Method of preparation Prepare as directed under Granules, with Roxithromycin.

Identification (1) Weigh about 0.1 g (potency) of Roxithromycin Granules according to the labeled potency, add methanol while shaking to mix to make 100 mL, filter and use the filtrate as the test solution. Separately, dissolve 0.1 g (potency) of roxithromycin RS in methanol to make 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of toluene, ethyl acetate and diethylamine (50 : 20 : 7) as the developing solvent, and dry the plate at 100 to 105 ℃ for 5 minutes. Spray evenly the coloring agent, previously prepared by adding 2.5 mL of sulfuric acid and 50 mL of acetic acid(100) to 2.5 g of phosphomolybdic acid, warm at 100 to 105 ℃; the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Particle size distribution estimation by analytical sieving Meets requirements.

Disintegration Meets the requirements.

Uniformity of dosage units (distribution) Meets the requirements.

Loss on drying NMT 3.0% (0.1 g, 0.7 kPa, 60 ℃, 3 hours).

Assay Weigh accurately about 0.1 g (potency) of Roxithromycin Granules according to the labeled potency,

dissolve in the mobile phase to make exactly 100 mL, and filter. Pipet 5 mL of the filtrate, add the mobile phase to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g (potency) of roxithromycin RS, proceed in the same manner as in the test solution, and use the resulting solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution according to the following conditions as directed under the Liquid Chromatography and determine the peak areas A_T and A_S of roxithromycin, respectively.

Amount [mg (potency)] of roxithromycin ($C_{41}H_{76}N_2O_{15}$)
= Amount [mg (potency)] of roxithromycin RS
× (A_T / A_S)

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 205 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 250 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of approximately 30 °C.

Mobile phase: Dissolve 2.876 g of ammonium dihydrogen phosphate in 800 mL of water, add 30 mL of 10% tetrabutylammonium hydroxide, adjust the pH to 6.0 with phosphoric acid, and add water to make 1000 mL. Add 1701 mL of methanol to 999 mL of this solution.

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the symmetry factor of the roxithromycin peak is NMT 1.5.

System repeatability: Repeat the test six times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of roxithromycin is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Roxithromycin Suspension
록시트로마이신 현탁액

Roxithromycin Suspension, as a suspension for internal use, contains NLT 90.0% and NMT 120.0% of the labeled amount of roxithromycin ($C_{41}H_{76}N_2O_{15}$: 837.05) per mg.

Method of preparation Prepare as directed under Suspensions, with Roxithromycin.

Identification Take 0.1 g (potency) of Roxithromycin Suspension according to the labeled potency, dissolve in methanol to make 100 mL, filter, and use the filtrate as the test solution. Separately, take 0.1 g (potency) of roxithromycin RS, dissolve in methanol to make 100 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of toluene, ethyl acetate and diethylamine (50 : 20 : 7) as the developing solvent, take out the plate, and dry at 100 to 105 ℃ for 5 minutes. Spray evenly a coloring agent, prepared by dissolving 2.5 mL of sulfuric acid and 50 mL of acetic acid(100) in 2.5 g of phosphomolybdic acid, onto the plate, and warm the plate at 100 to 105 ℃; the color and R_f values of the spots obtained from the test solution and the standard solution are the same.

pH Between 7.0 and 9.0.

Assay Perform the test as directed under the Assay under Roxithromycin Granules. Prepare the test solution by pipetting about 50 mg (potency) of Roxithromycin Suspension according to the labeled potency and dissolving in the mobile phase to make exactly 100 mL. Separately, prepare the standard solution by weighing accurately about 50 mg (potency) of roxithromycin RS and dissolving in the mobile phase to make exactly 100 mL.

Packaging and storage Preserve in tight containers.

Roxithromycin Tablets
록시트로마이신 정

Roxithromycin Tablets contains NLT 90.0% and NMT 120.0% of roxithromycin ($C_{41}H_{76}N_2O_{15}$: 837.05) of the labeled amount.

Method of preparation Prepare as directed under Tablets, with Roxithromycin.

Identification (1) Weigh an amount equivalent to 0.1 mg (potency) of Roxithromycin Tablets according to the labeled potency, add methanol, shake to dissolve to make 100 mL, and use the filtrate as the test solution. Separately, dissolve 0.1 mg (potency) roxithromycin RS in methanol to make 100 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of toluene, ethyl acetate and diethylamine (50 : 20 : 7), take the plate out, and dry the plate at 100 ℃ - 105 ℃ for 5 minutes. Prepare 2.5 g of phosphomolybdic acid in 2.5 mL of sulfuric acid and 50mL of acetic acid(100), spray evenly the agent on the plate, and heat the plate at 100 ℃ to 105 ℃; the colors and *R*f values of the spots from the test solution and the standard solution are the same.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Disintegration Perform the test with 1 tablet of Roxithromycin Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of the second solution as the dissolution solution. Take the dissolved solution 30 minutes after the start of the Dissolution, filter, and use the filtrate as the test solution. Separately, weigh accurately about 16.7 mg of roxithromycin RS, dissolve in 10 mL of methanol, add the test solution to make exactly 100 mL, and use this solution standard solution. Perform the test with 20 μL each of the test solution and the standard solution according to the Liquid Chromatography under the following conditions, and determine the peak areas A_T and A_S of roxithromycin ($C_{41}H_{76}N_2O_{15}$) in each solution. Meets the requirements if the dissolution rate of Roxithromycin Tablets in 30 minutes is NLT 80%.

$$\text{Dissolution rate (\%) the labeled amount of roxithromycin } (C_{41}H_{76}N_2O_{15}) = W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 900$$

*W*s: Amount (mg) of roxithromycin RS

C: Labeled amount (mg) of roxithromycin ($C_{41}H_{76}N_2O_{15}$) in 1 tablet

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 205 nm).

Column: A stainless-steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of 0.1 mol/L ammonium dihydrogen phosphate, acetonitrile and water (2: 2 : 1).

Flow rate: 1.5 mL/min

System suitability

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of roxithromycin is NMT 2.0%.

0.1 mol/L ammonium dihydrogen phosphate—Dissolve 11.5 g of ammonium dihydrogen phosphate in water to make 1000 mL.

Uniformity of dosage units Meets the requirements.

Water NMT 5.0% (0.2 g, volumetric titration, direct titration).

Assay Perform the test as directed under the Assay under Roxithromycin Granules. However, weigh accurately the mass of NLT 20 tablets of Roxithromycin Tablets, and powder it. Weigh accurately an amount equivalent to about 0.1 g (potency) according to the labeled potency, dissolve in the mobile phase to make exactly 100 mL, and filter. Pipet 5 mL of this solution, add the mobile phase to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g (potency) of roxithromycin RS, proceed in the same manner as in the test solution, and use this solution as the standard solution.

Packaging and storage Preserve in tight containers.

Royal Jelly and Hydrocortisone Cream
로얄젤리·히드로코르티손 크림

Royal Jelly and Hydrocortisone Cream contains NLT 90.0% of the labeled amount of 10-hydroxy-2-decenoic acid ($C_{10}H_{18}O_3$: 186.25) in royal jelly, and NLT 90.0% and NMT 110.0% of the labeled amount of hydrocortisone ($C_{21}H_{30}O_5$: 362.46).

Method of preparation Prepare as directed under Creams, with Royal Jelly and Hydrocortisone.

Identification (1) ***Royal jelly***—(i) Weigh an amount of Royal Jelly and Hydrocortisone Cream, equivalent to 50 mg of royal jelly, add 50 mL of acetone, extract, and filter. Evaporate to concentrate the filtrate under reduced pressure to make about 10 mL and use this solution as the test solution. Separately, weigh about 50 mg of Royal Jelly, add 50 mL of acetone, extract, and filter. Evaporate to concentrate the filtrate under reduced pressure to make about 10 mL and use this solution as the test solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution onto a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of n-propanol and strong ammonia water (7 : 3) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light or spray iodine vapor; the multiple spots from the test solution have the same color and R_f value as the spots from the standard solution.

(ii) Perform the test with Royal Jelly and Hydrocortisone Cream as directed under the Assay; it exhibits peaks at the same retention times with the reference standards.

(2) ***Hydrocortisone*** —Perform the test with Royal Jelly and Hydrocortisone Cream as directed under the Assay; The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Assay (1) ***10-hydroxy-2-decenoic acid in royal jelly***—Weigh accurately an amount of Royal Jelly and Hydrocortisone Cream, equivalent to about 5 mg of 10-hydroxy-2-decenoic acid, add 40 mL of methanol, soni-

cate for 20 minutes, and add methanol to make exactly 50 mL. Centrifuge this solution, pipet 2 mL of the clear supernatant, add methanol to make 10 mL, and use this solution as the test solution. Separately, weigh accurately about 5 mg of 10-hydroxy-2-decenoic acid RS and dissolve in methanol to make exactly 50 mL. Pipet 2 mL of this solution, add methanol to make 10 mL, use this solution as the test solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of10-hydroxy-2-decenoic acid, A_T and A_S, in each solution.

$$\text{Amount (mg) of 10-hydroxy-2-decenoic acid } (C_{10}H_{18}O_3) = \text{Amount (mg) of 10-hydroxy-2-decenoic acid RS} \times \frac{A_T}{A_S}$$

Operating conditions

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Mobile phase: A mixture of 2.5 mmol/L potassium dihydrogen phosphate TS (pH 3.0) and methanol (1 : 1).

Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the ratios of the peak area of 10-hydroxy-2-decenoic acid to that of the internal standard is NMT 1.0%.

2.5 mmol/L potassium dihydrogen phosphate TS (pH 3.0)—Dissolve 0.170 g of potassium dihydrogen phosphate in 980 mL of water, add phosphoric acid to adjust pH to 3.0, and add water to make 1000 mL.

(2) ***Hydrocortisone***—Weigh accurately an amount of Royal Jelly and Hydrocortisone Cream, equivalent to about 2.5 mg of hydrocortisone ($C_{21}H_{30}O_5$), add 80 mL of methanol, shake to mix, sonicate for 10 minutes, add methanol to make 100 mL, filter, and use this solution as the test solution. Separately, weigh accurately about 25 mg of hydrocortisone RS, dissolve in methanol to make 100 mL, pipet 5.0 mL of this solution, add methanol to make 50 mL, and use this solution as the standard solution. Perform the test with 15 μL each of the test solution and the standard solution as directed under the Liquid Chromatography and determine the peak area of hydrocortisone, A_T and A_S for each solution.

$$\text{Amount (mg) of hydrocortisone } (C_{21}H_{30}O_5) = \text{Amount (mg) of hydrocortisone RS} \times \frac{A_T}{A_S} \times$$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 254 nm).

Column: A stainless steel column 4.6 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of methanol and water (70:30).

Flow rate: 0.9 mL/min

Packaging and storage Preserve in tight containers.

Ruscogenin and Neoruscogenin
루스코게닌류물질

Ruscogenin and Neoruscogenin contains NLT 60.0% of the sterol material extracted from the rhizoma of *Ruscus aculeatus*.

Description Ruscogenin and Neoruscogenin occurs as a yellow granular powder. It has a slightly characteristic odor.

Identification (1) Dissolve 10 mg of Ruscogenin and Neoruscogenin in 10 mL of chloroform, and use this as the test solution. Separately, proceed with about 10 mg of ruscogenin and neoruscogenin RS in the same manner as in the test solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform and acetone (7 : 3) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Spray 10% phosphomolybdic acid-ethanol solution onto the plate. The Rf values and colors obtained from the test solution and the standard solution are the same.

(2) Dry Ruscogenin and Neoruscogenin at 105 ℃ for 4 hours, and perform the test with 3 mg of the resulting material as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; it exhibits absorption at the wavenumbers of 866 cm^{-1}, 900 cm^{-1}, 922 cm^{-1} and 982 cm^{-1}.

Purity ***Heavy metals***—Proceed with 1.0 g of Ruscogenin and Neoruscogenin according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 20 ppm).

Water NMT 4.5% (0.2 g, volumetric titration, direct titration).

Assay Weigh accurately about 0.15 g of Ruscogenin and Neoruscogenin, place in a 100-mL volumetric flask, dissolve in 80% ethanol, and add 80% ethanol to make 100.0 mL. Put 5.0 mL of this solution to a 100-mL volumetric flask, add 80% ethanol to fill up to the gauge line,

and use this solution as the test solution. Separately, weigh accurately about 0.15 g of ruscogenin and neoruscogenin RS, put it in a 100-mL volumetric flask, dissolve in 80% ethanol, and add 80% ethanol to make 100.0 mL. Put 5.0 mL of this solution in a 100-mL volumetric flask, add 80% ethanol to fill up to the gauge line, and use this solution as the standard solution. Put 1.0 mL each of the test solution and standard solution in a test tube, respectively, heat and evaporate to dryness in a 70 ℃ water bath, add 0.5 mL of p-methylaminobenzaldehyde-sulfuric acid solution, and heat again in a 70 ℃ water bath for 30 minutes. After cooling to room temperature, add 10 mL of acetic acid(100) solution (12 in 100) to each, and shake well for 20 minutes. Perform the test with each of the resulting solutions, using a blank test solution for comparison, as directed under the Ultraviolet-visible Spectroscopy and determine the absorbance of each solution at the wavelength 521 ± 3 nm, A_T and A_S, respectively.

$$\text{Amount (mg) of ruscogenin and neoruscogenin} = \text{Amount (mg) of neoruscogenin RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers in a cold and dark place.

Safflower Oil, Tocopherol Acetate and Pyridoxine Hydrochloride Capsules
홍화유·토코페롤아세테이트·피리독신염산염 캡슐

Safflower Oil, Tocopherol Acetate and Pyridoxine Hydrochloride Capsules contain NLT 90.0% of the labeled amount of linoleic acid ($C_{18}H_{32}O_2$: 280.45) in safflower oil, NLT 90.0% and NMT 150.0% of the labeled amount of tocopherol acetate ($C_{31}H_{52}O_3$: 472.74) and pyridoxine hydrochloride ($C_8H_{11}NO_3$·HCl: 205.64).

Method of preparation Prepare as directed under Capsules, with Safflower Oil, Tocopherol Acetate and Pyridoxine Hydrochloride.

Identification (1) ***Tocopherol acetate and pyridoxine hydrochloride***—Perform the test with the contents of Safflower Oil, Tocopherol Acetate and Pyridoxine Hydrochloride Capsules as directed under the Analysis for Vitamins.

(2) ***Safflower oil***—Weigh 0.1 g of the contents of Safflower Oil, Tocopherol Acetate and Pyridoxine Hydrochloride Capsules, transfer to a brown flask, and add 30 mL of methanol and 3 mL of potassium hydroxide solution (1 in 2). Perform saponification under a reflux condenser at 90 ℃ for 30 minutes. After cooling, transfer the mixture to a separatory funnel, wash the flask with 20 mL of water, collect to a separatory funnel, and add dilute hydrochloric acid to acidify. Then, extract 3 times with 30 mL each of ether, collect the ether extracts and wash with water until the washings become neutral. Dry the ether extracts using anhydrous sodium sulfate, filter, concentrate the filtrate in vacuum, dissolve the residue in 5 mL of methanol, and use this solution as the test solution. Separately, weigh 10 mg of linoleic acid RS, dissolve in 10 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography, Develop the plate with a mixture of heptane, ethanol, acetic acid and acetone (14 : 4 : 1 : 0.5) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray evenly 50% sulfuric acid on the plate; the color and R_f values of the spots obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Tocopherol acetate and pyridoxine hydrochloride***—Weigh accurately the mass of the contents of NLT 20 capsules of Safflower Oil, Tocopherol Acetate and Pyridoxine Hydrochloride Capsules and perform the test as directed under the Analysis for Vitamins.

(2) ***Linoleic acid in safflower oil***—Weigh accurately the mass of the contents of NLT 20 capsules of Safflower Oil, Tocopherol Acetate and Pyridoxine Hydrochloride Capsules. Weigh accurately an amount equivalent to 0.4 g of linoleic acid and dissolve in 100 mL of isooctane. Transfer 1 mL of this solution and 1 mL of the internal standard solution to a stoppered test tube, add 1.5 mL of 0.5 mol/L sodium hydroxide-methanol TS, and heat at 100 ℃ for 5 minutes for saponification. Cool this solution to 30 to 40 ℃, add 2 mL of boron trifluoride-methanol TS, and shake to mix. Then, heat for 5 minutes at 100 ℃ for derivatization, and cool to 30 to 40 ℃. Add 5 mL of saturated sodium chloride solution, shake to mix and take the isooctane layer in the upper layer. Remove water with anhydrous sodium sulfate and use this solution as the test solution. Separately, take 1 mL of a solution prepared by weighing accurately about 0.4 g of linoleic acid RS and dissolving in 100 mL of isooctane and 1 mL of internal standard solution and transfer to a stoppered test tube. Then, proceed in the same manner as the test solution and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, to the internal standard for each solution.

$$\text{Amount (mg) of linoleic acid } (C_{18}H_{32}O_2) = \text{Amount (mg) of linoleic acid RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh accurately about 0.2 g of pentadecanoic acid and dissolve in 50 mL of isooctane to prepare the solution.

Operating conditions

Detector: A flame ionization detector

Sample injection port temperature: 240 ℃

Detector temperature: 250 ℃

Column temperature: Maintain at 140 ℃ for the first 5 minutes, increase at a rate of 5 ℃ per minute to 250 ℃ and maintain this temperature for 5 minutes.

Column: A capillary column, about 0.32 mm in internal diameter and about 30 m in length, coated with polyethylene glycol for gas chromatography 0.25 μm in thickness.

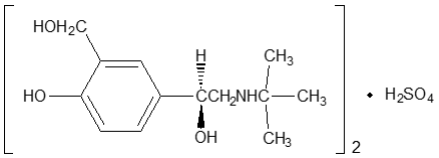
Carrier gas: Nitrogen

Flow rate: 1.0 mL/min

Split ratio: 5.0 : 1

Packaging and storage Preserve in tight containers.

Salbutamol Sulfate
살부타몰황산염



and enantiomer

$(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$: 576.70

Bis{*N*-*t*-butyl-2-hyroxy-2-[4-hydroxy-(3-hydroxymethyl)phenyl]ethanamine} sulfate [*51022-70-9*]

Salbutamol Sulfate, when dried, contains NLT 98.0% and NMT 101.0% of salbutamol sulfate [$(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$].

Description Salbutamol Sulfate occurs as a white powder.

It is freely soluble in water, slightly soluble in ethanol(95) or acetic acid(100), and practically insoluble in ether.

An aqueous solution of Salbutamol Sulfate (1 in 20) shows no optical rotation.

Identification (1) Determine the absorption spectra of the solutions of Salbutamol Sulfate and salbutamol sulfate RS in 0.1 mol/L hydrochloric acid TS (1 in 12500) as directed under the Ultraviolet-visible Spectrophotometry; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Salbutamol Sulfate and salbutamol sulfate RS, previously dried, according to the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Salbutamol Sulfate (1 in 20) responds to the Qualitative Analysis for sulfate.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Salbutamol Sulfate in 20 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Salbutamol Sulfate according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve 20 mg of Salbutamol Sulfate in 10 mL of water and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the plate made of silica gel for thin-layer chromatography. Then, develop the plate with a mixture of ethyl acetate, 2-propanol, water, and ammonia water(28) (25 : 15 : 8 : 2) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Allow the plate to stand for 5 minutes in a well-closed container saturated with diethylamine vapor, and spray evenly 4-nitrobenzenediazonium hydrochloride TS for spraying; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

(4) ***Boron***—Put about 50 mg of Salbutamol Sulfate and 5.0 mL of standard boron solution respectively into a platinum crucible, add 5 mL of potassium carbonate-sodium carbonate TS, and evaporate on a steam bath to dryness. After drying the mixture for 1 hour at 120 ℃, incinerate it by ignition. After cooling, add 0.5 mL of water and 3 mL of curcumin TS to the residue, and warm it gently on a steam bath for 5 minutes. After cooling, add 3 mL of acetic acid(100)-sulfuric acid TS to the mixture, mix, and allow it to stand for 30 minutes. Then, add ethanol(95) to make exactly 100 mL and filter it. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution and the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using ethanol(95) as the control; the absorbance of the test solution at 555 nm is not greater than that of the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum at the pressure not exceeding 0.67 kPa, 100 ℃, 3 hours).

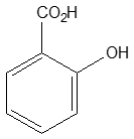
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.9 g of Salbutamol Sulfate, previously dried, add 50 mL of acetic acid(100), warm to dissolve, and cool. Then, titrate with 0.1 mol/L perchloric acid (indicator: 3 drops of methylrosaniline chloride TS). The endpoint of the titration is when the color of this solution changes from purple through blue to bluish green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 57.67 mg $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$

Packaging and storage Preserve in tight containers.

Salicylic Acid
살리실산



$C_7H_6O_3$: 138.12

2-Hydroxybenzoic acid [*69-72-7*]

Salicylic Acid, when dried, contains NLT 99.5% and NMT 101.0% of salicylic acid ($C_7H_6O_3$).

Description Salicylic Acid occurs as white crystals or a crystalline powder. It is odorless and has a slightly sour taste and irritant property.
It is freely soluble in ethanol(95), acetone or ether, and slightly soluble in water.

Identification (1) The Salicylic Acid aqueous solution (1 in 500) responds to the Qualitative Analysis (1) and (3) for salicylate.

(2) Determine the absorption spectra of solutions of Salicylic Acid and salicylic acid RS in ethanol(95) (3 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Salicylic Acid and salicylic acid RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 158 and 161 ℃.

Purity (1) ***Chloride***—To 5.0 g of Salicylic Acid, add 90 mL of water and heat to dissolve. After cooling, add water to make 100 mL, and filter. Discard the first 20 mL of the filtrate, take the subsequent 30 mL of the filtrate, and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.35 mL of 0.01 mol/L hydrochloric acid (NMT 0.008%).

(2) ***Sulfate***—Take 30 mL of the filtrate obtained in (1), add 1 mL of dilute hydrochloric acid, and put water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid (NMT 0.011%).

(3) ***Heavy metals***—Dissolve 2.0 g of Salicylic Acid in 25 mL of acetone, and add 4 mL of sodium hydroxide TS and 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 25 mL of acetone, 2 mL of dilute acetic acid and water to 2.0 mL of lead standard solution to make 50 mL (NMT 10 ppm).

(4) ***Related substances***—To 0.50 g of Salicylic Acid, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately 10 mg of phenol, 25 mg of 4-hydroxyisophthalic acid and 50 mg of p-hydroxybenzoate, and dissolve in the mobile phase to make exactly 100 mL. To 1 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test and standard solutions as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas from the respective solutions according to the automatic integration method. The peak areas of p-hydroxybenzoate, 4-hydroxyisophthalic acid and phenol in the test solution are not greater than those in the standard solution. The peak area other than salicylic acid in the test solution is not greater than that of 4-hydroxyisophthalic acid in the standard solution. The sum of all peak areas other than salicylic acid is not more than twice the peak area of p-hydroxybenzoate in the standard solution.

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 270 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of water, methanol and acetic acid(100) (60 : 40 : 1).

Flow rate: Adjust the flow rate so that the retention time of salicylic acid is about 17 minutes.

System suitability

Detection sensitivity: Pipet 2 mL of the standard solution, and add the mobile phase to make exactly 10 mL. Proceed with 10 μL of this solution according to the operating method. The resultant peak areas of p-hydroxybenzoate, 4-hydroxyisophthalic acid and phenol are between 14% and 26% of the respective peaks obtained from 10 μL of the standard solution.

System performance: Dissolve 10 mg of phenol, 25 mg of 4-hydroxyisophthalic acid and 50 mg of p-hydroxybenzoate in 100 mL of the mobile phase. To 1 mL of this solution, add the mobile phase to make exactly 10 mL, and use this solution as the standard solution. Proceed according to the above conditions; p-hydroxybenzoate, 4-hydroxyisophthalic acid and phenol are eluted in this order with the resolution between 4-hydroxyisophthalic acid and phenol being NLT 4.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of p-hydroxybenzoate, 4-hydroxyisophthalic acid and phenol is NMT 2.0%.

Time span of measurement: About twice the retention time of salicylic acid after the solvent peak.

(5) ***Sulfuric acid for readily carbonizable sub-***

***stances*—**Perform the test with 0.5 g of Salicylic Acid. The color of the solution is not more intense than that of the control solution C.

Loss on drying NMT 0.5% (2 g, silica gel, 3 hours).

Residue on ignition NMT 0.05%. (1 g).

Assay Weigh accurately about 0.5 g of Salicylic Acid, previously dried, dissolve in 25 mL of neutralized ethanol, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of phenolphthalein TS).

Each mL of 0.1 mol/L sodium hydroxide VS
= 13.812 mg of $C_7H_6O_3$

Packaging and storage Preserve in well-closed containers.

Salicylic Acid and Lactic Acid Solution
살리실산·락트산 액

Salicylic Acid and Lactic Acid Solution contains NLT 90.0% and NMT 110.0% of the labeled amount of salicylic acid ($C_7H_6O_3$: 138.12) and lactic acid ($C_3H_6O_3$: 90.08).

Method of preparation Prepare as directed under Liquids, with Salicylic Acid and Lactic Acid. Preservative(s) may be used, if necessary.

Identification (1) ***Salicylic Acid***—Use Salicylic Acid and Lactic Acid Solution as the test solution. Separately, dissolve 100 mg of salicylic acid RS in a small amount of ethanol(95), and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of 1-hexane and acetic acid (20 : 0.7) as the developing solvent, and air-dry the plate. Spray evenly 2% iron(III) chloride TS, hexachloroplatinic(IV) acid TS, and then 50% sulfuric acid TS on the plate. The *Rf* values and colors of the spots from the test solution and the standard solution are the same.

(2) ***Lactic acid***— The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Assay (1) ***Salicylic acid***—Pipet an amount, equivalent to 0.1 g of salicylic acid ($C_7H_6O_3$) according to the labeled amount of Salicylic Acid and Lactic Acid Solution. Add 20 mL of saturated solution of sodium bicarbonate and perform extraction 3 times with 20 mL of ether each time. Combine all the ether layers, perform extraction twice with 5 mL of saturated solution of sodium bicarbonate each time, and combine the extracts with the aforesaid saturated solution of sodium bicarbonate. Acidify with dilute hydrochloric acid, add ethanol(95) to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of salicylic acid RS, dissolve by adding dilute ethanol(95) (1 : 2) to make 100 mL, and use this solution as the standard solution. To 10.0 mL each of the test solution, the standard solution and the control solution (ethanol (95)), add 20 mL of 0.1 mol/L sodium hydroxide to each, shake for mixing, and allow to stand for 10 minutes. Add 20 mL of 0.1 mol/L hydrochloric acid to each, allow to stand for 10 minutes, and add water to make to 100 mL each. To 10.0 mL each of the respective solutions, add 5 mL of 0.5% iron(III) nitrate TS, add pH 2.0 hydrochloric acid-potassium chloride buffer solution to make 25 mL each, and allow to stand for exactly 10 minutes. Determine the absorbances, A_T and A_S, from the respective resulting solutions at the wavelength 530 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of salicylic acid ($C_7H_6O_3$)
$= \text{Amount (mg) of salicylic acid RS} \times \frac{A_T}{A_S}$

(2) ***Lactic acid***—Pipet an amount, equivalent to 0.2 g of lactic acid ($C_3H_6O_3$) according to the labeled amount of Salicylic Acid and Lactic Acid Solution. Add 20 mL of water and 10 mL of 1 mol/L sodium hydroxide, and boil on a steam bath for 10 minutes. After cooling, add water to make 50 mL. Centrifuge, take 10.0 mL of the supernatant, add the mobile phase to make 50 mL, and filter. Use this solution as the test solution. Separately, weigh accurately about 0.2 g of lactic acid RS and proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area, A_T and A_S of lactic acid from each of the solutions.

Amount (mg) of lactic acid ($C_3H_6O_3$)
$= \text{Amount (mg) of lactic acid RS} \times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Mobile phase: 0.3 mol/L potassium dihydrogen phosphate TS (adjust the pH to 2.4 with phosphoric acid).

Packaging and storage Preserve in tight containers.

Salicylic Acid, Phenol and *dl*-Camphor Solution
살리실산·페놀·*dl*-캄파 액

Salicylic Acid, Phenol and *dl*-Camphor Solution contains NLT 90.0% and NMT 110.0% of salicylic acid ($C_7H_6O_3$: 138.12), phenol C_6H_6O: 94.11) and NLT 90.0% and NMT 130.0% of *dl*-camphor ($C_{10}H_{16}O$: 152.23) of the labeled amount.

Method of preparation Prepare as directed under the Liquids, with Salicylic Acid, Phenol and *dl*-Camphor.

Identification (1) ***Salicylic acid and dl-camphor***—Use Salicylic Acid, Phenol and *dl*-Camphor Solution as the test solution. Separately, dissolve 0.1 g each of salicylic acid RS and dl-camphor RS in a small amount of ethanol(95), and use these solutions as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of 1-hexane and acetic acid (20 : 0.7), and air-dry the plate. Spray 2% iron(III) chloride TS evenly on the plate, spray hexachloroplatinic(IV) acid TS evenly to the plate, and spray 50% sulfuric acid TS evenly to the plate; the spots obtained from the test solution show the same R_f value and color as the spots obtained from the standard solution.

(2) ***Phenol***—Take 20 mL of Salicylic Acid, Phenol and *dl*-Camphor Solution and evaporate it on a steam bath to 1 mL. Mix it with 20 mL of ether, wash 2 times with 10 mL each of saturated solution of sodium bicarbonate, take the ether layer, and evaporate to dryness on a steam bath. Then, perform the test according to the Identification under Phenol of Korean Pharmacopoeia (KP).

Assay (1) ***Salicylic acid***—Take accurately an amount of Salicylic Acid, Phenol and *dl*-Camphor Solution, equivalent to 15 mg of salicylic acid ($C_7H_6O_3$) according to the labeled amount, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 15 mg of salicylic acid RS, dissolve in the mobile phase to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under Liquid Chromatography according to the following operating conditions. Determine the peak areas, A_T and A_S, of salicylic acid for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of salicylic acid } (C_7H_6O_3) = \text{Amount (mg) of salicylic Acid RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of 0.085% phosphoric acid and methanol (60 : 40).

Column temperature: A constant temperature of about 30 °C.

Flow rate: 1.0 mL/min

(2) ***Phenol***—Pipet an appropriate volume of Salicylic Acid, Phenol and *dl*-Camphor Solution, equivalent to 0.1 g of phenol (C_6H_6O), evaporate on a steam bath to 2 mL, and add 20 mL of 1 mol/L sodium hydroxide. Wash the solution 2 times with 10 mL each of ether, combine the ether layer, extract 2 times with 5 mL of 1 mol/L sodium hydroxide, and then combine the extract with the first 1 mol/L sodium hydroxide layer. Make the resulting solution acidic with dilute hydrochloric acid, saturate it with sodium bicarbonate, and extract it 5 times with 20 mL each of ether. Combine all ether layers, evaporate on a steam bath to dryness, add water to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of phenol RS, proceed in the same manner as the test solution, and use this solution as the standard solution. Pipet 10.0 mL each of the test solution, standard solution and control solution (water), add 1 mL of coloring agent, and allow the resulting solution to stand for 1 minute. Add 2 mL of 10% sodium bicarbonate solution, mix well while stirring, and add water to make 50 mL. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance A_T and A_S at the wavelength of 470 nm.

$$\text{Amount (mg) of phenol} = \text{Amount (mg) of phenol RS} \times \frac{A_T}{A_S}$$

(3) ***dl-camphor***—Weigh accurately an amount of Salicylic Acid, Phenol and *dl*-Camphor Solution, equivalent to 500 mg of *dl*-camphor ($C_{10}H_{16}O$), according to the labeled amount. Add ethanol(99.5) to make exactly 100 mL. Pipet 2 mL of this solution, transfer it to a 10-mL volumetric flask, add 1 mL of the internal standard solution and ethanol(99.5) to make exactly 10 mL. Use this solution as the test solution. Separately, weigh accurately about 500 mg of *dl*-camphor RS and add ethanol(99.5) to make exactly 100 mL. Pipet 2 mL of this solution, transfer to a 10-mL volumetric flask, and add 1 mL of the internal standard solution and ethanol(99.5) to make exactly 10 mL. Use this solution as the standard solution. Perform the test with 2 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of *dl*-camphor to the internal standard.

$$\text{Amount (mg) of } dl\text{-camphor } (C_{10}H_{16}O) = \text{Amount (mg) of } dl\text{-camphor RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of biphenyl in ethanol(99.5) (1 in 20000).

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A column, about 0.32 mm in internal diameter and 30 m in length, coated with dimethylpolysiloxane to 0.25 μm.

Column temperature: Maintain the temperature at 100 °C for 4 minutes, then raise to 140 °C at a rate of 40 °C per minute, and maintain it for 2 minutes. Raise the temperature again to 210 °C at a rate of 70 °C per minute.

Sample injection port temperature: 230 °C

Detector temperature: 230 °C

Carrier gas: Nitrogen

Flow rate: Between 150 and 160 mL/min.

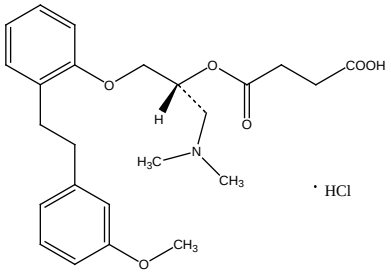
System suitability

System performance: Proceed with 2 μL of the standard solution under the above conditions; *dl*-camphor and the internal standard are eluted in this order with the resolution between these peaks being NLT 30 and the symmetry factor being NMT 1.5.

System repeatability: Repeat the test 6 times with 2 μL each of the standard solution under the above operating conditions; the relative standard deviation of the ratios of peak area of *dl*-camphor to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Sarpogrelate Hydrochloride
사르포그렐레이트염산염



and enantiomer

$C_{24}H_{31}NO_6 \cdot HCl$: 465.97

1-[2-(Dimethylamino)-1-[[2-[2-(3-methoxyphenyl)ethyl]phenoxy]methyl]ethyl hydrogen butanedioate hydrochloride [*135159-51-2*]

Sarpogrelate Hydrochloride contains NLT 98.5% and NMT 101.0% of sarpogrelate hydrochloride ($C_{24}H_{31}NO_6 \cdot HCl$: 465.97), calculated on the anhydrous basis.

Description Sarpogrelate Hydrochloride occurs as a white crystalline powder.

It is slightly soluble in water or ethanol(95).

It dissolves in 0.01 mol/L hydrochloric acid TS.

An aqueous solution of Sarpogrelate Hydrochloride (1 in 100) shows no optical rotation.

It shows polymorphism.

Identification (1) Determine the absorption spectra of the aqueous solutions of Sarpogrelate Hydrochloride and sarpogrelate hydrochloride RS in 0.01 mol/L hydrochloric acid TS (1 in 20000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Sarpogrelate Hydrochloride and sarpogrelate hydrochloride RS as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If there is a difference between the two spectra, add acetone each, heat, suspend, filter, and recrystallize. Perform the test in the same manner with the separated crystals dried for 1 hour at 50 ℃.

(3) To 0.3 g of Sarpogrelate Hydrochloride, add 6 mL of sodium hydroxide TS, shake well to mix, and allow it to stand for 10 minutes. Filter this solution, add 1 mL of dilute nitric acid in 1 mL of the filtrate; this solution responds to the Qualitative Analysis for chloride.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Sarpogrelate Hydrochloride according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Prepare the test solution with 2.0 g of Sarpogrelate Hydrochloride according to Method 4 and perform the test (NMT 1 ppm).

(3) ***Related substances***—Prepare the test solution and perform the test within 3 hours. Dissolve 20 mg of Sarpogrelate Hydrochloride in 10 mL of the mobile phase, and use this solution as the test solution. Pipet 2 mL of this solution, add the mobile phase to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution as directed in the automatic integration method; the peak area of decomposed substance A with a relative retention time to sarpogrelate of about 0.82 from the test solution is not greater than 1/5 of the peak area of sarpogrelate from the standard solution, and the peak area other than sarpogrelate and the above peak from the test solution is not greater than 1/10 of the peak area of sarpogrelate from the standard solution. The total area of the peaks other than sarpogrelate from the test solution is not greater than 1/ 2 of the peak area of sarpogrelate from the standard solution. The peak area of decomposed substance A with a relative retention time of about 0.82 to sarpogrelate is determined by mutiflying the area obtained by the automatic integration method by the relative response factor of 0.78.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, comply with the operating con-

ditions under the Assay.

System suitability

Test for required detectability: Take exactly 5 mL of the standard solution, and add the mobile phase to make exactly 50 mL. The peak area of sarpogrelate obtained from 10 μL of this solution is equivalent to 7 to 13% of the peak area of sarpogrelate from the standard solution.

System performance: Dissolve 50 mg of Sarpogrelate in 20 mL of water and use this solution as the sarpogrelate hydrochloride stock solution. To 1 mL of this solution, add 2 mL of sodium hydroxide TS, shake well to mix, allow it to stand for 10 minutes, and add 3 mL of 1 mol/L hydrochloric acid TS. To this solution, add 1 mL of sarpogrelate hydrochloride stock solution and add the mobile phase to make 50 mL. Perform the test with 10 μL of this solution according to the above conditions; decomposed substance A and sarpogrelate are eluted in this order with the resolution being NLT 3.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of sarpogrelate is NMT 2.0%

Time span of measurement: About 2.5 times the retention time of sarpogrelate after the solvent peak.

Water NMT 0.5% (0.1 g, coulometric titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg of Sarpogrelate Hydrochloride and sarpogrelate RS (determine the content of water before use, in the same manner as Sarpogrelate Hydrochloride), add exactly 2.5 mL each of the internal standard solution, add the mobile phase, and dissolve to make 50 mL. Pipet 5 mL each of these solutions, add the mobile phase to make exactly 50 mL, and use these solutions as the test solution and the standard solution. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions and calculate the ratios, Q_T and Q_S, of peak area of sarpogrelate to that of the internal standard, respectively.

$$\text{Amount (mg) of sarpogrelate hydrochloride } (C_{24}H_{31}NO_6\cdot HCl) = W_S \times \frac{Q_T}{Q_S}$$

W_S: Amount (mg) of sarpogrelate hydrochloride RS, calculated on the dried basis

Internal standard solution—A solution of isopropyl p-hydroxybenzoate in the mobile phase (3 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 272 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of water, acetonitrile and trifluoroacetic acid (1300 : 700 : 1).

Flow rate: Adjust the flow rate so that the retention time of sarpogrelate is about 8 minutes.

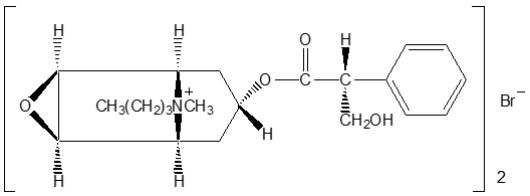
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; sarpogrelate and the internal standard are eluted in this order with the resolution being NLT 3.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the ratios of the peak area of sarpogrelate to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Scopolamine Butylbromide
부틸스코폴라민브롬화물



Hyoscine Butylbromide $C_{21}H_{30}BrNO_4$: 440.37

(1*S*,2*S*,4*R*,5*R*,7*S*)-9-Butyl-7-[(2*S*)-3-hydroxy-2-phenylpropanoyloxy]-9-methyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide [*149-64-4*]

Scopolamine Butylbromide, when dried, contains NLT 98.5% and NMT 101.0% of scopolamine butylbromide ($C_{21}H_{30}BrNO_4$).

Description Scopolamine Butylbromide occurs as white crystals or a crystalline powder.

It is very soluble in water, freely soluble in acetic acid(100), soluble in ethanol(95), sparingly soluble in methanol, slightly soluble in acetic anhydride, and practically insoluble in ether.

Melting point—About 140 °C (with decomposition).

Identification (1) To 1 mg of Scopolamine Butylbromide, add 3 to 4 drops of fuming nitric acid and evaporate to dryness on a steam bath. After cooling, dissolve the residue in 1 mL of *N*,*N*-dimethylformamide and add 6 drops of tetraethylammonium hydroxide TS; the solution exhibits a purple color.

(2) Determine the absorption spectra of solutions of Scopolamine Butylbromide and scopolamine butylbromide RS (1 in 1000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Scopolamine Butylbromide and scopolamine butylbromide RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) An aqueous solution of Scopolamine Butylbromide (1 in 20) responds to the Qualitative Analysis for bromide.

Optical rotation $[\alpha]_D^{20}$: Between -18.0° and -20.0° (1 g after drying, water, 10 mL, 100 mm).

pH Dissolve 1.0 g of Scopolamine Butylbromide in 10 mL of water; the pH of this solution is between 5.5 and 6.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Scopolamine Butylbromide in 10 mL of water; the solution is clear and the color is not more intense than following control solution.

Control solution—To 0.5 mL of Matching fluid F for color, add diluted hydrochloric acid (1 in 40) to make 20 mL.

(2) ***Heavy metals***—Proceed with 2.0 g of Scopolamine Butylbromide according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 0.10 g of Scopolamine Butylbromide, previously weighed, in the mobile phase to make exactly 10 mL and use this solution as the test solution. Separately, dissolve 10 mg of Scopolamine Hydrobromide, previously weighed, in the mobile phase to make exactly 100 mL. Pipet 10 mL of this solution. add the mobile phase to make exactly 50 mL and use this solution as the standard solution (1). Pipet 5 mL of the standard solution (1), add the mobile phase to make exactly 10 mL, and use this solution as the standard solution (2). Perform the test with 20 μL each of the test solution, standard solution (1) and standard solution (2) as directed under the Liquid Chromatography according to the following operating conditions. Determine each peak area of the solutions by the automatic integration method; the peak area of scopolamine from the test solution is not greater than that from the standard solution (2), and each area of the peaks other than the peak that appears first and the peak of scopolamine and butylscopolamine from the test solution are not greater than the peak area from the standard solution (1).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm to 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Dissolve 2 g of sodium lauryl sulfate in 370 mL of water and adjust the pH with diluted phosphoric acid (1 in 10) to 3.6.

Flow rate: Adjust the flow rate so that the retention time of butylscopolamine is about 7 minutes.

System suitability

Detection sensitivity: Adjust the detection sensitivity so that the peak height of scopolamine obtained from 20 μL of the standard solution (2) is between 5 mm and 30 mm.

System performance: Dissolve 5 mg each of Scopolamine Butylbromide and scopolamine butylbromide RS in 50 mL of the mobile phase. Proceed with 20 μL of this solution according to the above conditions; scopolamine and butylscopolamine are eluted in this order with the resolution being NLT 5.

Time span of measurement: About twice the retention time of butylscopolamine.

Loss on drying NMT 1.0% (1 g, 105 ℃, 4 h.).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately 0.8 g of Scopolamine Butylbromide, previously dried, dissolve in 40 mL of acetic acid(100) and 30 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 44.04 mg of $C_{21}H_{30}BrNO_4$

Packaging and storage Preserve in tight containers.

Scopolamine Butylbromide and Acetaminophen Tablets
부틸스코폴라민브롬화물·아세트아미노펜 정

Scopolamine Butylbromide and Acetaminophen Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of scopolamine butylbromide ($C_{21}H_{30}BrNO_4$: 440.37) and acetaminophen ($C_8H_9NO_2$: 151.16).

Method of preparation Prepare as directed under Tablets, with Scopolamine Butylbromide and Acetaminophen.

Identification The retention times of the major peaks obtained from the test solution and the standard solution under the Assay are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Scopolamine Butylbromide and Acetaminophen Tablets, and powder the tablets. Weigh accurately an amount, equivalent to about 10 mg of scopolamine butylbromide ($C_{21}H_{30}BrNO_4$) and about 500 mg of acetaminophen ($C_8H_9NO_2$), and add water to make exactly 500 mL. Sonicate this solution for about 20 minutes, filter through a membrane filter with a pore size NMT 0.45 μm, discard the first 2 mL, and use the subsequent filtrate as the test solution. Separately, weigh accurately 10 mg of scopolamine butylbromide RS and 500 mg of acetaminophen RS, add water to make to make exactly 500 mL, and use the resulting solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_{T1}, A_{T2}, A_{S1} and A_{S2}, of scopolamine butylbromide and acetaminophen in each solution.

$$\text{Amount (mg) of scopolamine butylbromide } (C_{21}H_{30}BrNO_4) = \text{Amount (mg) of scopolamine butylbromide RS} \times \frac{A_{T1}}{A_{S1}}$$

$$\text{Amount (mg) of acetaminophen } (C_8H_9NO_2) = \text{Amount (mg) of acetaminophen RS} \times \frac{A_{T2}}{A_{S2}}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: A mixture of 0.01 mol/L potassium phosphate buffer solution (pH 2.7) and acetonitrile (90 : 10).

Mobile phase B: Acetonitrile

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 6	100 → 80	0 → 20
6 - 11	80 → 10	20 → 90

Flow rate: 1.0 mL/min

System suitability

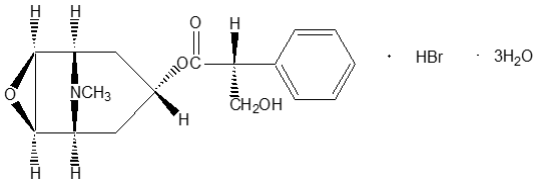
System performance: Proceed with 10 μL of the standard solution according to the above conditions; acetaminophen and scopolamine butylbromide are eluted in this order with the resolution being NLT 5.5.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak areas of acetaminophen and scopolamine butylbromide is NMT 1.0%.

0.01 mol/L potassium phosphate buffer solution (pH 2.7)—Dissolve 1.36 g of potassium dihydrogen phosphate in water, adjust the pH to 2.7 with phosphoric acid, and add water to make 1000 mL.

Packaging and storage Preserve in well-closed containers.

Scopolamine Hydrobromide Hydrate
스코폴라민브롬화수소산염수화물



Scopolamine Hydrobromide

$C_{17}H_{21}NO_4 \cdot HBr \cdot 3H_2O$: 438.31

(1*S*,2*S*,4*R*,5*R*,7*S*)-9-Methyl-3-oxa-9-azatricyclo[3.3.1.02,4]non-7-yl(2*S*)-3-hydroxy-2-phenylpropanoate hydrobromide trihydrate [*6533-68-2*]

Scopolamine Hydrobromide Hydrate, when dried, contains NLT 98.5% of scopolamine hydrobromide (C17H21NO4·HBr : 384.27).

Description Scopolamine Hydrobromide Hydrate occurs as a colorless or white crystal, or white granule or a powder and odorless.

It is freely soluble in water, sparingly soluble in acetic acid(100) or ethanol(95) and practically insoluble in ether.

Identification (1) To 1 mg of Scopolamine Hydrobromide Hydrate, add 3 to 4 drops of fuming nitric acid, evaporate to dryness on a steam bath. Cool and dissolve the residue in 1 ml of *N*,*N*-Dimethylformamide, and add 6 drops of tetraethylammonium hydroxide TS; the resulting solution exhibits a purple color.

(2) An aqueous solution of Scopolamine Hydrobromide Hydrate (1 in 20) responds to the Qualitative Analysis for bromide.

Optical rotation $[\alpha]_D^{20}$: Between -24.0° and -26.0° (0.5 g after drying, water, 10 mL, 100 mm).

Melting point Between 195 and 199 ℃ (after drying, heat the bath fluid to 180 ℃ in advance).

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Scopolamine Hydrobromide Hydrate in 10 mL of water; the solution is colorless and clear.

(2) ***Acid***—Dissolve 0.50 g of Scopolamine Hydrobromide Hydrate in 15 mL of water, and add 0.50 ml of 0.02 mol/L sodium hydroxide and 1 drop of methyl red-methylene blue TS; the resulting solution is green.

(3) ***Atropine***—Dissolve 0.20 g of Scopolamine Hydrobromide Hydrate in 20 mL of water, add 0.60 mL of 0.002 mol/L potassium permanganate, and allow to stand for 5 minutes; the red color does not disappear.

(4) ***Related substances***—Dissolve 0.15 g of Scopolamine Hydrobromide Hydrate in 3 mL of water, and use this solution as the test solution.

(i) To 1 mL of the test solution, add 2 to 3 drops of ammonia TS; the solution does not become turbid.

(ii) To 1 mL of the test solution, add 2 to 3 drops of potassium hydroxide TS; the solution produces a white turbidity, but it disappears clearly in a little while.

Loss on drying NMT 13.0% (1.5 g, first dry in a desiccator (silica gel) for 24 hours, then dry at 105 ℃ for 3 hours).

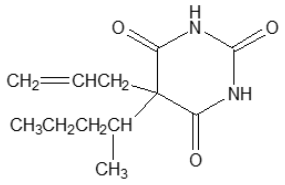
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Scopolamine Hydrobromide Hydrate, previously dried, and dissolve in 10 mL of acetic acid(100) by warming. After cooling, add 40 mL of acetic anhydride and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 38.426 mg of $C_{17}H_{21}NO_4 \cdot HBr$

Packaging and storage Preserve in light-resistant, tight containers.

Secobarbital
세코바르비탈



$C_{12}H_{18}N_2O_3$: 238.28

5-(Pentan-2-yl)-5-(prop-2-en-1-yl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione [*76-73-3*]

Secobarbital contains NLT 97.5% and NMT 100.5% of secobarbital ($C_{12}H_{18}N_2O_3$), calculated on the dried basis.

Description Secobarbital occurs as a white, amorphous or crystalline powder. It is odorless and has a slightly bitter taste.

It is very slightly soluble in water, freely soluble in ethanol(95) or ether, and soluble in chloroform.

It dissolves in sodium hydroxide TS or sodium carbonate solution.

The pH of the saturated solution of Secobarbital is about 5.6.

Identification Determine the infrared spectra of Secobarbital and secobarbital RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity ***Isomer content***—Weigh accurately about 0.3 g of Secobarbital, dissolve in 5 mL of sodium hydroxide solution (1 in 100), add a solution prepared by dissolving 300 ± 5 mg of 4-nitrobromobenzyl in 10 mL of ethanol(95), and reflux for 30 minutes. After cooling, filter the formed precipitates through a small filter, and wash well with water. Recrystallize the precipitates with 25 mL of ethanol(95), and dry at 105 ℃ for 30 minutes; the melting point is between 156 and 161 ℃.

Loss on drying NMT 1.0% (1 g, silica gel, 18 hours).

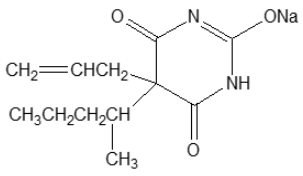
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.45 g of Secobarbital, and dissolve in 60 mL of dimethylformamide. While stirring to mix and avoiding absorption of carbon dioxide in the air, titrate with 0.1 mol/L sodium methoxide VS (indicator: 4 drops of thymol blue TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium methoxide VS
= 23.828 mg of $C_{12}H_{18}N_2O_3$

Packaging and storage Preserve in tight containers.

Secobarbital Sodium
세코바르비탈나트륨



$C_{12}H_{17}N_2NaO_3$: 260.27

4,6-Dioxo-5-(pentan-2-yl)-5-(prop-2-en-1-yl)-1,4,5,6-tetrahydropyrimidin-2-olate [*309-43-3*]

Secobarbital Sodium contains NLT 98.5% and NMT 100.5% of secobarbital sodium ($C_{12}H_{17}N_2NaO_3$), calculated on the dried basis.

Description Secobarbital Sodium occurs as a white powder. It is odorless and has a bitter taste.

It is very soluble in water, soluble in ethanol(95) and practically insoluble in ether.

It is hygroscopic.
A solution of Secobarbital Sodium is decomposed when allowed to stand, and the decomposition is accelerated when heated.

Identification (1) Determine the infrared spectra of respective solutions of the residue obtained under Assay and Secobarbital RS in chloroform as directed under the solution method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Ignite about 0.5 of Secobarbital Sodium. The residue exhibits bubbles when acid is added and responds to the Qualitative Analysis for sodium salt.

pH Dissolve 1.0 g of Secobarbital Sodium in 10 mL of water. The pH of this solution is between 9.7 and 10.5.

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Secobarbital Sodium in 10 mL of freshly boiled and cooled water, and examine after 1 minute; the solution is clear with no insoluble substances.

(2) ***Heavy metals*—**Proceed with 1.0 g of Secobarbital Sodium as directed under Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(3) ***Isomer content*—**Weigh accurately about 0.3 g of Secobarbital Sodium, dissolve in 5 mL of sodium hydroxide solution (1 in 100), add a solution prepared by dissolving 0.3 g of 4-nitrobromobenzyl in 10 mL of ethanol(95), and reflux for 30 minutes. After cooling, filter the formed precipitates through a small filter, and wash well with water. Recrystallize the precipitates with 25 mL of ethanol(95), and dry at 105 ℃ for 30 minutes; the melting point is between 156 and 161 ℃.

Bacterial endotoxins Less than 0.9 EU/mg of secobarbital sodium, when used in a non-oral preparation without a further procedure for the removal of bacterial endotoxins.

Loss on drying NMT 3.0% (1 g, 80 ℃, 5 hours).

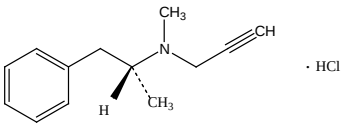
Assay Weigh accurately about 0.5 g of Secobarbital Sodium, and dissolve in 15 mL of water in a separatory funnel. To this, add 2 mL of hydrochloric acid, and shake well to mix. Extract the isolated secobarbital 8 times with 25 mL each of chloroform. To test for completion of the extraction, perform extraction with 10 mL of chloroform once more and then evaporate the solvent. The residue is NMT 0.5 mg. Filter the chloroform extract in a beaker, previously measured in the mass, and wash the separatory funnel and filter with a small amount of chloroform multiple times to filter. Combine the filtrate and washings, and evaporate to dryness on a steam bath while passing the air. To the residue, add 2 mL of ethanol(99.5), and evaporate to dryness. Again, add 2 mL of ethanol(99.5) to evaporate to dryness, and dry at 100 ℃ for 2 hours. After cooling, measure the mass.

Amount (mg) of secobarbital sodium ($C_{12}H_{17}N_2NaO_3$)

= Mass (mg) of residue × 1.092

Packaging and storage Preserve in tight containers.

Selegiline Hydrochloride
셀레길린염산염



$C_{13}H_{17}N \cdot HCl$: 223.74

(2*R*)-*N*-Methyl-*N*-prop-2-yn-1-yl-1-phenyl-propan-2-amine hydrochloride [*14611-52-0*]

Selegiline Hydrochloride contains NLT 98.0% and NMT 101.0% of selegiline hydrochloride ($C_{13}H_{17}N \cdot HCl$), calculated on the dried basis.

Description Selegiline Hydrochloride occurs as a white crystalline powder and is odorless.
It is freely soluble in water, chloroform or methanol.

Identification (1) Determine the absorption spectra of aqueous solutions of Selegiline Hydrochloride and selegiline hydrochloride RS (1 in 2000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Selegiline Hydrochloride and selegiline hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

(4) An aqueous solution of Selegiline Hydrochloride (1 in 50) responds to the Qualitative Analysis (2) for chloride.

Optic rotation $[\alpha]_D^{20}$: Between -10° and -12° (2.0 g, calculated on the dried basis, water, 20 mL, 100 mm).

Melting point Between 141 and 145 ℃.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Selegiline Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Weigh accurately about 50 mg of Selegiline Hydrochloride, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, to 10.0 mL of the system suitability solution, add the mobile phase to make exactly 100 mL, add the mobile phase to 10.0 mL of this solution to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the

Liquid Chromatography according to the following conditions, and determine peak areas of each solution by the automatic integration method. Each related substances in the test solution is NMT 0.2% and the total amount of related substances is NMT 1.0%.

$$\text{Content (\%) of related substances} = 5000 \times \frac{C}{W} \times \frac{A_1}{A_S}$$

C: Concentration (mg/mL) of selegiline hydrochloride in the standard solution

W: Amount (mg) of Selegiline Hydrochloride taken

A_i: Peak area of each related substances obtained from the test solution

A_S: Peak area of selegiline obtained from the standard solution

Operating conditions

For the detector, column, mobile phase, flow rate, and system compatibility solution, proceed as directed in the operating conditions under the Assay.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the resolution between methamphetamine and selegiline peaks is NLT 3.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of selegiline is NMT 5.0%.

Time span of measurement: 3 times the range of retention time of selegiline.

Loss on drying NMT 1.0% (1 g, 60 ℃, in vacuum, 3 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 50 mg each of Selegiline Hydrochloride and selegiline hydrochloride RS, dissolve in the mobile phase to make exactly 50 mL, add the mobile phase to 10.0 mL of these solutions to make exactly 100 mL, and use these solutions as the text solution and the standard solution. Perform the test with 20 μL of each of these solutions as directed under the Liquid Chromatography according to the following conditions, and determine the areas A_T and A_S of the major peak of each solution.

$$\text{Amount (mg) of selegiline hydrochloride } (C_{13}H_{17}N\cdot HCl) = \text{amount (mg) of selegiline hydrochloride RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of ammonium phosphate buffer solution and acetonitrile (80:20).

Flow rate: 1 mL/min

System suitability

System performance: Dissolve 10 mg of methamphetamine hydrochloride RS and 10 mg of selegiline hydrochloride RS in the mobile phase to make exactly 100 mL, and use this solution as the system suitability solution. With 20 μL of this solution, proceed according to the above conditions; the resolution between methamphetamine and selegiline peaks is not less 3.

System repeatability: Repeat the test 5 times with 20 μL each of the system suitability solution according to the above conditions; the relative standard deviation of the peak areas of selegiline is NMT 2.0%.

Ammonium phosphate buffer solution—Prepare 0.1 mol/L ammonium dihydrogen phosphate solution, and adjust the pH to 3.1 with phosphoric acid.

Packaging and storage Preserve in light-resistant, tight containers.

Selenium Powder 0.1%
셀레늄 가루0.1%

Selenium Powder 0.1% contains NLT 1 mg of selenium (Se : 78.96) per g.

Method of preparation Transfer 9.976 g of calcium hydrogen phosphate hydrate to a clean glass or plastic container, add 1000 mL of purified water (45 °C) and 24 g of sodium selenate, and dissolve it completely by stirring. Add this solution slowly into the mixer, and mix at a low speed. Dry in an oven until the water content reaches between 1% and 2%, grind the residue using a grinder, and pass it through a No. 16 sieve.

Description Selenium Powder 0.1% occurs as a white to grayish white powder and is odorless.

Identification (1) ***Calcium***—To 5 mL of an aqueous solution of Selenium Powder 0.1% (1 in 20), add 2 drops of methyl red TS (indicator), and neutralize with ammonia TS. Add dilute hydrochloric acid until the solution becomes acidic, and add ammonium hydroxide TS; a white precipitate is produced. The precipitate does not dissolve in acetic acid(100) and dissolves in hydrochloric acid. Moisten the precipitate with hydrochloric acid and place into the colorless flame of a Bunsen burner; it exhibits a yellowish red color.

(2) ***Phosphate***—To a neutral solution of Selenium Powder 0.1%, add silver nitrate TS: a yellow precipitate is produced. Add dilute nitric acid or ammonia TS subsequently; the precipitate dissolves.

(3) ***Sodium***—Place a small amount of Selenium Powder 0.1% into the colorless flame of a Bunsen burner; it exhibits a yellow color.

(4) Perform the test with Selenium Powder 0.1% and selenium powder 0.1% RS as directed under the Assay; the absorption spectrum of the test solution exhibits maxima at the same wavelengths as that of the standard solution.

Purity ***Lead***—Weigh 2.0 g of Selenium Powder 0.1% and perform the test as directed under the lead test in the US Pharmacopeia. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

Loss on drying NMT 3.0% (1 g, 105℃, 2 hours)

Assay Weigh accurately 0.5 g of Selenium Powder 0.1%, transfer to a 250-mL Erlenmeyer flask, add 5 mL of hydrochloric acid, 5 mL of nitric acid and 30 mL of water, and heat on a hot plate until it dissolves completely. After cooling, transfer the solution to a 200-mL volumetric flask, add diluent to make 200 mL, and use this solution as the test solution. Separately, weigh accurately about 1.0 g of selenium RS, transfer to a 100-mL volumetric flask, dissolve in 1 mL of dilute nitric acid (1 in 2) (warming gently, if necessary), add water to make 100 mL, and shake to mix. With this solution, prepare as follows and use the solution as the standard solution.

Element Name	Concentration of the standard solution (μg/mL)		
	High concentration	Medium concentration	Low concentration
Selenium	50	25	1

With the test solution and the standard solution, perform the test according to the Inductively Coupled Plasma Spectrochemistry at a wavelength of 196.03 nm, construct a calibration curve from the standard solution, and determine the concentration (μg/mL) of the test solution from the calibration curve.

$$\text{Content (\%) of selenium (Se)} = \frac{\text{Concentration (ppm) of selenium}}{\text{Amount (g) of sample taken}} \times \frac{1.0\ \text{g}}{5\ \text{(ppm)}} \times 100$$

5 ppm: A theoretical concentration of selenium per g of sample for 1.0 g of Selenium Powder 0.1% diluted 200 times.

Diluent—A mixture of 2% nitric acid and 6% hydrochloric acid (1 : 1).

Packaging and storage Preserve in tight containers.

Selenium in Dried Yeast
셀레늄함유건조효모

Selenium in Dried Yeast is obtained by cultivating yeast in a medium containing selenium and organically binding selenium to the yeast. Selenium in Dried Yeast contains NLT 540 μg of selenium (Se: 78.96) per g of the labeled amount.

Description Selenium in Dried Yeast occurs as yellowish brown to brown powder and has a yeast-like odor and taste.

Identification Weigh about 0.1 g of Selenium in Dried Yeast, add 10 mL of nitric acid, and heat at 60 °C for 10 minutes. Add 10 mL of water and 5 g of urea to this solution, heat to boiling, cool, and add 2 mL of potassium iodide solution (1 in 10); it exhibits a golden yellow to orange color and soon becomes dark.

Loss on drying NMT 7.0% (1 g, 100 °C, 5 hours).

Microbiological examination of non-sterile products The total aerobic microbial count is NMT 7,500 per g of Selenium in Dried Yeast.

Nitrogen NLT 8.0% (30 mg) (Nitrogen Determination).

Assay Weigh accurately Selenium in Dried Yeast, equivalent to about 0.1 mg of selenium and perform the test according to the selenium assay under the Analysis for Minerals.

Packaging and storage Preserve in light-resistant, tight containers.

Selenium in Dried Yeast and Tocopherol Acetate Capsules
셀레늄함유건조효모·
토코페롤아세테이트 캡슐

Selenium in Dried Yeast and Tocopherol Acetate Capsules contain NLT 90.0% and NMT 150.0% of the labeled amount of selenium (Se: 78.96) and tocopherol acetate ($C_{31}H_{52}O_3$: 472.75).

Method of preparation Prepare as directed under Capsules, with Selenium in Dried Yeast and Tocopherol Acetate.

Identification (1) ***Selenium in selenium in dried yeast***—Weigh an amount of Selenium in Dried Yeast and Tocopherol Acetate Capsules, equivalent to about 1 mg of selenium, according to the labeled amount, and perform the test as directed under the Analysis for Minerals.

(2) ***Tocopherol acetate***—Perform the test with Selenium in Dried Yeast and Tocopherol Acetate Capsules as directed under the Analysis for Vitamins.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Selenium in selenium in dried yeast***—Weigh accurately the mass of the contents of NLT 20 Selenium in Dried Yeast and Tocopherol Acetate Capsules, and perform the test as directed under the selenium assay of the Analysis for Minerals.

(2) ***Tocopherol acetate***—Weigh accurately the mass of the contents of NLT 20 Selenium in Dried Yeast and Tocopherol Acetate Capsules. Weigh accurately an amount equivalent to about 0.1 g of tocopherol acetate ($C_{31}H_{52}O_3$), and perform the test as directed under the tocopherol acetate assay of the Analysis for Vitamins.

Packaging and storage Preserve in tight containers.

Selenium in Dried Yeast, Chromium in Dried Yeast and Ascorbic Acid Capsules
셀레늄함유건조효모·크롬함유건조효모·아스코르브산 캡슐

Selenium in Dried Yeast, Chromium in Dried Yeast and Ascorbic Acid Capsules contain NLT 90.0% and NMT 150.0% of the labeled amount of selenium (Se: 78.96) in selenium in dried yeast, chromium (Cr: 52.00) in chromium in dried yeast, and ascorbic acid (C_6H8O_6: 176.13).

Method of preparation Prepare as directed under Capsules, with Selenium in Dried Yeast, Chromium in Dried Yeast, and Ascorbic Acid.

Identification (1) ***Selenium in selenium in dried yeast, chromium in chromium in dried yeast***—Perform the test with Selenium in Dried Yeast, Chromium in Dried Yeast and Ascorbic Acid Capsules as directed under the Analysis for Minerals.

(2) ***Ascorbic acid***—Perform the test with Selenium in Dried Yeast, Chromium in Dried Yeast and Ascorbic Acid Capsules as directed under the Analysis for Vitamins.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Selenium in selenium in dried yeast and chromium in chromium in dried yeast***—Weigh accurately the mass of contents of NLT 20 Selenium in Dried Yeast, Chromium in Dried Yeast and Ascorbic Acid Capsules, and perform the test as directed under the Assay for each component of the Analysis for Minerals.

(2) ***Cyanocobalamin***—Weigh accurately the mass of contents of NLT 20 Selenium in Dried Yeast, Chromium in Dried Yeast and Ascorbic Acid Capsules, and perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in well-closed containers.

Selenium Sulfide
황화셀레늄

Selenium Sulfide SeS_2: 143.09
[*7488-56-4*]

Selenium Sulfide contains NLT 52.0% and NMT 55.5% of selenium (Se: 78.96).

Description Selenium Sulfide occurs as reddish brown to orange crystals. It has a slight odor.
It is practically insoluble in water or organic solvents.

Identification (1) Filter 20 mL of the test solution from the Assay. To 10 mL of the filtrate, add 5 mL of water and 5 g of urea, and heat to boiling. After cooling, add 2 mL of potassium iodide solution (1 in 10); it exhibits an orange color, and the color immediately changes to a dark color.

(2) Allow to stand the solution obtained from (1) for 10 minutes, and then filter. To the filtrate, add 10 mL of barium chloride TS; the resulting solution is turbid.

Purity ***Soluble selenium compound***—Transfer 10.0 g of Selenium Sulfide into a 250-mL volumetric flask, add water, and shake to mix. Allow to stand for 1 hour while shaking occasionally, and filter. Pipet 10 mL of the filtrate, add 2 mL of 2.5 mol/L formic acid, add 50 mL of water, and shake to mix. Adjust the pH to 2.5 ± 0.5 if necessary. To this solution, add 2 mL of freshly prepared 3,3'-diaminobenzidine tetrahydrochloride solution (1 in 200), mix well, allow to stand for 45 minutes, and add ammonia TS to adjust the pH to 6.5 ± 0.5. Transfer this solution into a separatory funnel, add exactly 10 mL of toluene, and shake vigorously for 1 minute to mix. Discard the water layer, take the toluene layer, and use this solution as the test solution. Separately, pipet 50 mL of selenium standard stock solution, and add water to make 100 mL. Pipet 10 mL of this solution, add 2 mL of 2.5 mol/L formic acid, and proceed in the same manner as the test solution. Use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy. Without adding the test solution, the standard solution and Selenium Sulfide, proceed in the same manner as the test solution to make the blank test solution. Determine the absorption at a wavelength of 420 nm of the test solution and the standard solution as directed wavelength Ultraviolet-visible Spectroscopy using the blank test solution as the control solution (NMT 5 ppm).

Residue on ignition NMT 0.2% (1 g).

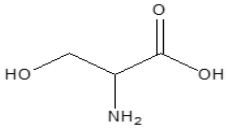
Assay Weigh accurately about 0.1 g of Selenium Sulfide, add 25 mL of fuming nitric acid, and decompose until it does not dissolve by gently heating. After cooling,

transfer this solution into a 250-mL volumetric flask filled with 100 mL of water, cool again, and add water to the gauge line to mix. Transfer 50 mL of this solution into a flask, add 25 mL of water and 10 g of urea, and heat to boiling. After cooling, add 3 mL of starch TS and 10 mL of potassium iodide solution (1 in 10), and immediately titrate with 0.05 mol/L sodium thiosulfate VS. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L sodium thiosulfate VS
= 0.987 mg of Se

Packaging and storage Preserve in well-closed containers.

DL-Serine
DL-세린



$C_3H_7NO_3$: 105.09
2-Amino-3-hydroxypropionic acid, [*302-84-1*]

DL-Serine, when dried, contains NLT 98.0% and NMT 102.0% of DL-serine ($C_3H_7NO_3$).

Description DL-Serine occurs as white crystals or a crystalline powder.
It is freely soluble in water and insoluble in ethanol(95) and in ether.

Melting point—About 246 ℃.

Identification To 5 mL of an aqueous solution of DL-Serine (1 in 1000), add 1 mL of 0.2% ninhydrin TS; the solution exhibits a bluish purple or violet color.

Purity (1) ***Arsenic*—**Proceed with 0.67 g of DL-Serine as directed under Method 3 and perform the test (NMT 3 ppm).

(2) ***Heavy metals*—**Proceed with 1.0 g of DL-Serine as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Loss on drying NMT 0.3% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 250 mg of DL-Serine, previously dried, add 25 mL of water, and heat on a steam bath to dissolve. After cooling, add 50 mL of water, add 2 to 3 drops of phenolphthalein TS, and titrate with 0.1 mol/L sodium hydroxide VS. The endpoint of titration is when the pink color persists for NLT 30 seconds. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 10.51 mg of C3H7NO3

Packaging and storage Preserve in tight containers.

Silver Nitrate
질산은

$AgNO_3$: 169.87

[*7761-88-8*]

Silver Nitrate, when dried, contains NLT 99.8% and NMT 101.0% of silver nitrate ($AgNO_3$).

Description Silver Nitrate occurs as lustrous, colorless or white crystals.
It is very soluble in ethanol(95) and practically insoluble in ether.
It is gradually colored to gray to blackish gray by light.

Identification An aqueous solution of Silver Nitrate (1 in 50) responds to the Qualitative Analysis for silver salt and nitrate.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Silver Nitrate in 10 mL of freshly boiled and cooled water; the solution is colorless, clear and neutral.

(2) ***Bismuth, copper and lead***—To 5 mL of an aqueous solution of Silver Nitrate (1 in 10), add 3 mL of ammonia TS; the solution is colorless and clear.

Loss on drying NMT 0.2% (2 g, silica gel, light-resistant, 4 hours).

Assay Weigh accurately about 0.7 g of Silver Nitrate, previously powdered and dried, dissolve in 50 mL of water, add 2 mL of nitric acid, and titrate with 0.1 mol/L ammonium thiocyanate VS (indicator: 2 mL of ammonium iron(III) sulfate TS).

Each mL of 0.1 mol/L ammonium thiocyanate VS
= 16.987 mg of $AgNO_3$

Packaging and storage Preserve in light-resistant, tight containers.

Silver Protein
프로테인은

Silver Protein contains NLT 7.5% and NMT 8.5% of silver (Ag: 107.87), calculated as a compound of silver and protein.

Description Silver Protein occurs as a pale yellowish brown to brown powder. It is odorless.
1 g of Silver Protein is slowly soluble in 2 mL of water,

and practically insoluble in ethanol(95), ether or chloroform.
The pH of a solution of 1.0 g of Sliver Protein dissolved in 10 mL of water is between 7.0 and 8.5.
It is slightly hygroscopic.
It is affected by light.

Identification (1) To 10 mL of an aqueous solution of Sliver Protein (1 in 100), add 2 mL of dilute hydrochloric acid, shake occasionally to mix for 5 minutes, and then filter. Add 5 mL of sodium hydroxide solution (1 in 10) to the filtrate, add 2 mL of diluted copper(II) sulfate TS (2 in 25); the resulting solution exhibits a violet color.

(2) To 5 mL of an aqueous solution of Silver Protein (1 in 100), add iron(III) chloride TS dropwise; the color of the solution fades and a precipitate slowly forms.

(3) Ignite 0.2 g of Silver Protein to incinerate, add 1 mL of nitric acid to the residue, heat to dissolve, and add 10 mL of water; the resulting solution responds to the Qualitative Analysis (1) for silver salt.

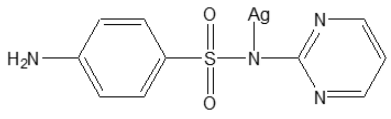
Purity ***Silver salt***—Dissolve 0.10 g of Silver Protein in 10 mL of water, filter, and add 1 mL of potassium chromate TS to the filtrate; the solution does not become turbid.

Assay Weigh accurately about 1 g of Silver Protein, put it to a 100-mL decomposition flask, add 10 mL of sulfuric acid, and boil under a funnel for 5 minutes. After cooling, carefully put 3 mL of nitric acid dropwise, and heat without boiling for 30 minutes. After cooling, add 1 mL of nitric acid and boil. If necessary, repeat this procedure until the solution is colorless when cooled. After cooling, transfer this solution to a 250-mL Erlenmeyer flask using 100 mL of water, and titrate with 0.1 mol/L ammonium thiocyanate VS (indicator: 3 mL of ammonium iron(III) sulfate TS).

Each mL of 0.1 mol/L ammonium thiocyanate VS
= 10.787 mg of Ag

Packaging and storage Preserve in light-resistant, tight containers.

Silver Sulfadiazine
설파디아진은



$C_{10}H_9AgN_4O_2S$: 357.14
Silver *N*-(4-aminobenzene)sulfonyl-*N'*-(pyrimidin-2-yl)azanide [*22199-08-2*]

Silver Sulfadiazine, when dried, contains NLT 99.0% and NMT 102.0% of silver sulfadiazine ($C_{10}H_9AgN_4O_2S$).

Description Silver Sulfadiazine occurs as a white to pale yellow crystalline powder. It is odorless.
It is practically insoluble in water, ethanol(95) or ether.
It is soluble in ammonia TS.
It is gradually colored by light.

Melting point—About 275 °C (with decomposition).

Identification Determine the infrared spectra of Silver Sulfadiazine and silver sulfadiazine RS, previously dried, as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Nitrate***—Weigh 1.0 g of Silver Sulfadiazine, add 250 mL of water, and shake for 50 minutes to mix. Filter it and use the filtrate as the test solution. Separately, weigh accurately 0.25 g of potassium nitrate and dissolve in water to make 2000 mL. Pipet 5 mL of this solution, add water to make exactly 200 mL, and use this solution as the standard solution. Take 2.0 mL each of the test solution and the standard solution, and add 5 mL of a solution of chromotropic acid in sulfuric acid (1 in 10000) and sulfuric acid to make exactly 10 mL. Separately, perform the test with these solutions as directed under the Ultraviolet-visible Spectroscopy, using a solution prepared by taking exactly 2.0 mL of water and proceeding in the same manner as the control solution, and determine the absorbances, A_T and A_S, at 408 nm of wavelength; A_T is not greater than A_S (NMT 0.05%).

(2) ***Related substances***—Dissolve 50 mg of Silver Sulfadiazine in 5 mL of a mixture of ethanol(95) and ammonia water(28) (3:2), and use this solution as the test solution. Pipet 2 mL of this solution and add a mixture of ethanol(95) and ammonia water(28) (3:2) to make exactly 20 mL. Pipet 2 mL of this solution, add a mixture of ethanol(95) and ammonia water(28) (3:2) to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography (fluorescent indicator added). Next, develop the plate with a mixture of chloroform, methanol, and ammonia water(28) (10:5:2) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet rays (main wavelength: 254 nm); the spots other than the principal spot and the spot of the starting point obtained from the test solution are not more intense than the principal spots from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, phosphorus pentoxide, 80 °C, 4 hours).

Residue on ignition Between 41.0 and 45.0% (1 g).

Silver content Weigh accurately about 50 mg of Silver Sulfadiazine, previously dried, dissolve in 2 mL of nitric acid, and add water to make exactly 100 mL. Pipet 1 mL of this solution, add water to make exactly 100 mL, and

use this solution as the test solution. Separately, pipet an appropriate amount of the standard silver solution for atomic absorption spectroscopy, make 1.0 to 2.0 μg of silver per mL (Ag: 107.87), and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the atomic absorption spectroscopy according to the following conditions, and calculate the content of silver using the calibration curve made from the absorbance of the standard solution; NLT 28.7% and NMT 30.8%.

Gas: Air–acetylene
Lamp: Hollow cathode lamp
Wavelength: 328.1 nm

Assay Weigh accurately about 0.1 g each of Silver Sulfadiazine and silver sulfadiazine RS, previously dried, and dissolve in ammonia TS to make exactly 100 mL. Pipet 1 mL each of this solution, add water to make exactly 100 mL, and use these solutions as the test solutions and the standard solutions. With these solutions, pipet 1 mL of ammonia TS and add water to make exactly 100 mL, and determine the absorbances, A_T and A_S, at 255 nm of wavelength, using the resulting solution as the control solution.

Amount (mg) of silver sulfadiazine ($C_{10}H_9AgN_4O_2S$)
= Amount (mg) of silver sulfadiazine RS × $\frac{A_T}{A_S}$

Packaging and storage Preserve in light-resistant, tight containers.

Simaldrate
시말드레이트

Simaldrate contains NLT 18.1% and NMT 22.1% of aluminum oxide (Al_2O_3: 101.96) and NLT 12.9% and NMT 18.1% of magnesium oxide (MgO: 40.30), calculated on the dried basis.

Description Simaldrate occurs as a white powder or grains, and is odorless and tasteless.
It is practically insoluble in water or in ethanol(95).
To 1 g of Simaldrate, add 10 mL of dilute hydrochloric acid and heat; almost all is dissolved.

Identification (1) To 0.5 g of Simaldrate, add 5 mL of dilute sulfuric acid (1 in 3), heat until white smoke is evolved, cool, add 20 mL of water, and filter (use the residue for Identification (3)). Add ammonia TS to the filtrate to neutralize; a precipitation is formed. Filter this precipitation (use the filtrate for Identification (2)). The solution obtained by adding dilute hydrochloric acid to residue responds to the Qualitative Analysis for aluminum salt.

(2) The filtrate of Identification (1) responds to the Qualitative Analysis for magnesium salt.

(3) Wash the residue obtained in Identification (1) with 30 mL of water, add 2 mL of methylene blue solution (1 in 10000), and then wash with another 30 mL of water; the precipitate exhibits a blue color.

Purity (1) ***Soluble salts***—To 10 g of Simaldrate, add 150 mL of water and slowly boil for 15 minutes, while shaking well to mix. After cooling, add water to make 150 mL and centrifuge. Take 75 mL of the supernatant, add water to make 100 mL, and use this solution as the test solution. Take 25 mL of the test solution, evaporate it to dryness on a steam bath, and ignite it again at 700 ℃ for 2 hours; the amount is NMT 20 mg.

(2) ***Alkalinity***—Take 20 mL of the test solution from (1) and add 2 drops of phenolphthalein TS and 0.5 mL of 0.01 mol/L hydrochloric acid VS; the resulting solution is colorless.

(3) ***Chloride***—Take 10 mL of the test solution from (1) and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test as directed under the Chloride. Prepare the control solution with 0.75 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.053%).

(4) ***Sulfate***—Take 2 mL of the test solution from (1) and add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid VS (NMT 0.48%).

(5) ***Heavy metals***—Weigh 1.0 g of Simaldrate, add 20 mL of water and 3 mL of hydrochloric acid, and evaporate to dryness on a steam bath. To the residue, add 2 mL of dilute acetic acid and 20 mL of water, boil for 2 minutes, filter, and wash the residue twice each time with 5 mL of water. Combine the filtrate and the washings, add 0.15 g of hydroxylamine hydrochloride, and heat to boil. After cooling, add 0.15 g of sodium acetate and water to make 50 mL. Use this solution as the test solution and perform the test as directed under the Heavy Metals. Evaporate 3 mL of hydrochloric acid to dryness on a steam bath. To the residue, add 3.0 mL of lead standard solution, 0.15 g of hydroxylamine hydrochloride, 0.15 g of sodium acetate and 2 mL of dilute acetic acid, and water to make 50 mL. Use this solution as the control solution (NMT 30 ppm).

(6) ***Iron***—Weigh 0.2 g of Simaldrate, add 8 mL of dilute hydrochloric acid, and boil for 1 minute. After cooling, add acetate-sodium acetate buffer solution (pH 4.5) for iron test to make 50 mL and centrifuge. Take 25 mL of the supernatant, add acetic acid-sodium acetate buffer solution (pH 4.5) to make 30 mL, and use this solution as the test solution. Perform the test according to Method A as directed under the Iron test methods under the General Tests.

Control solution—To 3 mL of standard iron standard solution, add 4 mL of dilute hydrochloric acid and acetate-sodium acetate buffer solution (pH 4.5) for iron test to make 30 mL. Proceed with this solution as the standard solution in the same way as in the preparation of the test solution.

(7) ***Arsenic***—Weigh 0.40 g of Simaldrate, add 10 mL of water and 1 mL of sulfuric acid, shake well to mix, cool, and use this solution as the test solution. Perform the test as directed under the Arsenic (NMT 5 ppm).

Loss on drying NMT 20.0% (1 g, 110 ℃, 7 hours).

Acid-neutralizing capacity Weigh accurately about 0.2 g of Simaldrate and transfer into a stoppered Erlenmeyer flask. Add exactly 100 mL of 0.1 mol/L hydrochloric acid VS, close the flask with a stopper, shake to mix at 37 ± 2 ℃ for 1 hour, and filter. Take 50.0 mL of the filtrate and titrate the excess hydrochloric acid with 0.1 mol/L sodium hydroxide VS, while shaking well to mix, until the pH becomes 3.5. 1 g of Simaldrate, calculated on the dried basis, consumes NLT 190 mL of 0.1 mol/L hydrochloric acid.

Assay (1) ***Aluminum oxide***—Weigh accurately about 0.5 g of Simaldrate, add 3.5 mL of dilute hydrochloric acid and 30 mL of water, and heat on a steam bath for 15 minutes. Add another 3.5 mL of hydrochloric acid, heat on a steam bath for 10 minutes, cool, and add water to make exactly 200 mL. Centrifuge this solution and use the supernatant as the test solution. Pipet 20 mL of the test solution, add exactly 20 mL of 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS, add 8 mL of acetic acid-ammonium acetate buffer solution (pH 4.8) and 20 mL of water. After boiling for 5 minutes and cooling, add 50 mL of ethanol(95) and titrate with 0.02 mol/L zinc sulfate VS (indicator: 2 mL of dithizone TS). However, The endpoint of the titration is when the color of the solution changes from pale dark green to pale red. Perform a blank test in the same manner and make any necessary correction.

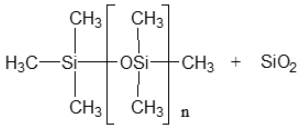
Each mL of 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS = 1.020 mg of Al_2O_3

(2) ***Magnesium oxide***—Pipet 50 mL of the test solution from Assay (1), add 50 mL of water and 10 mL of triethanolamine solution (1 in 2), and shake well to mix. Next, add 5 mL of ammonia-ammonium chloride buffer solution (pH 10.7) and titrate with 0.02 mol/L ethylenediaminetetraacetic disodium salt VS (indicator: 40 mg of eryochrome black T-sodium chloride indicator). However, The endpoint of the titration is when the color of the solution changes from reddish purple to blue and the blue color remains for 30 seconds. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.02 mol/L ethylenediaminetetraacetic acid disodium salt VS = 0.8060 mg of MgO

Packaging and storage Preserve in tight containers.

Simethicone
시메티콘



Poly(dimethylsiloxane), silicon dioxide [*8050-81-5*]

Simethicone is a mixture of methylated linear siloxane polymers containing repeating units of polydimethylsiloxane ($[-(CH_3)_2SiO-]_n$), stabilized with trimethylsiloxy ($[(CH_3)_3SiO-]$) as end-blocking units, and silicon dioxide. Simethicone contains NLT 90.5% and NMT 99.0% of polydimethylsiloxane ($[-(CH_3)_2SiO-]_n$), and NLT 4.0% and NMT 7.0% of silicon dioxide.

Description Simethicone occurs as a gray translucent, viscous liquid.
It is insoluble in water or ethanol(95).
The liquid phase is soluble in chloroform, ether and benzene but silicon dioxide remains as a residue in these solvents.

Identification Determine the absorbances of the test solution and the standard solution prepared according to the Assay using 0.5 mm cell as directed under the solution method under the Mid-infrared Spectroscopy; both spectra similar intensities of absorption at the same wavenumbers.

Purity ***Heavy metals***—Weigh 1.0 g of Simethicone, put in10 mL of chloroform to mix, and add additional chloroform to make 20 mL. Add 1.0 mL of a freshly prepared 0.002% solution of dithizone in chloroform, 0.5 mL of water and 9.5 mL of a mixture of ammonia TS and 0.2% solution of hydroxylamine hydrochloride (1 : 9), and use this solution as the test solution. Separately, add 1.0 mL of a freshly prepared 0.002% solution of dithizone in chloroform to 20 mL of chloroform, 0.5 mL of lead standard solution (10 μg/mL) and 0.5 mL of a mixture of ammonia TS and 0.2% solution of hydroxylamine hydrochloride (1 : 9), and use this solution as the standard solution. Shake vigorously these solutions for 1 minute, immediately; the red color of the test solution is not more intense than that of the standard solution. (NMT 5 μg/g).

Loss on drying NMT 18.0% (15.0 g, 200 °C, 4 hours).

Defoaming activity Dissolve 1.0 g of octoxynol 9 in 100 mL of water and use this solution as the foaming solution. Weigh accurately 0.2 g of simethicone and transfer into a 60-mL bottle. Add 50 mL of *t*-butyl alcohol, stopper the bottle, shake vigorously, and use this solution as the test solution. Warm the solution slightly, if necessary. Add 0.5 mL of the test solution dropwise to a clean, cylindrical 250-mL glass jar, fitted with a 50-mm cap, containing 100 mL of the foaming solution. Stopper the jar and clamp it in an upright position on a wrist-action

shaker, and then use a radius of 13.3 ± 0.4 cm (measured from center of shaft to center of bottle) and shake for 15 seconds with an arc of 10° per second at a frequency of 300 ± 30 strokes per minute. Record the time required for the foam to collapse. The time for the foam to collapse is determined at the instant the first portion of foam-free liquid surface appears, measured from the end of the shaking period. The defoaming activity time does not exceed 15 seconds.

Content of silicon dioxide Take 3.00 g each of Simethicone, simethicone RS and dimethicone (500 mm^2/s) into a screw-capped bottle, add 10.0 mL of *n*-hexane, stopper, and shake to mix. Use these solutions as the test solution, the standard solution, and the dimethicone solution, respectively. Perform the test with these solutions as directed under the solution method under the Mid-infrared Spectroscopy. Using fixed cells 0.1-mm in thickness, determine at the wavelength of 7 to 9 μm using *n*-hexane as the control solution. Determine the absorbances of the test solution, the standard solution and the dimethicone solution at the minimum absorbance wavelength of about 8.2 μm, obtained from the spectrum of the dimethicone solution.

$$\text{Content (\%) of silicon dioxide in simethicone} = \text{Content (\%) of silicon dioxide in the simethicone RS} \times \frac{A_T - A_D}{A_S - A_D}$$

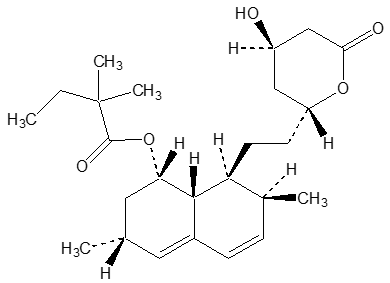
A_D: Absorbance of the dimethicone solution
A_T: Absorbance of the test solution
A_S: Absorbance of the standard solution

Assay Weigh accurately about 50 mg each of Simethicone and polydimethylsiloxane RS and transfer to a round, narrow-mouth, screw-capped, 120-mL flask, add 25.0 mL of toluene, and shake to disperse. Add 50 mL of diluted hydrochloric acid (2 in 5), stopper the bottle securely with a cap having an inert liner, and shake for 5 minutes, accurately timed, on a reciprocating shaker at a suitable rate about 200 oscillations per minute and a stroke of 38 ± 2 mm. Transfer the mixture to a 125-mL separatory funnel, and add about 5 mL of the upper toluene layer to a 15-mL screw-capped test tube containing 0.5 g of anhydrous sodium sulfate. Close the tube with a screw-cap having an inert liner, agitate vigorously, and centrifuge the mixture until a clear supernatant is obtained. Use these solutions as the test solution and the standard solution, respectively. Perform the test with these solutions as directed under the solution method under the Mid-infrared Spectroscopy using the control solution prepared by similarly proceeding 25.0 mL of toluene in the same manner as the test solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively at the absorbance maximum wavelength of about 7.9 μm, 0.5-mm in thickness.

$$\text{Amount (mg) of polydimethylsiloxane } ([-(CH_3)_2SiO-]_n) \text{ in simethicone} = \text{Concentration (mg/mL) of polydimethylsiloxane RS} \times \frac{A_T}{A_S} \times 25$$

Packaging and storage Preserve in tight containers.

Simvastatin
심바스타틴



$C_{25}H_{38}O_5$: 418.57
[(1*S*,3*R*,7*S*,8*S*,8*aR*)-8-[2-[(2*R*,4*R*)-4-Hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,6,7,8,8*a*-hexahydronaphthalen-1-yl] 2,2-dimethyl butanoate [*79902-63-9*]

Simvastatin contains NLT 98.0% and NMT 101.0% of simvastatin ($C_{25}H_{38}O_5$), calculated on the dried basis. Simvastatin may contain a suitable antioxidant.

Description Simvastatin occurs as a white powder.
It is freely soluble in methanol, ethanol(95) or chloroform, sparingly soluble in propylene glycol, very slightly soluble in hexane and practically insoluble in water.

Identification (1) Weigh 10 mg of Simvastatin and Simvastatin RS, respectively, dissolve in acetonitrile to make 100 mL, pipet 5.0 mL each of the solutions, and add acetonitrile to make 50 mL. Determine the absorption spectra of the solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Simvastatin and Simvastatin RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{25}$ Between +285° and +298° (after drying, 0.10 g, acetonitrile, 20 mL, 100 mm).

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Simvastatin in 10 mL of methanol; the resulting solution is clear and transparent. Also, perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at a wavelength of 440 nm is NMT 0.10.

(2) ***Heavy metals***—Proceed with 1.0 g of Simvastatin according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Weigh accurately about 30

mg of Simvastatin, dissolve in a mixture of acetonitrile and 0.01 mol/L potassium dihydrogen phosphate TS (pH 4.0) (3 : 2) to make exactly 20 mL, and use this solution as the test solution. With 5 μL of the test solution, perform the test as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of the test solution by the automatic integration method, and calculate the amount corresponding to each peak by the percentage peak area method; the amount of the related substance, having the relative retention times of 0.45, 0.80, 2.42, and 3.80 with respect to simvastatin, is NMT 0.2%, respectively, the amount of the related substance having the relative retention time of 2.38 is NMT 0.3%, the amount of the related substance having the relative retention time of 0.60 is NMT 0.4%, and each related substance other than simvastatin and other than those mentioned above is NMT 0.1%. The sum of the amounts of related substances other than simvastatin and the related substance having the relative retention time of about 0.60 with respect to simvastatin is NMT 1.0%.

Operating conditions

For the detector, column and column temperature, proceed as directed in the operating conditions under the Assay.

Mobile phase: Control the gradient elution by mixing mobile phases A and B with the ratio as directed under the following.

Mobile phase A: A mixture of diluted phosphoric acid (1 in 1000) and acetonitrile (1 : 1).

Mobile phase B: A solution of phosphoric acid in acetonitrile (1 in 1000).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 4.5	100	0
4.5 - 4.6	100 → 95	0 → 5
4.6 - 8.0	95 → 25	5 → 75
8.0 - 11.5	25	75

Flow rate: 3.0 mL/min

System suitability

System performance: Proceed as directed under the system suitability under the Assay.

Test for required detectability: Pipet 0.5 mL of the test solution, add a mixture of acetonitrile and 0.01 mol/L potassium dihydrogen phosphate TS (pH 4.0) (3 : 2) to make exactly 100 mL, and use this solution as the system suitability solution. Pipet 2 mL of the system suitability solution, and add a mixture of acetonitrile and 0.01 mol/L potassium dihydrogen phosphate TS (pH 4.0) (3 : 2) to make exactly 10 mL. Confirm that the peak area of simvastatin obtained from 5 μL of this solution is equivalent to 16 to 24% of that from the system suitability solution.

System repeatability: Repeat the test 6 times with 5 μL each of the system suitability solution under the above conditions; the relative standard deviation of the peak areas of simvastatin is NMT 1.0%.

Time span of measurement: About 5 times the retention time of simvastatin.

(4) ***Lovastatin***—Calculate the content (%) of lovastatin from the peak areas of the test solution and the standard solution, A_T and A_S, respectively, as directed under the Assay; the percentage of lovastatin is NMT 1.0%.

$$\text{Content (\%) of lovastatin} = 10000 \times \frac{C}{W} \times \frac{A_T}{A_S}$$

C: Concentration (mg/mL) of lovastatin RS in the standard solution

W: Amount (mg) of Simvastatin taken

Loss on drying NMT 0.5% (1.0 g, in vacuum, 60 ℃, 3 hours).

Residue on ignition NMT 0.1% (1.0 g).

Assay Weigh accurately about 30 mg each of Simvastatin and Simvastatin RS (previously determine the loss on drying in the same manner as Simvastatin), dissolve each in a mixture of acetonitrile and 0.01 mol/L potassium dihydrogen phosphate (pH 4.0) (3 : 2) to make exactly 20 mL, and use these solutions as the test solution and standard solution, respectively. Perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of simvastatin in each solution.

$$\text{Amount (mg) of simvastatin } (C_{25}H_{38}O_5) = W_S \times \frac{A_T}{A_S}$$

W_S: Amount (mg) of simvastatin RS, calculated on the dried basis

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 238 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 33 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of diluted phosphoric acid (1 in 1000) and acetonitrile (1 : 1).

Flow rate: Adjust the flow rate so that the retention time of simvastatin is about 3 minutes.

System suitability

System performance: Dissolve 3 mg of lovastatin in 2 mL of the standard solution. Proceed with 5 μL of this solution under the above operating conditions; lovastatin and simvastatin are eluted in this order with the resolution between these peaks being NLT 3.0.

System repeatability: Repeat the test 6 times with

5 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of simvastatin is NMT 1.0%.

Packaging and storage Preserve in well-closed containers filled with nitrogen gas.

Simvastatin Tablets
심바스타틴 정

Simvastatin Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of simvastatin ($C_{25}H_{38}O_5$: 418.57).

Method of preparation Prepare as directed under Tablets, with Simvastatin.

Identification Weigh an amount of Simvastatin Tablets, previously powdered, according to the labelled amount, equivalent to 2.5 mg of simvastatin, add 25 mL of acetonitrile, sonicate for 15 minutes, and centrifuge. Take 2 mL of the clear supernatant, add acetonitrile to make 20 mL, and determine the absorption spectrum at 229 nm as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima between 229 nm and 233 nm, between 236 nm and 240 nm and between 245 nm and 249 nm.

Purity ***Related substances*—**Weigh accurately and powder NLT 20 tablets of Simvastatin Tablets. Weigh an amount of the powder, equivalent to 50 mg of simvastatin, add 200 mL of diluent, and sonicate for 15 minutes. Add diluent to make exactly 250 mL and centrifuge. Take 5 mL of the clear supernatant, add diluent to make exactly 10 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add the diluent to make exactly 200 mL, and use this solution as the standard solution. Perform the test with each 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas in the spectra of each solution by the automatic integration method; the area of the peak eluted at a relative retention time of about 0.5 to simvastatin from the test solution is not greater than 1.6 times the simvastatin peak area from the standard solution (not greater than 0.8%); the area of the peak eluted at a relative retention time of about 2.0 to simvastatin from the test solution is not greater than the simvastatin peak area from the standard solution (not greater than 0.5%). The areas of the peaks other than the simvastatin peak from the test solution are not greater than that of the simvastatin peak from the standard solution. The total area of the peaks other than the simvastatin peak from the test solution is not greater than 4 times the simvastatin peak area from the standard solution (not larger than 2.0%).

Diluent—A mixture of acetonitrile and 0.05 mol/L acetate butter (pH 4.0) (4 : 1).

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

Time span of measurement: About 2.5 times the retention time of simvastatin after the solvent peak.

System suitability

Test for required detectability: Pipet 2 mL of the standard solution and add the mobile phase to make exactly 10 mL. Perform the test with 10 μL of this solution and confirm that the peak area of simvastatin from the test solution is between 14% and 26% of that of simvastatin from the standard solution.

Proceed with 10 μL of the standard solution according to the above operating conditions and perform the test; the number of theoretical plates and symmetry factor of the simvastatin peak are NLT 6000 and between 0.9 and 1.1, respectively.

System repeatability: Repeat the test 6 times with each 10 μL of the standard solution according to the above operating conditions; the relative standard deviation of the simvastatin peak areas is NMT 2.0%.

Dissolution Perform the test with 1 tablet of Simvastatin Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of the dissolution medium prepared by adding water to 3 g of polysorbate 80 to make 1000 mL. Take NLT 10 mL of the dissolved solution at 45 minutes after starting the test and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 5 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add water to make *V'* mL according to the labelled amount to obtain a solution having known concentration of about 5.6 μg (potency) of simvastatin and use this solution as the test solution. Separately, weigh accurately 22 mg of simvastatin RS (previously measure the loss on drying under the same conditions as simvastatin) and dissolve in acetonitrile to make exactly 100 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 200 mL, and use this solution as the standard solution. Perform the test with each 20 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the areas, A_T and A_S, from each solution. It meets the requirements if the dissolution rate of Simvastatin Tablets in 45 minutes is NLT 70%.

Dissolution rate (%) with respect to the labeled amount of simvastatin ($C_{25}H_{38}O_5$)

$$= W_S \times A_T / A_S \times V' / V \times 1 / C \times 45 / 2$$

W_S: Amount (mg) of simvastatin RS, calculated on the dried basis

C: Labeled amount (mg) of simvastatin ($C_{25}H_{38}O_5$) in 1 tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 238 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 50 °C.

Mobile phase: A mixture of methanol and 0.02 mol/L potassium dihydrogen phosphate TS (4 : 1).

Flow rate: Adjust the flow rate so that the retention time of simvastatin is about 4 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above operating conditions and perform the test; the number of theoretical plates and symmetry factor of the simvastatin peak is NLT 3000 and NMT 2.0, respectively.

System repeatability: Repeat the test 6 times with each 20 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas of simvastatin is NMT 1.0%.

Uniformity of dosage units It meets the requirements when the test is performed according to the following procedure. Take 1 tablet of Simvastatin Tablets, add *V* / 20 mL of water, and sonicate. Add a mixture of acetonitrile and 0.05 mol/L acetate buffer (pH 4.0) (4 : 1) to make exactly 3*V* / 4 mL and sonicate for 15 minutes. After cooling, add a mixture of acetonitrile and 0.05 mol/L acetate buffer (pH 4.0) (4 : 1) to make exactly *V* mL to obtain a solution having known concentration of about 0.1 mg of simvastatin per mL. Centrifuge this solution and use the clear supernatant as the test solution. Perform the test as directed under the Assay.

Amount (mg) of simvastatin ($C_{25}H_{38}O_5$)
$= W_S \times A_T / A_S \times V / 200$

W_S: Amount (mg) of simvastatin RS, calculated on the dried basis

Assay Weigh accurately and powder NLT 20 tablets of Simvastatin Tablets. Weigh accurately an amount of the powder, equivalent to about 50 mg of simvastatin add 200 mL of a mixture of acetonitrile and 0.05 mol/L acetate buffer (pH 4.0) (4 : 1), and sonicate for 15 minutes. After cooling, add a mixture of acetonitrile and 0.05 mol/L acetate buffer (pH 4.0) (4 : 1) to make exactly 250 mL and centrifuge. Pipet 5 mL of the clear supernatant, add a mixture of acetonitrile and 0.05 mol/L acetate buffer (pH 4.0) (4 : 1) to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of simvastatin RS (Previously, measure the loss on drying beforehand under the same conditions as simvastatin.), add a mixture of acetonitrile and 0.05 mol/L acetate buffer (pH 4.0) (4 : 1) to make exactly 200 mL, and use the solution as the standard solution. Perform the test with each 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions; determine the peak areas, A_T and *A*s, of simvastatin obtained from the solutions.

Amount (mg) of simvastatin ($C_{25}H_{38}O_5$)
$= W_S \times A_T / A_S \times 5 / 2$

W_S: Amount (mg) of simvastatin RS, calculated on the dried basis

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 238 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 45 °C.

Mobile phase: Dissolve 3.90 g of ammonium dihydrogen phosphate in 900 mL of water, adjust the pH to 4.5 with sodium hydroxide TS or phosphoric acid, and add water to make exactly 1000 mL. To 700 mL of this solution, add 1300 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of simvastatin is about 9 minutes.

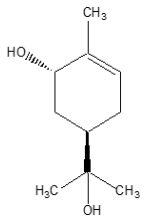
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions and perform the test; the number of theoretical plates and symmetry factor of the trimetazidine peak are NLT 6000 and between 0.9 and 1.1, respectively.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of simvastatin is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Sobrerol
소브레롤



$C_{10}H_{18}O_2$: 170.25

5-Hydroxy-α,α,4-trimethyl-3-cyclohexene-1-methanol; *p*-Menth-6-ene-2,8-diol, [*498-71-5*]

Sobrerol contains NLT 98.0% and NMT 101.0% of sobrerol ($C_{10}H_{18}O_2$), calculated on the anhydrous basis.

Description Sobrerol occurs as a white, crystalline powder, is odorless and has a slightly bitter taste.
It is freely soluble in methanol or ethanol(95), soluble in acetone, sparingly soluble in water or chloroform, slight-

ly soluble in ether, and practically insoluble in *n*-hexane. It is sparingly soluble in dilute acid or alkali.
The pH of a saturated solution of Sobrerol is between 4.4 and 5.0.

Identification (1) Dissolve about 10 mg of Sobrerol in 1 mL sulfuric acid, add 2 mL vanillin-ethanol solution; The resulting solution exhibits a reddish brown color, and changes to bluish purple on addition of 3 mL water.

(2) To 10 mg of Sobrerol, add 1 mL of a mixture of 0.5 mL of *p*-anisaldehyde, 1 mL of sulfuric acid and 50 mL acetic acid(100); the resulting solution is almost colorless, but changes to bright blue on heating gently.

(3) Determine the infrared spectra of Sobrerol and sobrerol RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) Dissolve 20 mg of Sobrerol in ethyl acetate to make 10 mL, and use this solution as the test solution. Dissolve 20 mg of sobrebol RS in ethyl acetate to make 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution onto a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate and anhydrous ethanol (8 : 1) as the developing solvent, and air-dry the plate. Spray a mixture of acetic acid, sulfuric acid and anisaldehyde (50 : 1 : 0.5) on the plate, heat at 110 ℃ for 15 minutes; the R_f values and colors of the spots obtained from the test solution and the standard solution are the same.

Refractive index n_D^{20}: Between 1.28 and 1.38 (10% anhydrous ethanol solution).

Melting point Between 131 and 132 ℃ (*dl-trans* form).

Boiling point Between 270 and 271 ℃ (*dl-trans* form).

Purity (1) ***Heavy metals***—Suspend 5.0 g of Sobrerol in 50 mL of water, filter, proceed with 10 mL of the filtrate according to Method 1, and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Proceed with 5 mL of the filtrate obtained from the heavy metals test according to the Arsenic and perform the test. (NMT 4 ppm).

Water NMT 0.1% (volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weight accurately 100 mg each of Sobrerol and sobrerol RS, and dissolve in methanol to make exactly 50 mL. Pipet 10 mL each of these solutions, add methanol to make exactly 20 mL, and use these solutions as the test solution and the standard solution. Pipet 10 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography, and determine the peak area of sobrerol A_T and A_S from the test solution and the standard solution.

Amount (mg) of sobrerol ($C_{10}H_{18}O_2$)
= Amount (mg) of sobrerol RS × (A_T / A_S)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of 0.02 mol/L potassium dihydrogen phosphate and methanol (11 : 9).

Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of sobrerol is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Sobrerol Capsules
소브레롤 캡슐

Sobrerol Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of sobrerol ($C_{10}H_{18}O_2$: 170.25).

Method of preparation Prepare as directed under Capsules, with Sobrerol.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Dissolution Perform the test with 1 capsule of Sobrerol Capsules at 100 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of solution 2 for dissolution as the dissolution solution. Take the dissolved solution after 60 minutes from the start of the test and filter. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add the dissolution medium to make exactly *V'* mL of a solution containing 110 μg of sobrerol per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately 110 mg of sobrerol RS, and dissolve in the dissolution medium to make 100 mL. Pipet 10 mL of this solution, add the dissolution medium to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and

determine the peak areas, A_T and A_S, of sobrerol in each solution. The acceptable dissolution criterion is NLT 70% of Sobrerol Capsules dissolved in 60 minutes.

Dissolution rate (%) of the labeled amount of sobrerol ($C_{10}H_{18}O_2$)
$= W_S \times (V' / V) \times (A_T / A_S) \times (1 / C)$

W_S: Amount (mg) of sobrerol RS
C: Labeled amount (mg) of sobrerol ($C_{10}H_{18}O_2$) in 1 tablet

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of 0.02 mol/L potassium dihydrogen phosphate TS (pH 3.5) and methanol (1 : 1).

Flow rate: 1.0 mL/min

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Sobrerol Capsules. Weigh accurately an amount equivalent to about 110 mg of sobrerol ($C_{10}H_{18}O_2$), and add the mobile phase to make exactly 100 mL. After filtering this solution, pipet 10 mL of the filtrate, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 110 mg of sobrerol RS, and add the mobile phase to make exactly 100 mL. Take 10 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of sobrerol in each solution.

Amount (mg) of sobrerol ($C_{10}H_{18}O_2$)
$=$ Amount (mg) of sobrerol RS $\times (A_T / A_S)$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of 0.02 mol/L potassium dihydrogen phosphate TS (pH 3.5) and methanol (1 : 1).

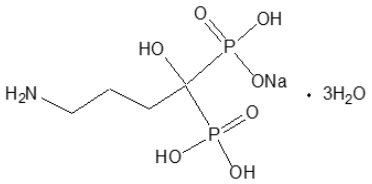
Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 mL of the standard solution according to the above conditions; the relative standard deviation of the peak area of sobrerol is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Sodium Alendronate Hydrate
알렌드론산나트륨수화물



$C_4H_{12}NNaO_7P_2 \cdot 3H_2O$: 325.12
Sodium hydrogen (4-amino-1-hydroxy-1-phosphonobutyl)phosphinate trihydrate [*121268-17-5*]

Sodium Alendronate Hydrate contains NLT 98.0% and NMT 102.0% of sodium alendronate ($C_4H_{12}NNaO_7P_2$: 257.07), calculated on the dried basis.

Description Sodium Alendronate Hydrate occurs as a white or almost white, crystalline powder.
It is soluble in water, very slightly soluble in methanol, and practically insoluble in dichloromethane.

Identification (1) Determine the infrared spectra of Sodium Alendronate Hydrate and sodium alendronate hydrate RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Sodium Alendronate Hydrate responds to the Qualitative Analysis (1) for sodium salt.

pH Dissolve 0.5 g of Sodium Alendronate Hydrate in 50 mL of water; the pH of the solution is between 4.0 and 5.0.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Sodium Alendronate Hydrate according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Weigh accurately 30 mg of Sodium Alendronate Hydrate, and dissolve in 2.94% sodium citrate solution to make exactly 50 mL. Take 5.0 mL of this solution, transfer into a 50 mL stoppered polypropylene centrifuge tube with 5 mL of 1.91% sodium borate, add 5 mL of acetonitrile and 5 mL of 0.4% 9-fluorenylmethyl chloroformate solution, prepared before use, shake for 45 seconds, and allow it to stand at room temperature for 30 minutes. Add 20 mL of dichloromethane, vigorously shake for 1 minute, and centrifuge for 5 to 10 minutes. Use the clear supernatant water layer as the test solution. Separately, proceed with 5.0 mL of

2.94% sodium citrate solution in the same manner as in the preparation of the test solution, and use this solution as the blank test solution. Perform the test with 20 μL each of the blank test solution and the test solution as directed under the Liquid Chromatography according to the following conditions. Exclude peaks with the same retention times as the peaks obtained from the blank test solution. Determine content (%) of each related substance from the test solution; the amount of each related substance is NMT 0.1%, and the total amount of all related substances is NMT 0.5%.

$$\text{Content (\%) of each related substance} = 100 \times \frac{A_\text{i}}{A_\text{S}}$$

Ai: Peak area of related substance
A_S: Sum of all peak areas of related substances

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 266 nm).

Column: A stainless steel column about 4.1 mm in internal diameter and 25 cm in length, packed with spherical styrene-
divinylbenzene copolymer for liquid chromatography (5 μm - 10 μm in particle diameter).

Column temperature: A constant temperature of about 45 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: A mixture of buffer solution and acetonitrile (17 : 3).

Mobile phase B: A mixture of acetonitrile and buffer solution (7 : 3).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0	100	0
0 - 15	100 → 50	0 → 50
15 - 25	50 → 0	50 → 100
25 - 27	0 → 100	100 → 0
27 - 32	100	0

Flow rate: 1.8 mL/min

System suitability

System performance: Weigh 60.0 mg of sodium alendronate hydrate RS, dissolve in 2.94% sodium citrate solution to make 100 mL, and use this solution as the standard stock solution. Take 5.0 mL of this solution, proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Separately, take 0.1 mL of this standard stock solution, add 2.94% sodium citrate solution to make 100 mL, take 5.0 mL of this solution, proceed in the same manner as in the preparation of the test solution, and use this solution as the diluted standard solution. Proceed with 20 mL each of the standard solution and the diluted standard solution according to the above conditions; the symmetry factor of major peaks obtained from the standard solution is NMT 2.0, and the peak at the same position obtained from the diluted standard solution is detected at a signal-to-noise ratio of NLT 3.

Buffer solution—Dissolve 5.88 g of sodium citrate dihydrate and 2.84 g of anhydrous sodium dihydrogen phosphate in water to make 2000 mL. To this solution, add phosphoric acid to adjust pH to 8.

Loss on drying Between 16.1% and 17.1% (1 g, in vacuum, 145 °C, constant mass).

Assay Weigh accurately about 25 mg of Sodium Alendronate Hydrate, and dissolve in 2.94% sodium citrate solution to make exactly 250 mL. Take 5.0 mL of this solution, transfer into a 50 mL stoppered polypropylene centrifuge tube containing 5 mL of 1.91% sodium borate, add 5 mL of acetonitrile and 5 mL of a solution of 0.05% 9-fluorenylmethyl chloroformate in acetonitrile, prepared before use, and shake for 30 seconds. Allow it to stand at room temperature for 25 minutes.
Add 25 mL of dichloromethane, vigorously shake, and centrifuge for 5 to 10 minutes. Use the clear supernatant water layer as the test solution. Separately, weigh accurately 10 mg of sodium alendronate hydrate RS, dissolve in 2.94% sodium citrate solution to make exactly 100 mL, and use this solution as the standard stock solution. Take 5.0 mL of this standard stock solution, and proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Also, proceed with 5.0 mL of 2.94% sodium citrate solution in the same manner as in the preparation of the test solution, and use this solution as the blank test solution. Perform the test with 10 μL each of the blank test solution, the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the area, A_T and A_S of the major peak from the test solution and the standard solution.

$$\text{Amount (mg) of sodium alendronate } (C_4H_{12}NNaO_7P_2) = 250 \times C \times \frac{A_\text{T}}{A_\text{S}}$$

C: Concentration (mg/mL) of anhydrous sodium alendronate in the standard stock solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 266 nm).

Column: A stainless steel column about 4.1 mm in internal diameter and 25 cm in length, packed with spherical styrene-
divinylbenzene copolymer for liquid chromatography (5 μm - 10 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of buffer solution, acetonitrile and methanol (70 : 25 : 5).

Flow rate: 1.8 mL/min

System suitability

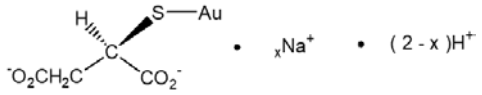
System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; the number of theoretical plates and symmetry factor of the major peak from the standard solution are NLT 1500 and NMT 1.5, respectively.

System repeatability: Repeat the test 5 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of sodium alendronate is NMT 2.0%.

Buffer solution—Dissolve 14.7 g of sodium citrate dihydrate and 7.05 g of anhydrous sodium dihydrogen phosphate in water to make 1000 mL. To this solution, add phosphoric acid to adjust pH to 8.

Packaging and storage Preserve in well-closed containers at 15 ℃ to 30 ℃.

Sodium Aurothiomalate
금티오말산나트륨



and enantiomer

Mixture of $C_{15}H_3N_2O_4S$: 390.08 and $C_4H_4AuNaO_4S$: 368.10

Disodium; gold(1+); 2-sulfidobutanedioate [*12244-57-4*]

Sodium Aurothiomalate contains NLT 49.0% and NMT 52.5% of gold (Au: 196.97), calculated on the anhydrous basis.

Description Sodium Aurothiomalate occurs as a white to pale yellow powder or grain.
It is very soluble in water and practically insoluble in ethanol(95).
It is hygroscopic.
It is colored by light to greenish pale yellow.

Identification (1) Add 1 mL of calcium nitrate tetrahydrate solution (1 in 10) to 2 mL of the aqueous solution of Sodium Aurothiomalate (1 in 10); a white precipitate is produced and it dissolves in dilute nitric acid. It reappears with the addition of ammonium acetate TS.

(2) Add 3 mL of silver nitrate TS to 2 mL of the aqueous solution of Sodium Aurothiomalate (1 in 10); a yellow precipitate is produced and it dissolves in an excess of ammonia TS.

(3) Pipet 2 mL of the aqueous solution of Sodium Aurothiomalate (1 in 10) in a porcelain crucible, add 1 mL of ammonia TS and 1 mL of hydrogen peroxide water (30), evaporate to dryness, and ignite. Add 20 mL of water to the residue and filter; the residue on the filter paper occurs as a yellow or dark yellow powder or grain.

(4) The filtrate obtained in (3) responds to the Qualitative Analysis for sodium salt.

(5) The filtrate obtained in (3) responds to the Qualitative Analysis for sulfate.

pH Dissolve 1.0 g of Sodium Aurothiomalate in 10 mL of water; the pH of this solution is between 5.8 and 6.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Sodium Aurothiomalate in 10 mL of water; the resulting solution is clear and pale yellow.

(2) ***Heavy metals***—Proceed with 1.0 g of Sodium Aurothiomalate as directed under Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(3) ***Arsenic*—**Proceed with 1.0 g of Sodium Aurothiomalate as directed under Method 3 and perform the test (NMT 2 ppm).

(4) ***Ethanol*—**Weigh accurately about 0.125 g of Sodium Aurothiomalate, add exactly 5 mL of the internal standard solution, and put water again to make exactly 25 mL. Use this solution as the test solution. Separately, pipet 2 mL of ethanol(99.5), add water to make exactly 100 mL, and use this solution as the standard stock solution. Pipet 0.25 mL of the standard stock solution, add exactly 5 mL of the internal standard solution, and put water again to make exactly 25 mL. Use this solution as the standard solution. Perform the test with 1 μL each of the test and standard solutions as directed under the Gas Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S of ethanol to internal standard (NMT 3.0%).

$$\text{Amount (mg) of ethanol} = Q_T / Q_S \times 5 \times 0.79$$

0.79: Density (g/mL) of ethanol at 20 °C.

Internal standard solution—A solution of 1− propanol (1 in 1000).

Operating conditions

Detector: A flame ionization detector

Column: A fused silica column 0.53 mm in internal diameter and 30 m in length, packed with 6% cyanopropylphenyl-94% dimethylpolysiloxane for gas chromatography (3 μm in particle diameter).

Column temperature: Maintain at 50 °C for 5 minutes, then raise the temperature at a rate of 50 °C per minute until it reaches 200 °C, and maintain at 200 °C for 4 minutes.

Injection port temperature: 210 ℃

Detector temperature: 280 °C

Carrier gas: Nitrogen

Flow rate: 5 mL/min

Split ratio: 1 : 5

System suitability

System performance: Proceed with 1 μL of the standard solution under the above conditions; ethanol and internal standard solution are eluted in this order.

System repeatability: Repeat the test 5 times with

1 μL each of the standard solutions under the conditions above; the relative standard deviation of the peak area is NMT 2.0%.

(5) ***Glycerin*** This procedure is based on the absorption characteristics of a complex of sodium, copper and glycerin. For the stability of the complex compound, all measurements should be taken within 1 hour, and all glassware used in this procedure should be thoroughly rinsed with water to avoid the blank test errors.
Weigh accurately about 400 mg of Sodium Aurothiomalate, transfer to a 10-mL volumetric flask, dissolve in 5.0 mL of water, and use this solution as the test solution. Separately, pipet a certain amount of glycerin and dissolve in water to make exactly the concentration of the solution 8 mg/mL. Take 1.0 mL, 2.0 mL and 3.0 mL each of this solution, transfer to a 10-mL volumetric flask respectively, add 4.0 mL, 3.0 mL and 2.0 mL of water to each flask and use these solutions as the standard solution (1), (2) and (3) of glycerin. Put 5.0 mL of water to a 10-mL volumetric flask, and use this solution as the blank test solution. Add 1.0 mL of sodium hydroxide solution to each of the standard solution of glycerin, blank test solution and test solution, and mix. Put 0.1 mL of copper chloride solution to each solution by shaking well, while observing the turbidity upon every addition. Add copper chloride solution until the solution becomes slightly turbid, and put more 0.1 mL additionally. With the stopper closed, shake for 1 minute. Fill up to the mark with water, and mix. Centrifuge this solution using a conical centrifuge tube with a 15-mL graduation line. A 1 mm to 4 mm precipitate of copper hydroxide is observed. Determine the absorption spectrum of the clear supernatant as directed under the Ultraviolet-visible Spectroscopy in a 1 cm cell at 635 nm wavelength, using water as a control, and subtract the absorbance of the blank test solution (NMT 0.040) from the determined value to calculate the absorbances of the test solution and the standard solutions, respectively. Create a calibration curve using the absorbance of each of the standard solution, determine the amount of glycerin in the test solution by calculating from the calibration curve, and calculate the amount of glycerin in the sample (NMT 5.5%).

Sodium hydroxide solution—Dissolve 23.6 g of sodium hydroxide in water to make 100 mL.

Copper chloride solution—Dissolve 3.8 g of copper chloride in water to make 100 mL.

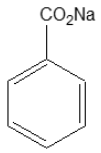
Water NMT 5.0% (0.1 g, coulometric titration). Use a water vaporizer (heating temperature: 105 ℃; heating time: 30 minutes).

Assay Weigh accurately 25 mg of Sodium Aurothiomalate, dissolve in 2 mL of aqua regia by heating, cool it down, and add water to make exactly 100 mL. Pipet 2 mL of this solution, add water to make exactly 25 mL, and use this solution as the test solution. Separately, pipet 5 mL, 10 mL and 15 mL each of the standard solution of gold for the atomic absorption spectroscopy, add water to make exactly 25 mL, and use these solutions as the standard solutions. Perform the test with the test and standard solutions as directed under the Atomic Absorption Spectroscopy under the following conditions, and determine the amount of gold in the test solution using the calibration curve obtained from the absorbances of the standard solutions.

Gas: Air–acetylene
Lamp: Gold hollow-cathode lamp
Wavelength: 242.8 nm

Packaging and storage Preserve in light-resistant, tight containers.

Sodium Benzoate
벤조산나트륨



$C_7H_5NaO_2$: 144.10
Sodium benzoate [*532-32-1*]

Sodium Benzoate, when dried, contains NLT 99.0% and NMT 101.0% of sodium benzoate ($C_7H_5NaO_2$).

Description Sodium Benzoate occurs as white grains, crystals or a crystalline powder. It is odorless and has a sweet and saline taste.
It is freely soluble in water, slightly soluble in ethanol(95) and practically insoluble in ether.

Identification An aqueous solution of Sodium Benzoate (1 in 100) responds to the Qualitative Analysis (1) and (2) for benzoate and sodium salt.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Sodium Benzoate in 5 mL of water; the solution is colorless and clear.

(2) ***Acid or alkali***—Dissolve 2.0 g of Sodium Benzoate in 20 mL of freshly boiled and cooled water and add 2 drops of phenolphthalein TS and 0.20 mL of 0.05 mol/L sulfuric acid; the resulting solution is colorless. To this solution, add 0.40 mL of 0.1 mol/L sodium hydroxide TS; the resulting solution turns red.

(3) ***Sulfate***—Dissolve 0.40 g of Sodium Benzoate in 40 mL of water, add 3.5 mL of dilute hydrochloric acid slowly while stirring thoroughly to mix, allow to stand for 5 minutes, and filter. Discard the first 5 mL of the filtrate, take the subsequent 20 mL of the filtrate, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid (NMT 0.120%).

(4) ***Heavy metals***—Dissolve 1.0 g of Sodium Benzoate in 44 mL of water, add 6 mL of dilute hydrochloric acid slowly while stirring thoroughly to mix, and filter. Discard the first 5 mL of the filtrate, take the subsequent 25 mL of the filtrate, neutralize with ammonia TS, and add 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 2 mL of dilute acetic acid and water to 1.0 mL of lead standard solution to make 50 mL (NMT 10 ppm).

(5) ***Arsenic***—Mix 1.0 g of Sodium Benzoate well with 0.40 g of calcium hydroxide, ignite, and dissolve the residue in 10 mL of dilute hydrochloric acid. Use this solution as the test solution and perform the test (NMT 2 ppm).

(6) ***Chlorinated compounds***—Dissolve 1.0 g of Sodium Benzoate in 10 mL of water, add 10 mL of dilute sulfuric acid, and extract twice each time with 20 mL of ether. Combine the ether extracts and evaporate the ether on a steam bath. Place 0.5 g of the residue and 0.7 g of calcium carbonate in a crucible, mix with a small amount of water, and dry. Next, ignite the resulting residue at about 600 ℃, dissolve in 20 mL of dilute nitric acid, and filter. Wash the residue with 15 mL of water, combine the filtrate and the washings, and add water to make 50 mL. To this solution, add 0.5 mL of silver nitrate TS; the resulting solution is not more turbid than the following control solution.

Control solution—Dissolve 0.7 g of calcium carbonate in 20 mL of dilute nitric acid and filter. Wash the residue with 15 mL of water, combine the filtrate and the washings, thereto add 1.2 mL of 0.01 mol/L hydrochloric acid and water to make 50 mL, and add 0.5 mL of silver nitrate TS.

(7) ***Phthalic acid***—Weigh accurately about 100 mg of Sodium Benzoate, dissolve it in 1 mL of water, add 1 mL of resorcinol-sulfuric acid TS, and evaporate the water by heating in an oil bath at between 120 and 125 ℃, and heat again for 90 minutes. After cooling, dissolve the resulting residue in 5 mL of water. Take 1 mL of this solution, add 10 mL of a solution of sodium hydroxide (43 in 500) and use this solution as the test solution. Separately, take exactly 61 mg of potassium hydrogen phthalate and dissolve it in 1000 mL of water. Take 1 mL of this solution and proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under Ultraviolet-visible Spectroscopy, and determine the absorbances of these solutions at the wavelength of 495 nm; the absorbance of the test solution is NMT that of the standard solution.

Loss on drying NMT 1.5% (2 g, 110 ℃, 4 hours).

Assay Weigh accurately about 1.5 g of Sodium Benzoate, previously dried, and transfer it to a 300-mL glass-stoppered flask, dissolve in 25 mL of water, add 75 mL of ether and 10 drops of bromophenol blue TS, and titrate with 0.5 mol/L hydrochloric acid VS. Mix the water and ether layers by vigorous shaking during the titration. The endpoint of the titration is when the water layer turns a persistent and pale green color.

Each mL of 0.5 mol/L hydrochloric acid VS
= 72.05 mg of $C_7H_5NaO_2$

Packaging and storage Preserve in well-closed containers.

Sodium Bicarbonate
탄산수소나트륨

$NaHCO_3$: 84.01

Sodium hydrogen carbonate [*144-55-8*]

Sodium Bicarbonate contains NLT 99.0% and NMT 101.0% of sodium bicarbonate ($NaHCO_3$).

Description Sodium Bicarbonate occurs as white crystals or a crystalline powder. It is odorless and has a characteristic salty taste.
It is soluble in water and practically insoluble in ethanol(95) or ether.
It slowly decomposes in humid air.

Identification An aqueous solution of Sodium Bicarbonate (1 in 30) responds to the Qualitative Analysis for sodium salt and hydrogen carbonate.

pH Dissolve 1.0 g of Sodium Bicarbonate in 20 mL of water; the pH of this solution is between 7.9 and 8.4.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Sodium Bicarbonate in 20 mL of water; the resulting solution is clear and colorless.

(2) ***Chloride***—To 0.40 g of Sodium Bicarbonate, add 4 mL of dilute nitric acid, and heat to boiling. After cooling, add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.45 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.040%).

(3) ***Sulfide***—Weigh accurately 0.2 g of Sodium Bicarbonate, dissolve in 20 mL of water, boil to make 5 mL, and add 1 mL of bromine TS. Evaporate to dryness and cool. Dissolve the residue in 10 mL of 3 mol/L hydrochloric acid VS, evaporate to dryness, and cool. Dissolve this residue in 5 mL of 3 mol/L hydrochloric acid VS, evaporate to dryness, and cool. To this residue, add 10 mL of water, and adjust the pH to 2 with 3 mol/L hydrochloric acid TS or ammonia TS. To obtain the clear solution, filter this solution, and wash the filtrate twice each with 2 mL of water. Combine these solutions, add water to make 20 mL, and use this solution as the test solution. Separately, to 0.30 mL of 0.01 mol/L sulfuric acid TS, add 1 mL of 0.06 mol/L hydrochloric acid TS, add water to make 20 mL, and use this solution as the

standard solution. To each of the test solution and the standard solution, add 1 mL of barium chloride TS, mix, and allow to stand for 30 minutes; the turbidity of the test solution is not more intense than the standard solution (NMT 0.015%).

(4) ***Carbonate***—To 1.0 g of Sodium Bicarbonate, add 20 mL of freshly boiled and cooled water, dissolve by gently shaking at NMT 15 ℃, and add 2.0 mL of 0.1 mol/L hydrochloric acid VS and 2 drops of phenolphthalein TS; the resulting solution does not immediately exhibit a red color.

(5) ***Ammonium***—Heat 1.0 g of Sodium Bicarbonate; the gas evolved does not change the color of a moistened red litmus paper to blue.

(6) ***Heavy metals***—Dissolve 4.0 g of Sodium Bicarbonate in 5 mL of water and 4.5 mL of hydrochloric acid, and evaporate to dryness on a steam bath, dissolve the residue in 2 mL of dilute acetic acid, 35 mL of water, and 1 drop of ammonia TS, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by evaporating 4.5 mL of hydrochloric acid to dryness and adding 2 mL of dilute acetic acid, 2.0 mL of lead standard solution, and water to make 50 mL (NMT 5 ppm).

(7) ***Copper***—Weigh 5.0 g of Sodium Bicarbonate, transfer into a 100 mL plastic volumetric flask, add 4 mL of nitric acid, and shake to mix. Sonicate for 30 minutes, add water to make 100 mL, and use this solution as the test solution. Separately, dissolve 1.0 g of copper RS in 20 mL of nitric acid, and add 0.2 mol/L nitric acid VS to make 1000 mL. Take 10 mL of this solution, add 0.2 mol/L nitric acid to make 1000 mL, and use this solution as the standard stock solution. Preserve the standard stock solution in a polyethylene bottle. Take an appropriate amount of the standard stock solution, dilute with 0.2 mol/L nitric acid VS to make solutions containing 0.1 μg/mL, 0.05 μg/mL, and 0.01 μg/mL, respectively, and use these solutions as the standard solution (1), the standard solution (2), and the standard solution (3). Perform the test with the test solution, the standard solution (1), the standard solution (2), and the standard solution (3) according to the following conditions, as directed under the Atomic Absorption Spectroscopy, and calculate the content of copper using the calibration curve obtained from the standard solution (NMT 1 ppm). Perform a blank test with the nitric acid solution (40 in 1000) and make any necessary correction.

Gas: Air–acetylene
Lamp: Copper hollow cathode lamp
Wavelength: 324.7 nm

(8) ***Iron***—Perform the test when used for the manufacturing of hemodialysis preparations. Weigh accurately 2.0 g of Sodium Bicarbonate, neutralize with hydrochloric acid, and record the consumed amount. Transfer this solution into a 25 mL volumetric flask using a small amount of water, and use this solution as the test solution. Separately, transfer 1.0 mL of iron standard solution into a 25 mL volumetric flask, add an equivalent amount of hydrochloric acid as the test solution, and use this solution as the standard solution. Also, take separately an amount of hydrochloric acid used to prepare the test solution, transfer into a 25 mL volumetric flask, and use this solution as the blank test solution. To each of the test solution, the standard solution, and the blank test solution, add 50 mg of ammonium peroxydisulfate and 30% ammonium thiocyanate solution, and add water to make 25 mL. Determine the absorbances at the absorption maximum wavelength of about 480 nm of the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy using the blank test solution as the blank test solution; the absorbance of the test solution is not greater than that of the standard solution (NMT 5 ppm).

(9) ***Calcium***—Perform the test when used for the manufacturing of hemodialysis preparations. Weigh accurately 3.0 g of Sodium Bicarbonate, add 6 mL of 6 mol/L hydrochloric acid TS, 1 g of potassium chloride, and water, mix, and make 100 mL. Use this solution as the test solution. Separately, weigh 0.25 g of calcium carbonate, previously dried at 300 ℃ for 3 hours and cooled in a desiccator for 2 hours, dissolve in 6 mL of 6 mol/L hydrochloric acid TS, and add 1 g of calcium carbonate and water to make 100 mL. Pipet 10.0 mL of this solution, and add potassium chloride solution to make 100 mL so that the solution contains 100 μg of calcium per mL. To 2.0 mL, 3.0 mL, 4.0 mL, and 5.0 mL of this solution, add 6 mL of hydrochloric acid TS, add potassium chloride solution to make each solution 100 mL, and use these solutions as 2.0, 3.0, 4.0, and 5.0 μg/mL calcium standard solution. Perform the test with the test solution and the standard solutions as directed under the Atomic Absorption Spectroscopy according to the following conditions, and calculate the content of calcium in the test solution using the calibration curve obtained from the standard solution absorbance; it is NMT 0.01%.

Potassium chloride solution—Dissolve 10 g of potassium chloride in 1000 mL of 0.36 mol/L hydrochloric acid VS.

Gas: Nitrous oxide-acetylene
Lamp: Calcium hollow cathode lamp
Blank test solution: Potassium chloride TS
Wavelength: 422.7 nm

(10) ***Arsenic***—Dissolve 1.0 g of Sodium Bicarbonate in 3 mL of water and 2 mL of hydrochloric acid, use this solution as the test solution, and perform the test (NMT 2 ppm).

Assay Weigh accurately about 2 g of Sodium Bicarbonate, dissolve in 100 mL of water, and titrate with 1 mol/L hydrochloric acid VS. Add slowly 1 mol/L hydrochloric acid until the solution exhibits a pale purple color, and boil by heating. After cooling, titrate with 1 mol/L hydrochloric acid VS until the purple color no longer disappears (indicator: 2 drops of methyl red TS).

Each mL of 1 mol/L hydrochloric acid VS
= 84.01 mg of $NaHCO_3$

Packaging and storage Preserve in tight containers.

Sodium Bicarbonate Injection
탄산수소나트륨 주사액

Sodium Bicarbonate Injection is an aqueous solution for injection and contains NLT 95.0% and NMT 105.0% of the labeled amount of sodium bicarbonate ($NaHCO_3$: 84.01).

Method of preparation Prepare as directed under Injections, with Sodium Bicarbonate.

Description Sodium Bicarbonate Injection occurs as a clear, colorless liquid.

Identification Weigh a volume of Sodium Bicarbonate Injection, equivalent to 1 g of sodium bicarbonate, according to the labeled amount, and add water to make 30 mL; the solution responds to the Qualitative Analysis for sodium salt and bicarbonate.

Purity ***Carbonate***—Weigh a volume of Sodium Bicarbonate Injection, equivalent to 0.10 g of sodium bicarbonate according to the labeled amount, add water, freshly boiled and cooled to 10 °C, to make a 1.0 w/v% solution and determine the pH immediately; the pH of the solution is between 7.9 and 8.6.

Sterility Meets the requirements.

Bacterial endotoxins Less than 5.0 EU per mEq of Sodium Bicarbonate Injection.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Take exactly a volume of Sodium Bicarbonate Injection, equivalent to about 2 g of sodium bicarbonate ($NaHCO_3$), titrate with 1 mol/L hydrochloric acid VS, and proceed as directed under the Assay under Sodium Bicarbonate.

Each mL of 1 mol/L hydrochloric acid VS
= 84.01 mg of $NaHCO_3$

Packaging and storage Preserve in hermetic containers. Plastic containers for aqueous injections may be used.

Sodium Bicarbonate Tablets
탄산수소나트륨 정

Sodium Bicarbonate Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of sodium bicarbonate ($NaHCO_3$: 84.01).

Method of preparation Prepare as directed under Tablets, with Sodium Bicarbonate.

Identification Perform the test according to the Identification under Sodium Bicarbonate.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately NLT 20 Sodium Bicarbonate Tablets and powder them. Weigh accurately an amount, equivalent to about 2 g of sodium bicarbonate (NaHCO3), dissolve in 100 mL of water, and titrate with 1 mol/L hydrochloric acid VS. Heat to boiling while adding slowly 1 mol/L hydrochloric acid until the solution exhibits a pale violet, cool, and titrate with 1 mol/L hydrochloric acid VS until the violet color does not disappear (indicator: 2 drops of methyl red TS).

Each mL of 1 mol/L hydrochloric acid
= 84.01 mg of $NaHCO_3$

Packaging and storage Preserve in well-closed containers.

Sodium Borate
붕사

$Na_2B_4O_7 \cdot 10H_2O$: 381.37
Disodium [oxido(oxoboranyloxy)boranyl]oxy-oxoboranyloxyborinate decahydrate [*1303-96-4*]

Sodium Borate, when dried, contains NLT 99.0% and NMT 103.0% of sodium borate ($Na_2B_4O_7 \cdot 10H_2O$).

Description Sodium Borate is colorless or white crystals or a white, crystalline powder. It is odorless and has a slightly distinctive, salty taste.
It is freely soluble in glycerin, soluble in water, and practically insoluble in ethanol(95), dehydrated ethanol(99.5) or ether.
When allowed to stand in dry air, it effloresces is weathered, and thus coated with a white powder.

Identification An aqueous solution of Sodium Borate (1 in 20) responds to the Qualitative Analysis for sodium salt and borate.

pH Dissolve 1.0 g of Sodium Borate in 20 mL of water;

the pH of this solution is between 9.1 and 9.6.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Sodium Borate in 20 mL of water by warming slightly; the solution is clear and colorless.

(2) ***Carbonate or bicarbonate***—Dissolve 1.0 g of powdered Sodium Borate in 20 mL of freshly boiled and cooled water and add 3 mL of dilute hydrochloric acid; the solution does not effervesce.

(3) ***Heavy metals***—Dissolve 1.5 g of Sodium Borate in 25 mL of water and 7 mL of 1 mol/L hydrochloric acid TS, add 1 drop of phenolphthalein TS, and add ammonia TS until a pale red color develops. Then add 1 drop of dilute acetic acid at a time until it becomes colorless and add 2 mL of diluted acetic acid and water to this solution to make 50 mL. Use this as the test solution and perform the test. Prepare the control solution by adding 2 mL of dilute acetic acid and water to 3.0 mL of lead standard solution to make 50 mL (NMT 20 ppm).

(4) ***Arsenic***—Proceed with 0.40 g of Sodium Borate according to Method 1 and perform the test (NMT 5 ppm).

Assay Weigh accurately about 2 g of Sodium Borate, dissolve it in 50 mL of water, and titrate with 0.5 mol/L hydrochloric acid VS (Indicator: 3 drops of Methyl red TS).

Each mL of 0.5 mol/L hydrochloric acid VS
= 95.34 mg of $Na_2B_4O_7 \cdot 10H_2O$

Packaging and storage Preserve in tight containers.

Sodium Bromide
브롬화나트륨

NaBr : 102.89

Sodium bromide [*7647-15-6*]

Sodium Bromide, when dried, contains NLT 99.0% and not more 101.0% of sodium bromide (NaBr).

Description Sodium Bromide occurs as colorless or white crystals or a crystalline powder. It is odorless.
It is freely soluble in water and soluble in ethanol(95).
It is hygroscopic but is not deliquescent.

Identification An aqueous solution of Sodium Bromide (1 in 10) responds to the Qualitative Analysis for sodium salt and bromide.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Sodium Bromide in 3 mL of water; the resulting solution is clear and colorless.

(2) ***Alkalinity***—Dissolve 1.0 g of Sodium Bromide in 10 mL of water, add 0.10 mL of 0.005 mol/L sulfuric acid and 1 drop of phenolphthalein TS, heat to boiling, and cool it down; the resulting solution is colorless.

(3) ***Chloride***—Perform the test as directed under the Assay; the amount of 0.1 mol/L silver nitrate solution equivalent to 1 g of Sodium Bromide is NMT 97.9 mL.

(4) ***Sulfate***—Perform the test with 2.0 g of Sodium Bromide. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.024%).

(5) ***Iodide***—Dissolve 0.5 g of Sodium Bromide in 10 mL of water, add between 2 and 3 drops of iron(III) chloride TS and 1 mL of chloroform, and shake well to mix; the chloroform layer does not exhibit a purple to violet color.

(6) ***Bromate***—Dissolve 1.0 g of Sodium Bromide in 10 mL of newly boiled and cooled water, add 2 drops of potassium iodide TS, 1 mL of starch TS and 3 drops of dilute sulfuric acid, shake gently to mix, and allow to stand for 5 minutes; the resulting solution does not exhibit a blue color.

(7) ***Heavy metals***—Proceed with 2.0 g of Sodium Bromide according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(8) ***Magnesium and alkaline earth metals***—To 200 mL of water, add 0.1 g of hydroxylamine hydrochloride, 10 mL of ammonium chloride buffer solution, pH 10, 1 mL of 0.1 mol/L zinc sulfate solution and 0.2 g of eryochrome black T-sodium chloride indicator, and warm at 40℃. To this solution, drop 0.01 mol/L ethylenediaminetetraacetic acid disodium salt until the purple color of the solution turns to bluish purple. To this solution, add a solution of 10.0 g of Sodium Bromide dissolved in 100 mL of water. If the color of the solution changes to purple, titrate with 0.01 mol/L ethylenediaminetetraacetic acid disodium salt until the color of the solution exhibits a bluish purple color; the consumed volume is NMT 5.0 mL (NMT 0.02%, calculated as calcium).

(9) **B*arium***—Dissolve 0.5 g of Sodium Bromide in 10 mL of water, add 0.5 mL of dilute hydrochloric acid and 1 mL of potassium sulfate TS, and allow to stand for 10 minutes; the resulting solution is not turbid.

(10) ***Iron***—Dissolve 0.5 g of Sodium Bromide in water to make 10 mL and use this solution as the test solution. To 1 mL of the iron standard solution, add water to make 10 mL, and use this solution as the standard solution. To the test solution and the standard solution, add 2.0 mL of citric acid (1 in 5) and 0.1 mL of thioglycolic acid, add ammonia water(28) until this solution makes the litmus paper alkaline, and add water to make 20 mL. The color obtained from the test solution after 5 minutes is not more intense than the color from the standard solution (NMT 20 ppm).

(11) ***Arsenic***—Proceed with 1.0 g of Sodium Bromide according to Method 1 and perform the test (NMT 2 ppm).

Loss on drying NMT 5.0% (1 g, 110 °C, 4 hours).

Assay Weigh accurately about 0.4 g of Sodium Bromide, previously dried, dissolve in 50 mL of water, add 10 mL of dilute nitric acid, add exactly 50 mL of 0.1 mol/L silver nitrate solution, and titrate the excess silver nitrate with 0.1 mol/L ammonium thiocyanate VS (indicator: 2

mL of ammonium iron(III) sulfate TS). Perform a blank test in the same manner.

Each mL of 0.1 mol/L silver nitrate VS
= 10.289 mg of NaBr

Packaging and storage Preserve in tight containers.

Sodium Chloride
염화나트륨

NaCl : 58.44

Sodium Chloride [*7647-14-5*]

Sodium Chloride contains NLT 98.0% and NMT 100.5% of sodium chloride (NaCl), calculated on the dried basis.

Description Sodium Chloride occurs as a white or almost white powder, colorless crystal, or white or almost white crystalline powder.
It is freely soluble in water and practically insoluble in ethanol(99.5).

Identification (1) An aqueous solution of Sodium Chloride (1 in 20) responds to the Qualitative Analysis for sodium salt.

(2) An aqueous solution of Sodium Chloride (1 in 20) responds to the Qualitative Analysis for chloride.

Purity (1) ***Clarity and color of solution***—Dissolve about 20.0 g of Sodium Chloride in 100.0 mL of freshly boiled and cooled water; the resulting solution is clear and colorless.

(2) ***Acidity or alkalinity***—To 20 mL of the solution obtained in (1), add 0.1 mL of bromothymol blue solution and 0.5 mL of 0.01 mol/L hydrochloric acid TS; the color of the solution is yellow. To 20 mL of the solution obtained in (1), add 0.1 mL of bromothymol blue solution and 0.5 mL of 0.01 mol/L sodium hydroxide TS; the color of the solution is blue.

Bromothymol blue solution—Dissolve 50 mg of bromothymol blue in a mixture of 20 mL of 0.02 mol/L diluted sodium hydroxide TS (1 in 10) and ethanol(95), and add water to make 100 mL.

(3) ***Bromide***—To 0.50 mL of the solution obtained in (1), add 4.0 mL of water, 2.0 mL of dilute phenol red TS and 1.0 mL of sodium toluenesulfonchloramide solution (1 in 10000), and mix immediately. After allowing to stand for 2 minutes, add 0.15 mL of 0.1 mol/L sodium thiosulfate solution, mix well, add water to make exactly 10 mL, and use this solution as the test solution. Separately, take 5.0 mL of potassium bromide solution (3 in 1000000), add 2.0 mL of dilute phenol red TS and 1.0 mL of sodium toluenesulfonchloramide solution (1 in 10000), and mix immediately. Proceed in the same manner as in the preparation of the test solution, and use it as the standard solution. Determine the absorbances of these solutions as directed under the Ultraviolet-visible Spectroscopy, using water as the blank; the absorbance of the test solution at 590 nm is not larger than that of the standard solution (NMT 100 ppm).

(4) ***Nitrites***—Take 10 mL of the solution obtained in (1), add 10 mL of water, and determine the absorbance as directed under the Ultraviolet-visible Spectroscopy; the absorbance at the wavelength of 354 nm is NMT 0.01.

(5) ***Iodides***—Wet about 5 g of Sodium Chloride by adding dropwise a freshly prepared mixture of soluble starch TS, 0.5 mol/L sulfuric acid TS and sodium nitrite TS (1000 : 40 : 3), allow to stand for 5 minutes, and examine under the direct sunlight; the solution does not exhibit a blue color.

(6) ***Phosphates***—To 2.0 mL of the solution obtained in (1), add water to make 100.0 mL, and then add 4 mL of ammonium molybdate-sulfuric acid TS and 0.1 mL of tin(II) chloride-hydrochloric acid TS, and allow to stand for 10 minutes; the color of the solution is not more intense than the following control solution (NMT 25 ppm).

Control solution—To 1.0 mL of standard phosphoric acid solution, add 12.5 mL of 2 mol/L sulfuric acid TS and water to make exactly 250 mL. To 100 mL of this solution, add 4 mL of ammonium molybdate-sulfuric acid TS and 0.1 mL of tin(II) chloride-hydrochloric acid TS, and proceed in the same manner as above.

(7) ***Sulfates***—To 7.5 mL of the solution obtained in (1), add water to make 30 mL, and use this solution as the test solution. Separately, dissolve 0.181 g of potassium sulfate in diluted ethanol(99.5) (3 in 10) to make exactly 500 mL. Pipet 5 mL of this solution, and add diluted ethanol(99.5) (3 in 10) to make exactly 100 mL. To 4.5 mL of this solution, add 3 mL of barium chloride solution (1 in 4), shake to mix, and allow to stand for 1 minute. To 2.5 mL of this solution, add 15 mL of the test solution and 0.5 mL of acetic acid(31), and allow to stand for 5 minutes; the solution is not more turbid than the following control solution (NMT 0.02%).

Control solution—Dissolve 0.181 g of potassium sulfate in water to make exactly 500 mL. Pipet 5 mL of this solution, and add water to make exactly 100 mL. Proceed in the same manner using this solution instead of the test solution.

(8) ***Ferrocyanides***—Dissolve about 2.0 g of Sodium Chloride in 6 mL of water, and add 0.5 mL of a mixture of iron(II) sulfate heptahydrate solution (1 in 100) and a solution of ammonium iron(III) sulfate dodecahydrate in diluted sulfuric acid (1 in 400) (1 in 100) (19 : 1); the resulting solution does not develop a blue color within 10 minutes.

(9) ***Magnesium and alkaline-earth metals***—To 200 mL of water, add 0.1 g of hydroxylamine hydrochloride, 10 mL of ammonium chloride buffer solution, pH 10, 1

mL of 0.1 mol/L zinc sulfate solution and 0.15 g of Eryochrome black T-sodium chloride indicator, and warm at 40 °C. Add 0.01 mol/L ethylenediaminetetraacetic acid disodium salt solution dropwise until the purple color of the solution turns blue. To this solution, add a solution prepared by dissolving 10.0 g of Sodium Chloride in 100 mL of water. If the resulting solution turns purple, add 0.01 mol/L ethylenediaminetetraacetic acid disodium salt solution until the color of the solution turns blue. The amount of 0.01 mol/L ethylenediaminetetraacetic acid disodium salt solution used in the second titration is NMT 2.5 mL (NMT 100 ppm).

(10) ***Barium***—To 5.0 mL of the solution obtained in (1), add 5.0 mL of water and 2.0 mL of dilute sulfuric acid, and allow to stand for 2 hours; the solution is not more turbid than the following control solution.

Control solution—To 5.0 mL of the solution obtained in (1), add 7.0 mL of water and allow to stand for 2 hours.

(11) ***Aluminum***—Perform the test when used in the manufacturing of hemodialysis preparations. Weigh accurately about 20 g of Sodium Chloride, dissolve in 100 mL of water, add 10 mL of acetic acid-ammonium acetate buffer solution, pH 6.0, and extract with 20 mL, 20 mL and 10 mL of 0.5% solutions of 8-hydroxyquinoline in chloroform. Collect in a 50-mL volumetric flask, add chloroform to make 50 mL, and use this solution as the test solution. Separately, weigh 0.352 g of aluminum potassium sulfate, dissolve in small amount of water, add 20 mL of dilute sulfuric acid, and then add water to make 100 mL. Pipet 1.0 mL of this solution immediately before use and add water to make 100 mL. Again, take 2.0 mL of this solution, add 10 mL of acetic acid-ammonium acetate buffer solution, pH 6.0, and then add 98 mL of water, and extract in the same manner as the test solution. Collect in a 50-mL volumetric flask, add chloroform to make 50 mL, and use this solution as the standard solution. To 10 mL of acetic acid-ammonium acetate buffer solution, pH 6.0, add 100 mL water, extract with chloroform in the same manner as the test solution, and use this solution as the blank test solution. Perform the test with the test solution and the standard solution as directed under the Fluorescence Spectroscopy with the blank test solution as the blank, and determine the fluorescence intensity at the excitation wavelength of 392 nm and the fluorescence wavelength of 518 nm; the fluorescence intensity obtained from the test solution is not greater than that from the standard solution (NMT 0.2 ppm).

(12) ***Iron***—To 10 mL of the solution obtained in (1), add 2 mL of citric acid monohydrate solution (1 in 5) and 0.1 mL of mercaptoacetic acid, alkalize with ammonia TS, then add water to make exactly 20 mL. Allow to stand for 5 minutes; the color of the solution is not more intense than that of the following control solution (NMT 5 ppm).

Control solution—Pipet 1 mL of iron standard solution, and add water to make exactly 25 mL. To 10 mL of this solution, add 2 mL of citric acid monohydrate solution (1 in 5) and 0.1 mL of mercaptoacetic acid, and proceed in the same manner as above.

(13) ***Potassium***—When used in the manufacturing of injections or preparations for peritoneal dialysis, hemodialysis or blood filtration, perform this test. Weigh accurately about 1 g of Sodium Chloride, add water, dissolve by mixing well to make 100 mL, and use this solution as the test solution. Separately, weigh accurately 1.144 g of potassium chloride, previously dried at 105 °C for 3 hours, dissolve in water to make 1000 mL to obtain a solution having known concentration of 600 μg of potassium per mL and use this solution as the standard stock solution. Dilute the standard stock solution to make three standard solutions at different concentrations to the extent the potassium content in the test solution is detectable. Perform the test with the test solution and each standard solution as directed under the Atomic Absorption Spectroscopy according to the following conditions at least three times.
Measure the potassium content using the calibration curve derived from the absorbance of the standard solution; it is NMT 500 ppm.

Gas: Air–acetylene
Wavelength: 766.5 nm

(14) ***Arsenic***—Proceed with 2.0 g of Sodium Chloride according to Method 1, and perform the test (NMT 1 ppm).

Bacterial endotoxins Less than 5 EU per g of Sodium Chloride when used in the manufacturing of injections. However, it is excluded in cases where there is an appropriate additional procedure for the removal of bacterial endotoxins in manufacturing of injections.

Loss on drying NMT 0.5% (1 g, 105 °C, 2 hours).

Assay Weigh accurately about 50 mg of Sodium Chloride, dissolve in 50 mL of water, and titrate with 0.1 mol/L silver nitrate VS (potentiometric titration under the Titrimetry).

Each mL of 0.1 mol/L silver nitrate VS
= 5.844 mg of NaCl

Packaging and storage Preserve in tight containers.

10% Sodium Chloride Injection
10% 염화나트륨 주사액

10% Sodium Chloride Injection is an aqueous solution for injection and contains NLT 9.5 w/v% and NMT 10.5 w/v% of sodium chloride (NaCl: 58.44).

Method of preparation

Sodium chloride	100 g
Water for injection	A sufficient amount
Total amount	1000 mL

Prepare as directed under Injections, with the above.

Description 10% Sodium Chloride Injection occurs as a clear, colorless liquid and has a saline taste.
It is neutral.

Identification 10% Sodium Chloride Injection responds to the Qualitative Tests for sodium salt and for chloride.

Sterility Meets the requirements.

Bacterial endotoxins Less than 3.6 EU/mL of Glucose Injection.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet 10 mL of 10% Sodium Chloride Injection and add water to make exactly 100 mL. Pipet 20 mL of this solution, add 30 mL of water and titrate with 0.1 mol/L silver nitrate VS while shaking vigorously (indicator: 3 drops of fluorescein sodium TS).

Each mL of 0.1 mol/L silver nitrate VS
= 5.844 mg of NaCl

Pipet 20 mL of this solution, add 30 mL of water and shake vigorously to mix, and titrate with 0.1 mol/L silver nitrate solution VS (indicator: 3 drops of fluorescein sodium TS).

Each mL of 0.1 mol/L silver nitrate VS
= 5.844 mg of NaCl

Packaging and storage Preserve in hermetic containers. Plastic containers for aqueous injections may be used for 10% Sodium Chloride Injection.

Sodium Chloride, Sodium Acetate, Potassium Chloride, Calcium Chloride, Magnesium Chloride and Dextrose Dialysis Solution

염화나트륨·아세트산나트륨수화물·염화칼륨·염화칼슘·염화마그네슘·포도당 투석액

Sodium Chloride, Sodium Acetate, Potassium Chloride, Calcium Chloride, Magnesium Chloride and Dextrose Dialysis Solution contains NLT 90.0% and NMT 110.0% of the labeled amounts of glucose ($C_6H_{12}O_6$: 180.16), total sodium (Na: 22.99) [sodium chloride (NaCl: 58.44) and sodium acetate hydrate ($CH_3COONa \cdot 3H_2O$: 136.08)], calcium (Ca: 40.08)[calcium chloride hydrate ($CaCl_2 \cdot 2H_2O$: 147.02)], magnesium (Mg: 24.31) [magnesium chloride hydrate ($MgCl_2 \cdot 6H_2O$: 203.30)], potassium (K: 39.10) [potassium chloride (KCl: 74.55)], sodium acetate hydrate ($CH_3COONa \cdot 3H_2O$: 136.08) and total chlorine (Cl: 35.45).

Method of preparation Prepare as directed under Dialysis Solutions, with Glucose, Sodium Chloride, Sodium Acetate Hydrate, Potassium Chloride, Calcium Chloride Hydrate and Magnesium Chloride Hydrate.

Identification (1) Take 20 mL of Sodium Chloride, Sodium Acetate, Potassium Chloride, Calcium Chloride, Magnesium Chloride and Dextrose Dialysis Solution, add 5 mL of hot Fehling's TS; a red precipitate is produced (glucose).

(2) Sodium Chloride, Sodium Acetate, Potassium Chloride, Calcium Chloride, Magnesium Chloride and Dextrose Dialysis Solution responds to the Qualitative Analysis for potassium salt, magnesium salt, chloride, sodium salt, calcium salt and acetate.

pH Between 6.0 and 8.0.

Purity (1) ***Heavy metals***—Proceed with 5.0 mL of Sodium Chloride, Sodium Acetate, Potassium Chloride, Calcium Chloride, Magnesium Chloride and Dextrose Dialysis Solution according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 4 ppm).

(2) ***Arsenic***—Take 2.0 mL of Sodium Chloride, Sodium Acetate, Potassium Chloride, Calcium Chloride, Magnesium Chloride and Dextrose Dialysis Solution, add water to make 5 mL, add 5 mL of dilute sulfuric acid and 1 mL of bromine TS, and heat on a steam bath for 5 minutes. Concentrate again to make 5 mL, cool, and perform the test using this solution as the test solution (NMT 1 ppm).

(3) ***5-hydroxymethylfurural***—Take 15 mL of Sodium Chloride, Sodium Acetate, Potassium Chloride, Calcium Chloride, Magnesium Chloride and Dextrose Dialysis Solution, and add water to make 100 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at a wavelength 284 nm is NMT 0.1.

Sterility It meets the requirements when used in manufacturing of sterile preparations.

Bacterial endotoxins Less than 0.5 EU per mL of Sodium Chloride, Sodium Acetate, Potassium Chloride, Calcium Chloride, Magnesium Chloride and Dextrose Dialysis Solution.

Pyrogen It meets the requirements when the bacterial

endotoxins is unavailable.

Assay (1) ***Total sodium***—Take an amount of Sodium Chloride, Sodium Acetate, Potassium Chloride, Calcium Chloride, Magnesium Chloride and Dextrose Dialysis Solution, equivalent to 1.1 g of sodium (Na), according to the labeled amount, and add water to make 1000 mL. Take 5.0 mL of this solution, add water to make 200 mL, take 5.0 mL of the resulting solution, and add water to make 100 mL. Use this solution as the test solution. Separately, weigh accurately about 254.2 mg (equivalent to about 100 mg of sodium) of sodium chloride standard reagent, previously dried at 105 °C for 2 hours, dissolve in water to make 1000 mL, and use this solution as the standard stock solution (about 100 μg/mL of sodium). Make a solution at a concentration of 0 to 20 μg Na/mL with the standard stock solution, and use this solution as the standard solution. Perform the test using the test solution and the standard solution as directed under the Atomic Absorption Spectroscopy according to the following conditions. Determine the amount of sodium (Na) in the test solution using the calibration curve obtained from the absorbance of the standard solution.

Gas: Air–acetylene
Lamp: Sodium hollow cathode lamp
Wavelength: 589 nm

(2) ***Potassium***—Pipet an amount of Sodium Chloride, Sodium Acetate, Potassium Chloride, Calcium Chloride, Magnesium Chloride and Dextrose Dialysis Solution, equivalent to 30 mg of potassium (K), according to the labeled amount, and add water to make exactly 200 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 190 mg of potassium chloride standard reagent, previously dried at 105 °C for 2 hours, add water to make 1000 mL, and use this solution as the standard stock solution (about 100 μg/mL of potassium). Weigh accurately 1.689 g of sodium chloride standard reagent, dissolve in water to make 100 mL, add the standard stock solution to 10.0 mL of this solution to make a solution of potassium at concentration of 0 to 20 μg/mL, and use this solution as the standard solution. Perform the test using the test solution and standard solution as directed under the Atomic Absorption Spectroscopy according to the following conditions. Determine the amount of potassium (K) in the test solution using the calibration curve obtained from the absorbance of the standard solution.

Gas: Air–acetylene
Lamp: Potassium hollow cathode lamp
Wavelength: 766 nm

(3) ***Calcium***—Pipet an amount of Sodium Chloride, Sodium Acetate, Potassium Chloride, Calcium Chloride, Magnesium Chloride and Dextrose Dialysis Solution, equivalent to 20 mg of calcium (Ca), according to the labeled amount, and add water to make exactly 100 mL. Pipet 20 mL of this solution again, add 20.0 mL of lanthanum oxide TS and water to make exactly 100 mL and use this solution as the test solution. Separately, weigh accurately about 1.249 g of calcium chloride standard reagent, dissolve in 50 mL of water and 10 mL of hydrochloric acid, add water to make exactly 1000 mL, and use this solution as the standard stock solution (about 500 μg/mL of calcium). Make a solution of calcium at a concentration of 0 to 16 μg/mL with the standard stock solution, and use this solution as the standard solution. Perform the test using the test solution and standard solution as directed under the Atomic Absorption Spectroscopy according to the following conditions. Determine the amount of calcium (Ca) in the test solution using the calibration curve obtained from the absorbance of the standard solution.

Gas: Air–acetylene
Lamp: Calcium hollow cathode lamp
Wavelength: 422.7 nm

(4) ***Magnesium***—Pipet an amount of Sodium Chloride, Sodium Acetate, Potassium Chloride, Calcium Chloride, Magnesium Chloride and Dextrose Dialysis Solution, equivalent to 4 mg of magnesium (Mg), according to the labeled amount, and add water to make 200 mL. Take 10.0 mL of this solution and add water to make 100 mL. Again, take 20.0 mL of this solution, add water to make 200 mL, and use this solution as the test solution. Separately, weigh accurately about 1.0 g of metal magnesium standard reagent, dissolve in a small amount of hydrochloric acid (1 in 2), add 1% hydrochloric acid TS to make 1000 mL, and use this solution as the standard stock solution (about 1000 μg/mL of magnesium). Make a solution of magnesium at a concentration of 0 to 10 μg/mL with the standard stock solution, and use this solution as the standard solution. Perform the test using the test solution and standard solution as directed under the Atomic Absorption Spectroscopy according to the following conditions. Determine the amount of magnesium (Mg) in the test solution using the calibration curve obtained from the standard solution.

Gas: Air–acetylene
Lamp: Magnesium hollow cathode lamp
Wavelength: 285 nm

(5) ***Sodium acetate hydrate***—Pipet an amount of Sodium Chloride, Sodium Acetate, Potassium Chloride, Calcium Chloride, Magnesium Chloride and Dextrose Dialysis Solution, equivalent to 0.25 g of sodium acetate hydrate ($CH_3COONa \cdot 3H_2O$), according to the labeled amount, and evaporate to dryness on a steam bath. Dissolve in 50 mL of acetic acid(100) for non-aqueous titration and 10 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS. However, the endpoint of the titration is when the purple color of the solution turns blue (indicator: 1 mL of methylrosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 13.610 mg of $CH_3COONa \cdot 3H_2O$

(6) ***Total chlorine***—Pipet an amount of Sodium Chloride, Sodium Acetate, Potassium Chloride, Calcium Chloride, Magnesium Chloride and Dextrose Dialysis Solution, equivalent to 70 mg of total chlorine (Cl), according to the labeled amount, add 50 mL of water, shake well to mix, and titrate with 0.1 mol/L silver nitrate VS (indicator: 1 mL of potassium chromate TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L silver nitrate VS
= 3.545 mg of Cl

(7) ***Glucose***—Pipet an amount of Sodium Chloride, Sodium Acetate, Potassium Chloride, Calcium Chloride, Magnesium Chloride and Dextrose Dialysis Solution, equivalent to 4g of glucose ($C_6H_{12}O_6$), according to the labeled amount, add 0.2 mL of ammonia TS and water to make 100 mL, and allow to stand for 30 minutes. Determine the optical rotation α_D at 25 °C with a layer length of 100 mm.

Amount (mg) of glucose ($C_6H_{12}O_6$)
= $\alpha_D \times 1985.4$

Packaging and storage Preserve in hermetic containers.

Sodium Chloride, Sodium Lactate Solution, Calcium Chloride, Magnesium Chloride and Dextrose Irrigation
염화나트륨·락트산나트륨액·염화칼슘·염화마그네슘·포도당 관류액

Sodium Chloride, Sodium Lactate Solution, Calcium Chloride, Magnesium Chloride and Dextrose Irrigation contains NLT 90.0% and NMT 110.0% of the labeled amounts of total sodium (Na: 22.99), calcium (Ca: 40.08), magnesium (Mg: 24.31), total chlorine (Cl: 35.45), lactate ($C_3H_5O_3$: 89.07) and glucose ($C_6H_{12}O_6$: 180.16).

Method of preparation Prepare as directed under Irrigations, with Sodium Chloride, Sodium Lactate Solution, Calcium Chloride, Magnesium Chloride and Glucose.

Identification (1) ***Glucose***—Take an amount of Sodium Chloride, Sodium Lactate Solution, Calcium Chloride, Magnesium Chloride and Dextrose Irrigation, equivalent to 0.1 g of glucose, according to the labeled amount, add water or concentrate on a steam bath, if necessary, to make 2 mL. Add 2 to 3 drops of this solution to 5 mL of boiling Fehling's TS; a red precipitate is produced.

(2) Sodium Chloride, Sodium Lactate Solution, Calcium Chloride, Magnesium Chloride and Dextrose Irrigation responds to the Qualitative Analysis for sodium salt, calcium salt, magnesium salt, lactate and chloride.

pH Between 4.5 and 6.5.

Purity (1) ***5-hydroxymethylfurural***—Add water to Sodium Chloride, Sodium Lactate Solution, Calcium Chloride, Magnesium Chloride and Dextrose Irrigation so that the glucose content becomes about 0.4% according to the labeled amount, and perform the test as directed under the Ultraviolet-visible Spectroscopy; the absorbance at the wavelength of 284 nm is NMT 0.25.

Bacterial endotoxins Less than 0.5 EU per mL of Sodium Chloride, Sodium Lactate Solution, Calcium Chloride, Magnesium Chloride and Dextrose Irrigation.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay (1) ***Total sodium***—Pipet an amount of Sodium Chloride, Sodium Lactate Solution, Calcium Chloride, Magnesium Chloride and Dextrose Irrigation, equivalent to 1.1 g of sodium (Na), according to the labeled amount, and add water to make 1000 mL. Take 5.0 mL of this solution and add water to make 200 mL. Take 5.0 mL of this solution and add 100 mL of water. Use this solution as the test solution. Separately, weigh accurately about 0.25 g (equivalent to about 100 mg of sodium) of sodium chloride standard reagent, previously dried at 105 °C for 2 hours, add water to make 1000 mL, and use this solution as the standard stock solution (about 100 μg/mL of sodium). Make a solution of sodium at a concentration 0 to 20 μg/mL with the standard stock solution, and use this solution as the standard solution. Perform the test using the test solution and the standard solution as directed under the Atomic Absorption Spectroscopy according to the following conditions. Determine the content of sodium (Na) in the test solution by using the calibration curve obtained from the absorbance of the standard solution.

Gas: Air–acetylene
Lamp: Sodium hollow cathode lamp
Wavelength: 589 nm

(2) ***Calcium***—Pipet an amount of Sodium Chloride, Sodium Lactate Solution, Calcium Chloride, Magnesium Chloride and Dextrose Irrigation, equivalent to 20 mg of calcium (Ca), according to the labeled amount, and add water to make 100 mL. Again, take 20 mL of this solution, add 20 mL of lanthanum oxide TS to make 100 mL,

and use this solution as the test solution. Separately, weigh accurately about 1.25 g of calcium chloride standard reagent, dissolve in 50 mL of water and 10 mL of hydrochloric acid, add water to make 100 mL, and use this solution as the standard stock solution (about 500 μg/mL of calcium). Prepare a solution of calcium at a concentration of 0 to 16 μg/mL with the standard stock solution, and use this solution as the standard solution. Perform the test using the test solution and standard solution as directed under the Atomic Absorption Spectroscopy according to the following conditions. Using the calibration curve obtained by the absorbance of the standard solution, determine the calcium (Ca) content in the test solution.

Gas: Air–acetylene
Lamp: Calcium hollow cathode lamp
Wavelength: 422.7 nm

(3) ***Magnesium***—Pipet an amount of Sodium Chloride, Sodium Lactate Solution, Calcium Chloride, Magnesium Chloride and Dextrose Irrigation, equivalent to 4 mg of magnesium (Mg), according to the labeled amount, and add water to make 200 mL. Take 10.0 mL of this solution and add water to make 100 mL. Again, take 20.0 mL of this solution, add water to make 200 mL, and use this solution as the test solution. Separately, weigh accurately about 1.0 g of metal magnesium standard reagent, dissolve in a small amount of hydrochloric acid (1 in 2), add 1% hydrochloric acid TS to make 1000 mL, and use this solution as the standard stock solution (about 1000 μg/mL of magnesium). Make a solution of magnesium at a concentration 0 to 10 μg/mL with the standard stock solution, and use this solution as the standard solution. Perform the test using the test solution and the standard solution as directed under the Atomic Absorption Spectroscopy according to the following conditions. Using the calibration curve obtained by the absorbance of the standard solution, determine the magnesium (Mg) content in the test solution.

Gas: Air–acetylene
Lamp: Magnesium hollow cathode lamp
Wavelength: 285 nm

(4) ***Glucose***—Pipet an amount of Sodium Chloride, Sodium Lactate Solution, Calcium Chloride, Magnesium Chloride and Dextrose Irrigation, equivalent to 4g of glucose ($C_6H_{12}O_6$), according to the labeled amount, add 0.2 mL of ammonia TS and water to make 100 mL, and allow to stand for 30 minutes. Determine the optical rotation α_D at 25 °C using a cell with a length of 200 mm.

Amount (mg) of glucose ($C_6H_{12}O_6$)
$= \alpha_D \times 947.7$

(5) ***Total chlorine***—Pipet an amount of Sodium Chloride, Sodium Lactate Solution, Calcium Chloride, Magnesium Chloride and Dextrose Irrigation, equivalent to 70 mg of total chlorine (Cl), according to the labeled amount, add 50 mL of water, shake well to mix, and titrate with 0.1 mol/L silver nitrate VS (indicator: 1 mL of potassium chromate TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L silver nitrate VS
= 3.545 mg of Cl

(6) ***Lactate***—Take an appropriate amount of Sodium Chloride, Sodium Lactate Solution, Calcium Chloride, Magnesium Chloride and Dextrose Irrigation, equivalent to a certain amount of lactate ($C_3H_5O_3$), according to the labeled amount, and use it as the test solution. Separately, dissolve sodium lactate RS in water to make 3 mg/mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of sodium lactate, A_T and A_S, in each solution.

Amount (mg) of sodium lactate ($C_3H_5O_3$)
= Concentration (mg/mL) of sodium lactate RS
$\times \frac{A_T}{A_S} \times \frac{89.07}{112.06}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelengths: 210 nm).

Column: A stainless steel column, about 4.6 mm in internal diameter and 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about drug 5 μm to 10 μm in particle diameter).

Mobile phase: A solution obtained by adding 1 mL of formic acid and 1 mL of dicyclohexylamine to 800 mL of water, and adding water to make 1000 mL.

Flow rate: 1.0 mL/min

System suitability

Inject a solution containing 3 mg of anhydrous sodium acetate RS and 3 mg of sodium lactate RS; the resolution is NLT 2. Repeat the test 5 times with 20 μL of the standard solution according to the above operating conditions; the relative standard deviation of the ratios of the peak areas is NMT 2.0%, and the symmetry factor is NMT 2.0.

Packaging and storage Preserve in hermetic containers.

Sodium Chondroitin Sulfate
콘드로이틴설페이트나트륨

Sodium Chondroitin Sulfate is a mucopolysaccharide that is the sodium salt of glycosaminoglycan sulfate, which is obtained from the cartilage tissue or trachea of healthy cattle, pigs, fish, or birds used for food by humans. Sodium Chondroitin Sulfate consists of the sodium salt of the sulfate ester of *N*-acetylcondrosamine (2-acetamino-2-deoxy-β-*D*-galactopyranose) and *D*-

glucuronic acid copolymer. These hexoses are alternatively linked β-1,4 and β-1,3 bonds in the polymer.

Sodium Chondroitin Sulfate, when dried, contains NLT 90.0% and NMT 105.0% of sodium chondroitin sulfate

Description Sodium Chondroitin Sulfate occurs as a white to pale yellowish white powder and has no odor or a slight characteristic odor.
It is freely soluble in water and practically insoluble in ethanol, acetone or ether.
It is hygroscopic.

Identification (1) Add 6 mL of sulfuric acid to 1 mL of an aqueous solution of Sodium Chondroitin Sulfate (1 in 1000), heat for 10 minutes on a steam bath, cool, add 0.2 mL of ethanolic solution of 0.125% carbazole and allow to stand at room temperature; the test solution exhibits a red to reddish purple color. Determine the absorption spectra as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at about 530 nm.

(2) Determine the spectra of Sodium Chondroitin Sulfate and sodium chondroitin sulfate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Sodium Chondroitin Sulfate (1 in 100) responds to the Qualitative Analysis (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: Between -20.0° and -30.0° (0.3 g, previously dried, water, 10 mL, 100 mm).

pH Between 5.5 and 7.5 (1% aqueous solution).

Purity (1) ***Clarity and color of solution***—Dissolve 2.5 g of Sodium Chondroitin Sulfate in 50 mL of water, and perform the test as directed under the Ultraviolet-visible Spectroscopy using water as the control; the absorbance at 420 nm is NMT 0.35.

(2) ***Chloride***—Perform the test with 0.10 g of Sodium Chondroitin Sulfate. Prepare the control solution with 0.7 mL of 0.02 mol/L hydrochloric acid (NMT 0.50%).

(3) ***Sulfate***—Dissolve 0.2 g of Sodium Chondroitin Sulfate in 40 mL of water, add 10 mL of 4.0% cetylpyridinium chloride solution, shake to mix, and filter. Use 25 mL of the filtrate as the test solution, and perform the test as directed under the Sulfate. Prepare the control solution with 0.25 mL of 0.02 mol/L sulfuric acid instead of Sodium Chondroitin Sulfate (NMT 0.24%).

(4) ***Heavy metals***—Proceed with 1.0 g of Sodium Chondroitin Sulfate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(5) ***Arsenic***—Weigh about 1.0 g of Sodium Chondroitin Sulfate according to Method 2 and perform the test (NMT 2 ppm).

(6) ***Protein***—Weigh accurately about 0.1 g of Sodium Chondroitin Sulfate, previously dried, dissolve in 10 mL of water, and use this solution as the test solution. Pipet 100 μL of this solution and dissolve in 700 μL of water, add 200 μL of colorimetric protein reagent and shake to mix. Determine the absorbance at 595 nm as directed under the Ultraviolet-visible Spectroscopy. Separately, serially dilute bovine serum albumin with water to concentrations of 5, 10, 15 and 20 μg/mL, proceed in the same manner as for the test solution and construct the calibration curve. Apply the absorbance of the test solution and determine the protein content of sodium chondroitin sulfate (NMT 3.5%).

Loss on drying NMT 10.0% (1 g, 105 ℃, 4 hours).

Residue on ignition Between 20.0% and 30.0% (1 g, calculated on the dried basis).

Assay Weight accurately about 0.1 g of Sodium Chondroitin Sulfate, previously dried, dissolve in water to make exactly 10 mL, filter with a membrane filter (0.45 μm), and use this solution as the test solution. Pipet 100 μL of the test solution and mix with 800 μL of 50 mM tris buffer solution (pH 8.0), add 100 μL of chondroitinase ABC enzyme solution and react for 1 hour at 37 ℃. Heat the solution for 5 minutes at 100 ℃ to stop the enzyme reaction, cool, centrifuge, filter the clear supernatant with a membrane filter (0.45 μm), and use the filtrate as the test solution. Separately, weigh accurately about 0.1 g of sodium chondroitin sulfate RS, proceed in the same manner as the test solution, and use this solution as the standard solution. Perform the test with 100 μL each of the test solution and standard solution [the column is pre-stabilized with water (pH 3.5).] as directed under the Liquid Chromatography, and measure the sum of peak areas for sodium chondroitin sulfate, A_T and A_S, of each solution.

$$\text{Amount (mg) of sodium chondroitin sulfate} = \text{Amount (mg) of sodium chondroitin sulfate RS} \times \frac{A_T}{A_S}$$

Sum of peak areas—Sum of peak areas of disaccharides (Di-0S, Di-6S, Di-4S) that appear in this order in the test solution and standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 232 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with silica gel coated with strong basic quaternary ammonium exchange resin for liquid chromatography.

Mobile phase: Control the step or gradient elution by mixing mobile phase A and mobile phase B as directed under the following table.

Mobile phase A: Water (pH 3.5)

Mobile phase B: 2 mol/L sodium chloride solution (pH 3.5)

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)

0 - 4	100	0
4 - 45	100 → 50	0 → 50
45 - 50	50	50

Flow rate: 1.0 mL/min

Packaging and storage Preserve in light-resistant, tight containers.

Sodium Chondroitin Sulfate Capsules
콘드로이틴설페이트나트륨 캡슐

Sodium Chondroitin Sulfate Capsules contain NLT 90.0% and NMT 110.0% of the labeled amounts of sodium chondroitin sulfate.

Method of preparation Prepared as directed under Capsules, with Sodium Chondroitin Sulfate.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the content NLT 20 Sodium Chondroitin Sulfate Capsules. Weigh an amount of Sodium Chondroitin Sulfate Capsules, equivalent to about 50 mg of sodium chondroitin sulfate, transfer into a 50-mL volumetric flask, add water to the volume, and transfer to a separatory funnel on the basis of quantity. Add 50 mL of n-hexane, shake well to mix, and allow to stand at room temperature. Pipet 200 μL of the water layer, and dilute with 800 μL of water. Add 1 mL of a mixture of phenol, chloroform and isoamyl alcohol (25 : 24 : 1), and shake well for 20 minutes to mix. Centrifuge at 15000 × g for 20 minutes, transfer 100 μL of the clear supernatant to a 1.5 mL test tube, dry completely (for example, use a speedvac at 60 ℃, etc.), and add 900 μL of 50 mM Tris buffer solution (pH 8.0). Mix for 10 minutes, add 100 μL of chondroitinase ABC enzyme solution, and react at 37 ℃ for 1 hour. Heat this solution at 100 ℃ for 5 minutes to stop the enzyme reaction, cool, centrifuge, and filter the clear supernatant with a membrane filter (0.45 μm). Inject 100 μL of the filtrate into the column, previously conditioned with water (pH 3.5). Separately, weigh accurately about 50 mg of sodium chondroitin sulfate RS, add 30 mL of water, shake to mix, and then add water to make 50 mL. Filter with a membrane filter (0.45 μm), transfer 100 μL of the filtrate to a 1.5-mL test tube, dry completely (for example, use a speedvac at 60 ℃, etc.), degrade by enzymes in the same manner as the test solution, and use this solution as the standard solution. Perform the test with 100 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions [However, use a column previously conditioned with water (pH 3.5)], and determine the sum of the peak areas, A_T and A_S, of sodium chondroitin sulfate in each solution.

$$\text{Amount (mg) of sodium chondroitin sulfate} = \text{Amount (mg) of sodium chondroitin sulfate RS} \times \frac{A_T}{A_S}$$

Sum of peak areas—Sum of peak areas of disaccharide (Di-0S, Di-6S, Di-4S) sequentially detected in the test solution and the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 232 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with silica gel coated with the strong basic quaternary ammonium anion exchange resin for liquid chromatography.

Mobile phase: Control the gradient by mixing the mobile phase A and mobile phase B as directed under the following table.

Mobile phase A: Water (pH 3.5)

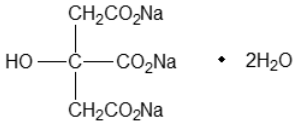
Mobile phase B: 2 mol/L sodium chloride solution (pH 3.5)

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 4	100	0
4 - 45	100 → 50	0 → 50
45 - 50	50	50

Flow rate: 1.0 mL/min

Packaging and storage Preserve in light-resistant, tight containers.

Sodium Citrate Hydrate
시트르산나트륨수화물



Sodium Citrate

$C_6H_5Na_3O_7 \cdot 2H_2O$: 294.10

Trisodium 2-hydroxypropane-1,2,3-tricarboxylate dihydrate [*6132-04-3*]

Sodium Citrate Hydrate, when dried, contains NLT 99.0% and NMT 101.0% of sodium citrate ($C_6H_5Na_3O_7$: 258.07).

Description Sodium Citrate Hydrate occurs as colorless crystals or a white crystalline powder. It is odorless and has a cool salty taste.

It is freely soluble in water and practically insoluble in ethanol(95) or ether.

Identification An aqueous solution of Sodium Citrate Hydrate (1 in 20) responds to the Qualitative Analysis for citrate and sodium salt.

pH Dissolve 1.0 g of Sodium Citrate Hydrate in 20 mL of water; the pH of this solution is between 7.5 and 8.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Sodium Citrate Hydrate in 10 mL of water; the solution is clear and colorless.

(2) ***Chloride***—Perform the test with 0.6 g of Sodium Citrate Hydrate. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid (NMT 0.015%).

(3) ***Sulfate***—Dissolve 0.5 g of 33.3% Sodium Citrate Hydrate in water to make 40 mL. Add 3.0 mL of dilute nitric acid and water to make 50 mL, and use this solution as the test solution. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid (NMT 0.048%).

(4) ***Heavy metals***—Proceed with 2.5 g of Sodium Citrate Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.5 mL of lead standard solution (NMT 10 ppm).

(5) ***Arsenic***—Prepare the test solution with 1.0 g of Sodium Citrate Hydrate, according to Method 1 and perform the test (NMT 2 ppm).

(6) ***Tartrate***—Add 2 mL of water, 1 mL of potassium acetate TS and 1 mL of acetic acid(31) to 1.0 g of Sodium Citrate Hydrate; a crystalline precipitate is not formed when scratching the inner wall with a glass rod.

(3) ***Oxylate***—Dissolve 1.0 g of Sodium Citrate Hydrate in 1 mL of water and 3 mL of dilute hydrochloric acid, add 4 mL of ethanol(95) and 0.2 mL of calcium chloride TS, and allow it to stand for 1 hour; the solution is clear.

(8) ***Readily carbonizable substances***—Proceed with 0.5 g of Sodium Citrate Hydrate and perform the test. Heat at 90 ℃ for 1 hour. The color of the solution is not more intense than that of the matching fluid K.

Loss on drying Between 10.0 and 13.0% (1 g, 180 °C, 2 hours).

Assay Weigh accurately about 0.1 g of Sodium Citrate Hydrate, previously dried, dissolve in water, put exactly 10 mL of internal standard solution and add water to make exactly 100 mL. Use this solution as the test solution. Weigh accurately about 0.1 g of sodium citrate hydrate RS, previously dried, dissolve in water, put 10 mL of internal standard solution and add water to make exactly 100 mL; use this solution as the test solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of sodium citrate to that of internal standard, respectively.

Amount (mg) of sodium citrate ($C_6H_5Na_3O_7$)
= Amount (mg) of sodium citrate in sodium citrate hydrate RS $\times \frac{Q_T}{Q_S}$

Internal standard solution—A solution of acetic acid (1 in 100).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 214 nm).

Column: A stainless steel column, about 4 mm in internal diameter and 15 cm to 30 cm in length is filled with octadecylsilanized silica gel for liquid chromatography.

Mobile phase: Dissolve 2.64 g of dibasic ammonium phosphate and 2 mL of triethylamine in 1000 mL of water, and adjust the pH to 2.5 with phosphoric acid.

Flow rate: Adjust the flow rate so that the retention time of sodium citrate is about 5 minutes.

Selection of column: When the procedure is run with 20 μL each of the standard solution according to the above conditions, internal standard and sodium citrate are eluted in this order with the resolution between their peaks being NLT 2.0.

Packaging and storage Preserve in tight containers.

Sodium Citrate Injection for Transfusion
수혈용 시트르산나트륨 주사액

Sodium Citrate Injection for Transfusion is an aqueous solution for injection, which contains NLT 9.5 w/v% and NMT 10.5 w/v% of sodium citrate hydrate ($C_6H_5Na_3O_7 \cdot 2H_2O$: 294.10).

Method of preparation

Sodium citrate hydrate	100 g
Water for injection	An appropriate amount
Total volume	1000 mL

Prepare as directed under Injections, with the above.
No preservative is added.

Description Diagnostic Sodium Citrate Solution occurs as a clear, colorless liquid.

Identification Sodium Citrate Injection for Transfusion responds to the Qualitative Analysis for sodium salt and citrate.

pH Between 7.0 and 8.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 5.6 EU per mL.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet 5 mL of Sodium Citrate Injection for Transfusion, and add water to make exactly 25 mL. Pipet 10 mL of this solution and evaporate to dryness on a steam bath. Dry the residue at 180 ℃ for 2 hours, add 30 mL of acetic acid(100), and dissolve by warming. After cooling, titrate with 0.1 mol/L perchloric acid VS (indicator: 3 drops of methylrosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 9.803 mg of $C_6H_5Na_3O_7 \cdot 2H_2O$

Packaging and storage Preserve in hermetic containers.

Diagnostic Sodium Citrate Solution
진단용 시트르산나트륨 액

Diagnostic Sodium Citrate Solution contains NLT 3.3 w/v% and NMT 4.3 w/v% of sodium citrate hydrate ($C_6H_5Na_3O_7 \cdot 2H_2O$: 294.10).

The requirements as described for aqueous injections under Injections are applicable.

Method of preparation

Sodium Citrate Hydrate	38 g
Water for injection	An appropriate amount
Total volume	1000 mL

Prepare as directed under Injections with the above.
No preservative is added.

Description Diagnostic Sodium Citrate Solution occurs as a clear, colorless liquid.

Identification Diagnostic Sodium Citrate Solution responds to the Qualitative Analysis for sodium salt and for citrate.

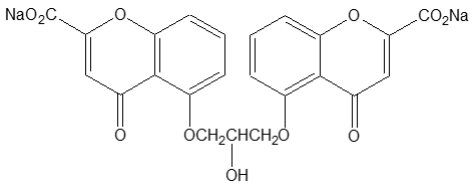
pH Between 7.0 and 8.5.

Assay Pipet 5.0 mL of Diagnostic Sodium Citrate Solution and evaporate on a steam bath to dryness. Dry the residue at 180 °C for 2 hours and dissolve in 30 mL of acetic acid(100) by warming. After cooling, titrate with 0.1 mol/L perchloric acid VS (indicator: 3 drops of methylrosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 9.803 mg of $C_6H_5Na_3O_7 \cdot 2H_2O$

Packaging and storage Preserve in hermetic containers.

Sodium Cromoglicate
크로모글리크산나트륨



$C_{23}H_{14}Na_2O_{11}$: 512.33
Disodium 5-[3-(2-carboxylato-4-oxochromen-5-yl)oxy-2-hydroxypropoxy]-4-oxochromene-2-carboxylate [*15826-37-6*]

Sodium Cromoglicate contains NLT 98.0% and NMT 101.0% of sodium cromoglicate ($C_{23}H_{14}Na_2O_{11}$), calculated on the dried basis.

Description Sodium Cromoglicate occurs as a white, crystalline powder. It is odorless and initially tasteless but later has a slightly bitter taste.
It is freely soluble in water, sparingly soluble in propylene glycol, very slightly soluble in ethanol(95) and practically insoluble in 2-propanol or ether.
It is hygroscopic.
It is gradually changed to yellow by light.

Identification (1) Dissolve 0.1 g of Sodium Cromoglicate in 2 mL of water, add 2 mL of sodium hydroxide TS and boil for 1 minute; the solution exhibits a yellow color. Cool the solution and add 0.5 mL of concentrated diazobenzenesulfonic acid TS; the solution exhibits a dark red color.

(2) Determine the absorption spectra of solutions of Sodium Cromoglicate and sodium cromoglicate RS in the phosphate buffer solution, pH 7.4 (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Sodium Cromoglicate responds to the Qualitative Analysis for sodium salt.

Purity (1) ***Clarity and color of solution***—Dissolve 0.50 g of Sodium Cromoglicate in 10 mL of water; the solution is clear and colorless to pale yellow.

(2) ***Acid or alkali***—Dissolve 2.0 g of Sodium Cromoglicate in 40 mL of freshly boiled and cooled water, add 6 drops of bromothymol blue TS and use this solution as the test solution. To 20 mL of the test solution, add 0.25 mL of 0.1 mol/L sodium hydroxide; the color of the solution is blue. To 20 mL of the test solution, add 0.25 mL of 0.1 mol/L hydrochloric acid; the

color of the solution is yellow.

(3) ***Heavy metals***—Proceed with 1.0 g of Ceftazidime Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Oxalate***—Weigh 0.25 g of Sodium Cromoglicate, dissolve in water to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately 49 mg of oxalate and dissolve in water to make exactly 100 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Pipet 20 mL each of the test solution and the standard solution, add exactly 5 mL of iron salicylate TS, and add water to make exactly 50 mL. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using water as the control; the absorbance of the solution obtained from the test solution at 480 nm is NLT that from the standard solution.

(5) ***Related substances***—Dissolve 0.20 g of Sodium Cromoglicate in 10 mL of water, and use this solution as the test solution. Pipet 1 mL of this solution and add water to make exactly 10 mL. Pipet 1 mL of this solution, add water to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of methanol, chloroform and acetic acid(100) (9 : 9 : 2) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 10.0% (1 g, in vacuum, 105 ℃, 4 hours).

Assay Weigh accurately about 0.18 g of Sodium Cromoglicate, add 25 mL of propylene glycol and 5 mL of 2-propanol, heat to dissolve and cool, and add 30 mL of 1,4-dioxane and titrate with 0.1 mol/L perchloric acid-1,4-dioxane VS (potentiometric titration under Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid-1,4-dioxane solution VS
= 25.62 mg of $C_{23}H_{14}Na_2O_{11}$

Packaging and storage Preserve in light-resistant, tight containers.

Sodium Ferric Gluconate Complex
글루콘산제이철나트륨착염

$[[Fe(OH)_3]_2 \cdot C_6H_{11}O_7Na]_n$

Sodium Ferric Gluconate Complex contains NLT 320 mg and NMT 380 mg of iron (Fe: 55.85) in each g of Sodium Ferric Gluconate Complex, calculated on the anhydrous basis. Sodium Ferric Gluconate Complex is a double salt obtained by reacting ferric hydroxide and sodium gluconate, and the equivalence ratio of iron and gluconic acid is 2 : 1.

Description Sodium Ferric Gluconate Complex occurs as a dark brown crystalline powder.

Identification (1) Add 2 mL of 25.0% hydrochloric acid to 1 mL of the aqueous solution of Sodium Ferric Gluconate Complex, heat it, and add 1 mL of 7.6% potassium thiocyanate TS; it turns red (iron).

(2) Weigh an appropriate amount of Sodium Ferric Gluconate Complex equivalent to 50 mg of iron, add water to make exactly 10 mL, and use this solution as the test solution. Separately, weigh an appropriate amount of sodium ferric gluconate complex RS equivalent to 50 mg of iron, add water to make exactly 10 mL, and use this solution as the standard solution. Put a cellulose acetate strip in Tris buffer solution, pH 9.0 for 10 minutes in advance, dry by sandwiching it between two sheets of paper, and put it in an electrophoresis chamber with Tris buffer solution, pH 9.0. Spot each of the test solution and the standard solution on the anode side of the strip, close the electrophoresis chamber, and perform an electrophoresis at 200 V for 30 minutes. Take out the strip and soak it in 1 mol/L hydrochloric acid for 3 minutes and then in 0.5% potassium ferrocyanide solution for 10 minutes. Soak the strip in a fixative (a solution in which methanol was added to 50 mL of a mixture of acetic acid, phenol, and water (800 : 90 : 110) to make 250 mL) for 1 minute, place it on a glass plate to air-dry; the standard solution and the test solution show a single blue band at the same R_f value.

(3) Dissolve 0.1 g of Sodium Ferric Gluconate Complex in water to make 100 mL. Take 10 mL of this solution, apply it in the strong acid ion exchange resin (H type) for column chromatography, flow it with water until the eluate becomes neutral, and use this solution as the test solution. Separately, weigh 0.1 g of sodium gluconate and add water to make 100 mL. Use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. and then air dry the plate. Next, develop the plate with a mixture of ethanol, water, ammonia and ethyl acetate (50 : 30 : 10 : 10) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Spray the coloring agent to the dried plate, and heat at 110 ℃ for 10 minutes; the R_f values of the spots obtained from the test and standard solutions are the same (gluconic acid).

(4) Determine the infrared spectra of Sodium Ferric Gluconate Complex and sodium ferric gluconate complex RS as directed in the potassium bromide disk method

under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(5) Weigh 0.1 g of Sodium Ferric Gluconate Complex, dissolve it in water to make exactly 50 mL, and use this solution as the test solution. Separately, weigh 100 mg of sodium ferric gluconate complex RS, dissolve it in water to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating; the test solution shows a peak at the same retention time as the standard solution.

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 254 nm).

Column: A stainless steel column about 7.8 mm in internal diameter and about 15 cm in length, packed with silica gel for liquid chromatography stabilized at a pH that can separate dextran with a molecular weight of 1000 to 30,000 Da (5 μm in particle diameter).

Mobile phase: A solution containing 0.05 mol/L, 0.15 mol/L, and 50 ppm of potassium monohydrogen phosphate, sodium chloride, and sodium azide (NaN_3), respectively, in 1000 mL of water, adjusted to pH 7.2 with 80.0% phosphoric acid, and filtered.

Flow rate: 0.6 mL/min

Dissolved state Dissolve 1.0 g of Sodium Ferric Gluconate Complex in 20 mL of water; the resulting solution is brown and clear.

pH Dissolve 5.0 g of Sodium Ferric Gluconate Complex in 40 mL of water; the pH of this solution is between 7.7 and 9.7.

Purity (1) ***Free Iron***—Weigh accurately about 0.25 g of Sodium Ferric Gluconate Complex, dissolve in water to make 10 mL, and use this solution as the test solution. Separately, dissolve about 172.5 mg of ammonium ferric sulfate dodecahydrate (an amount equivalent to about 20 mg as iron) in water to make 100 mL. Use this solution as the standard solution. Weigh 1 g of 80 - 100 mesh styrene-divinylbenzene copolymer (sodium type) (or its equivalent), suspend it in about 20 mL of distilled water for several minutes, pack it in a glass column (1 cm in diameter and 15 cm in height), and wash with water until it is decolorized. Next, elute subsequently with 5 mL of 1 mol/L hydrochloric acid, 7.5 mL of water and 5 mL of 1 mol/L sodium hydroxide, put it in a 50-mL volumetric flask, add 5 mL of 20.0% potassium thiocyanate aqueous solution, and make exactly 50 mL with 1 mol/L hydrochloric acid. Take 0.5 mL of the standard solution, proceed in the same way as the test solution, perform the test with each solution obtained from the standard solution and the test solution as directed under the Ultraviolet-visible Spectroscopy using 1 mol/L hydrochloric acid as the control solution, and determine the absorbance A_S and A_T at the wavelength of 470 nm. When calculated according to the following equation, free iron is NMT 2.0% of the total amount of iron.

$$\text{Content (\%) of free iron} = \frac{\text{Amount (mg) of iron in RS}}{\text{Amount (mg) of iron in sample}} \times \frac{A_T}{A_S} \times 5$$

(2) ***Free sodium gluconate***—Dissolve 5.0 g of Sodium Ferric Gluconate Complex in water to make 100 mL, and use this solution as the test solution. Separately, weigh 0.1 g of sodium gluconate, add water to make 100 mL, and use this solution as the standard solution. Spot each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography, and then air-dry the plate. Next, develop the plate with a mixture of ethanol, water, ammonia and ethyl acetate (50 : 30 : 10 : 10) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Spray a coloring agent on the dried plate and heat it at 110 ℃ for 10 minutes; the spots other than the principal spot from the test solution are not more intense than the spot from the standard solution (NMT 2.0%).

(3) ***Gluconic acid***—Weigh accurately about 200 mg of Sodium Ferric Gluconate Complex, add 18 mL of acetic anhydride, stir for 10 minutes, add 5 mL of distilled water, and stir for 10 minutes. To this solution, add 25 mL of acetic acid, stir for 10 minutes, and titrate with 0.1 mol/L perchloric acid VS. Perform a blank test in the same manner and make any necessary correction. The amount of total gluconic acid in Sodium Ferric Gluconate Complex is between 39.0 & and 62.0%, calculated on the anhydrous basis.

$$\text{Each mL of 1 mol/L perchloric acid VS} = 19.616 \text{ mg of } C_6H_{12}O_7$$

Water NMT 10.0%.

Assay Weigh accurately about 0.1 g of Sodium Ferric Gluconate Complex, add water to make 200 mL, and use this solution as the test solution. Separately, weigh accurately about 172.5 mg of ammonium ferric sulfate dodecahydrate (an amount equivalent to about 20 mg as iron) and dissolve in water to make 200 mL. Use this solution as the standard solution. Take 1 mL each of the test and standard solutions, transfer each to a 100-mL volumetric flask filled with 40 mL of water, add 10 mL of 20.0% sulfuric acid and 1 mL of nitric acid, and boil for 10 minutes. After cooling, add 10 mL of 20.0% potassium thiocyanate solution, add water to make exactly 100 mL, and filter. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy using water as the control solution, and determine the absorbance A_S and A_T at the wavelength of 470 nm.

$$\text{Amount (mg) of iron (Fe)} = \text{Amount (mg) of the reference standard taken}$$

$$\times \frac{A_T}{A_s} \times 0.1158 \times \frac{100}{100 - \text{water}(\%)}$$

0.1158: Atomic weight of iron (55.85) / Molecular weight of ferric sulfate dodecahydrate (482.25).

Coloring agent—Add 2.5 g of ammonium molybdate to a 100-mL volumetric flask containing 50 mL of 1 mol/L sulfuric acid, add 1.0 g of cerium sulfate, dissolve completely, and add 1 mol/L sulfuric acid to make exactly 100 mL.

Packaging and storage Preserve in tight containers.

Sodium Fluoride
플루오르화나트륨

NaF: 41.99

[*7681-49-4*]

Sodium Fluoride contains NLT 98.0% and NMT 102.0% of sodium fluoride (NaF), calculated on the dried basis.

Description Sodium Fluoride occurs as a white powder, which is odorless.
It is soluble in water and practically insoluble in ethanol(95).

Identification (1) Put 1 g of Sodium Fluoride into a platinum crucible, add 15 mL of sulfuric acid, cover with a plate, heat for 1 hour on a steam bath, then wash the glass plate with water, and dry; the surface of the glass plate is corroded.

(2) An aqueous solution of Sodium Fluoride (1 in 25) responds to the Qualitative Analysis for sodium salt.

Purity (1) ***Acidity or alkalinity***—Weigh 2.0 g of Sodium Fluoride, put in a platinum dish, and dissolve in 40 mL of water. Add 10 mL of saturated potassium nitrate solution, cool to 0 °C, then add 3 drops of phenolphthalein TS. If no color appears at this time, add 0.10 mol/L sodium hydroxide solution until a pale red color appears, which lasts for 15 seconds; the consumed amount is NMT 2.0 mL. If a pale red color appears immediately after adding phenolphthalein TS dropwise, add 0.05 mol/L sulfuric acid until the color fades; the consumed amount is NMT 0.50 mL. This neutral solution is used in the fluorosilicate test.

(2) ***Fluorosilicate***—Heat the neutral solution obtained in (1) until it boils, and titrate with 0.01 mol/L sodium hydroxide solution VS while hot until a persistent pale red color appears; the consumed amount is NMT 1.5 mL.

(3) ***Chloride***—Dissolve 0.3 g of Sodium Fluoride in 20 mL of water, add 0.2 mg of boric acid, 1 mL of nitric acid and 1 mL of 0.1 mol/L silver nitrate solution; the color of the resulting solution is not more intense than that of the control solution (NMT 0.012%).

Control solution—To 1 mL of 0.0010 mol/L hydrochloric acid, add 0.2 mg of boric acid, 1 mL of nitric acid and 1 mL of 0.1 mol/L silver nitrate solution.

(4) ***Heavy metals***—Weigh 1.0 g of Sodium Fluoride, put in a platinum crucible, add 1 mL of water and 3 mL of sulfuric acid, then heat at as low a temperature as possible until all the sulfuric acid is evaporated to dryness. Dissolve the residue in 20 mL of water, neutralize with ammonia water(28) with phenolphthalein TS as the indicator, add 1 mL of acetic acid(100) and water to make 45 mL, and filter. Use 30 mL of filtrate as the test solution and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

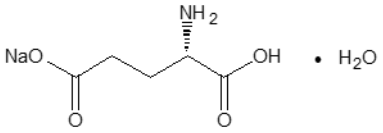
Loss on drying NMT 1.0% (1 g, 150 °C, 4 hours).

Assay Weigh accurately about 80 mg of Sodium Fluoride, dissolve in 25 mL of a mixture of acetic anhydride and acetic acid(100) (1 : 4), and titrate with 0.1 mol/L perchloric acid VS (indicator: methylrosaniline chloride TS). However, the endpoint of the titration is when the color turns green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 4.199 mg of NaF

Packaging and storage Preserve in well-closed containers.

Sodium L-Glutamate Hydrate
L-글루탐산나트륨수화물



$C_5H_8O_4NNa \cdot H_2O$: 187.13

L-Glutamic acid monosodium salt hydrate; Sodium(2S)-2-amino-5-hydroxy-5-oxopentanoate hydrate, [142-47-2, anhydrous]

Sodium L-Glutamate Hydrate, when dried, contains NLT 90.0% and NMT 101.0% of sodium L-glutamate ($C_5H_8O_4NNa$).

Description Sodium L-Glutamate Hydrate occurs as colorless or white columnar crystals or white crystalline powder.

Identification (1) Sodium L-Glutamate Hydrate responds to the Qualitative Analysis for sodium salt.

(2) Add 1 mL of ninhydrin TS to 5 mL of the aqueous solution (1 in 1000) of Sodium L-Glutamate Hydrate and heat for 3 minutes; the solution appears purple.

(3) Dry Sodium L-Glutamate Hydrate and sodium

L-glutamate hydrate RS, and determine the absorption spectra as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Clarity and color of solution***—Dissolve 1 g of Sodium L-Glutamate Hydrate in 10 mL of water; the solution is clear and colorless.

(2) ***Chloride***—Proceed with 0.5 g of Sodium L-Glutamate Hydrate according to the Chloride and perform the test. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.021%).

(3) ***Sulfate***—Proceed with 0.6 g of Sodium L-Glutamate Hydrate according to the sulfate limit test and perform the test. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid VS (NMT 0.028%).

(4) ***Ammonium***—Proceed with 0.25 g of Sodium L-Glutamate Hydrate according to the Ammonium and perform the test. Prepare the control solution with 5.0 mL of ammonium standard solution (NMT 0.020%).

(5) ***Heavy metals***—Proceed with 2 g of Sodium L-Glutamate Hydrate according to the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(6) ***Iron***—Place 1.0 g of Sodium L-Glutamate Hydrate in a separatory funnel, dissolve in 10 mL of diluted hydrochloric acid, add 10 mL of methyl isobutyl ketone, and shake for 3 minutes to mix. Repeat the above procedure 3 times. Take the organic solvent layer, add 10 mL of water to it and shake for 3 minutes. It meets the requirement, when the Iron is performed with the water layer (NMT 10 ppm).

(7) ***Arsenic***—Proceed with 2.0 g of Sodium L-Glutamate Hydrate according to Method 1 under the Arsenic and perform the test (NMT 1 ppm).

(8) ***Other amino acids***—Weigh 0.50 g of Sodium L-Glutamate Hydrate, dissolve in 50 mL of water, and use this solution as the test solution. Perform the test with the solution as directed under the Paper Chromatography. Spot 5 mL of the test solution onto the filter paper, develop the filter paper with a mixture of n-butanol, water and acetic acid(100) (2 : 1 : 1) to the distance of about 30 cm and air-dry the filter paper. Spray the ninhydrin-acetone solution (1 in 50) evenly onto this and heat at 90 ℃ for 10 minutes; no spots other than a single purple spot appear.

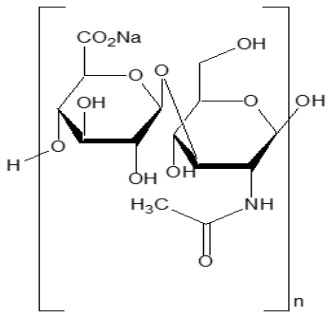
Loss on drying NMT 0.20% (1 g, 98 ± 1 °C, 5 hours).

Assay Weigh accurately 0.15 g of sodium L-glutamate hydrate, previously dried, dissolve it in 3 mL of formic acid, add 50 mL of acetic acid(100) for mixing, and titrate with 0.1 mol/L perchloric acid VS (indicator: 0.5 mL of α-naphthol benzene TS) until the solution turns from brown to green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 8.456 mg of $C_5H_8O_4NNa$

Packaging and storage Preserve in tight containers.

Sodium Hyaluronate
히알루론산나트륨



Sodium Hyaluronate $(C_{14}H_{20}NNaO_{11})n$
Sodium (2*S*,3*S*,4*R*,5*R*,6*R*)-3-{[(2*S*,3*R*,5*S*,6*R*)-3-(acetylamino)-5-hydroxy-6-(hydroxymethyl)tetra-hydro-2*H*-pyran-2-yl]oxy}-4,5,6-trihydroxytetrahydro-2*H*-pyran-2-carboxylate [*9067-32-7*]

Sodium Hyaluronate is prepared by extracting from the comb of the rooster or by fermenting *Streptococcus* Lancefield Groups A and C, through minimizing or removing infectious agents. When prepared by fermenting Gram-positive bacteria, indicate the process to reduce or remove cell wall components causing heating or inflammation.

Sodium Hyaluronate is the sodium salt of hyaluronic acid, glycosaminoglycans, composed of D-Glucuronic acid and N-acetyl-D-glucosamine disaccharide units.

Sodium Hyaluronate contains NLT 95.0% and NMT 105.0% of sodium hyaluronate $(C_{14}H_{20}NNaO_{11})n$, calculated on the dried basis. Sodium Hyaluronate has the intrinsic viscosity of between 90% and 120% of the labeled amount.

Description Sodium Hyaluronate occurs as a white powder, granules or fibrous masses.
It is sparingly soluble in water and practically insoluble in ethanol(95).
It is hygroscopic.

Identification (1) Determine the infrared spectra of Sodium Hyaluronate and sodium hyaluronate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve 0.1 g of Sodium Hyaluronate in 2 mL of water; it responds to the Qualitative Analysis for sodium.

pH Dissolve 50 mg of Sodium Hyaluronate, calculated on the dried basis, in 10 mL of water; the pH of this solution is between 5.0 and 8.5.

Intrinsic viscosity Since Sodium Hyaluronate is extremely hygroscopic, avoid the humidity during weighing. Weigh accurately 0.200 g (m_{0p}) of Sodium Hyaluronate (this value is only a labeled value and should be adjusted after measuring the initial viscosity of the test solution (1)), add 50.0 g (m_{0s}) of the buffer solution at 4 ℃, and shake to mix. Weigh accurately 5.00 g (m_{1p}) of this solution, add 100.0 g (m_{1s}) of the buffer solution at 25 ℃, shake to mix for 20 minutes, and filter with a glass filter. Discard the first 10 mL of the filtrate, and use the subsequent filtrate for the test solution (1) with concentration, C_1. Weigh accurately 30.0 g (m_{2p}) of the test solution (1), add 10.0 g (m_{2s}) of the buffer solution at 25 ℃, shake to mix for 20 minutes, and filter with a glass filter. Discard the first 10 mL of the filtrate, and use the subsequent filtrate for the test solution (2) with concentration, C_2. Take 20.0 g (m_{3p}) of the test solution (1), add 20.0 g (m_{3s}) of the buffer solution at 25 ℃, shake to mix for 20 minutes, and filter with a glass filter. Discard the first 10 mL of the filtrate, and use the subsequent filtrate for the test solution (3) with concentration, C_3. Take 10.0 g (m_{4p}) of the test solution (1), add 30.0 g (m_{4s}) of the buffer solution at 25 ℃, shake to mix for 20 minutes, and filter with a glass filter. Discard the first 10 mL of the filtrate, and use the subsequent filtrate for the test solution (4) with concentration, C_4. Measure the flow times at 25.00 ± 0.03℃ of the test solution (1), (2), (3) and (4), and the buffer solution, and take as t_1, t_2, t_3, t_4 and t_0, respectively. Measure the time of each solution until it flows from the upper capillary B mark to the lower mark 3 times applying the same capillary viscometer (viscometer constant: 0.005 mm^2/s^2, dynamic viscosity range: 1 - 5 mm^2/s^2, internal diameter of capillary below sphere C: 0.53 mm, volume of sphere B: 5.6 mL, internal diameter of capillary 2: 2.8 - 3.2 mm). The test is invalid if any of the measured values deviate by more than 0.35% from the mean value, and if the flow time t_1 is NMT 1.6 times or NLT 1.8 times t_0. In this case, repeat the test with adjusting the value m_{0p}.

Calculation of relative viscosity: As the density of sodium hyaluronate and the solvent are similar, the relative viscosities (η_{ri})(η_{r1}, η_{r2}, η_{r3} and η_{r4}) are calculated from the ratio of the flow time t_i (t_1, t_2, t_3, t_4) of each test solution to the flow time t_0 of the solvent.

$$n_{r1} = \frac{t_1 - \frac{B}{t_1^2}}{t_0 - \frac{B}{t_0^2}}$$

B: Correction factor for dynamic energy of the capillary (30800 s3).

Calculation of concentration: the concentration of sodium hyaluronate of the test solution (1)

Calculation of C_1 (kg/m3)

$$C_1 = m_{0\rho} \times \frac{x}{100} \times \frac{100-h}{100} \times \frac{1}{m_{0\rho}+m_{0s}} \times \frac{m_{1\rho}}{m_{1\rho}+m_{1s}} \times \rho_{25}$$

χ: Sodium hyaluronate content (%) obtained from the test solution of Assay

h: Loss on drying (%)

ρ_{25}: 1005 kg/m^3 (density of the test solution at 25℃).

Calculation of other concentrations

$$C_2 = C_1 \times \frac{m_{2\rho}}{m_{2\rho}+m_{2s}}$$

$$C_3 = C_1 \times \frac{m_{3\rho}}{m_{3\rho}+m_{3s}}$$

$$C_4 = C_1 \times \frac{m_{4\rho}}{m_{4\rho}+m_{4s}}$$

Calculation of intrinsic viscosity: the intrinsic viscosity [η] (m^3/kg) is determined from Least Squares Regression (PLSR) following Martin equation, and obtained from the antilog of the intercept value.

$$\log \{(\eta_r - 1)/C\} = \log [\eta] + k[\eta]c$$

Buffer solution—Prepare the solution A by dissolving 0.78 g of sodium dihydrogen phosphate dihydrate and 4.50 g of sodium chloride in 500.0 mL of water, and the solution B by dissolving 1.79 g of sodium hydrogen phosphate docahydrate and 4.50 g of sodium chloride in 500.0 mL of water. Add the solution B to the solution A, adjust the pH to 7.0 and filter using a glass filter.

Purity (1) ***Clarity and color of solution***—Take Sodium Hyaluronate, equivalent to 0.1 g, calculated on the dried basis, add 30 mL of 0.9 w/v% sodium chloride solution, and shake it gently for 12 hours; the solution is clear. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at 600 nm is NMT 0.01.

(2) ***Chloride***—Dissolve 67 mg of Sodium Hyaluronate in 100 mL of water, and to 15 mL of this solution, add 1 mL of dilute nitric acid and 1 mL of silver nitrate TS. Prepare the control solution with 10 mL of chloride standard solution and 5 mL of water, and add 1 mL of dilute nitric acid and 1 mL of silver nitrate TS.

Chloride standard solution—Weigh accurately 0.824 g of sodium chloride, add water to make exactly 1000 mL, and to 1 mL of this solution, add water to make exactly 100-mL before use.

(3) ***Heavy metals***—Prepare 1.0 g of Sodium Hyaluronate in a combustion flask of 100mL, add a mixture of nitric acid and sulfuric acid (5 : 4) until the sample is moistened enough, and heat gently. Repeat this operation until using 18 mL of the mixture of nitric acid and sulfuric acid (5 : 4). Boil until the solution turns black. After cooling, add 2 mL of nitric acid, and heat again until the solution turns black. Repeat the operation until the solution no longer turns black, and heat vigorously until dense white fumes appear. After cooling, add 5 mL of water, boil gently until dense white fumes appear, and heat until the volume of the solution becomes between 2

and 3 mL. After cooling, add 5 mL of water; if the solution still exhibits a yellow color, add 1 mL of concentrated hydrogen peroxide, and heat until the volume of the solution becomes between 2 and 3 mL. After cooling, add 2 - 3 mL of water to dilute, transfer to a Nessler tube, add water to make 25 mL, and use this solution as the test solution. Separately, take 2.0 mL of lead standard solution in a combustion flask of 100 mL, add 18 mL of a mixture of nitric acid-sulfuric acid (5 : 4) and the same amount of nitric acid as in the preparation of the test solution, and heat until dense white fumes appear. After cooling, add 10 mL of water; if concentrated hydrogen peroxide is used in the preparation of the test solution, add the same volume of concentrated hydrogen peroxide, proceed in the same manner as the test solution, and use this solution as the standard solution. Add ammonia water(28) to the test solution and the control solution to adjust the pH of the solutions between 3.0 and 4.0, and add water to make 40 mL. To each solution, add 1.2 mL of thioacetamide TS, 2 mL of acetate buffer solution, pH 3.5 and water to make 50 mL, allow to stand for 5 minutes, and compare the color of the solutions using a white paper. The color of the test solution is not more intense than that of the control solution (NMT 20 ppm). However, when used in the manufacturing of parenteral preparations, NMT 10 ppm. In this case, perform the test in the same manner specified above with 1.0 g of Sodium Hyaluronate and 1.0 mL of the lead standard solution for the test solution.

(4) ***Iron***—Weigh accurately Sodium Hyaluronate, equivalent to 0.25 g, calculated on the dried basis, add 1 mL of nitric acid, heat on a steam bath to dissolve, cool, add water to make exactly 10 mL, and use this solution as the test solution. Prepare another 2 solutions in the same manner as the test solution, previously cooled, add 1.0 mL and 2.0 mL of the iron standard solution, and use these solutions as the standard solution (1) and (2) respectively. Perform the test using the test solution and the standard solution (1) and (2) according to the Atomic Absorption Spectroscopy under the following conditions.

Gas: Air–acetylene
Lamp: Iron hollow cathode lamp
Wavelength: 248.3 nm

(5) ***Sulfated glycosaminoglycans***—Sodium Hyaluronate, when extracted from the comb of roosters, is suitable for the following test. Weigh Sodium Hyaluronate, equivalent to 50.0 mg, calculated on the dried basis, put in a test tube with a length of 150 mm and an internal diameter of 16 mm, add 1.0 mL of perchloric acid, and use this solution as the test solution. Dissolve 0.149 g of sodium sulfate decahydrate in water to make100.0 mL, take 10.0 mL of this solution, and add water to make 100.0 mL. Pipet 1.0 mL of this solution into a test tube, evaporate to dryness at between 90 and 95 ℃, dissolve the residue in 1.0 mL of perchloric acid, and use this solution as the standard solution. Seal each test tube of solution with glass wool, heat at 180 ℃ for 12 hours to make clear and transparent solution, and cool to room temperature. Add 3.0 mL of 3.33 w/v% barium chloride solution in each test tube, close the lid, shake vigorously, and allow to stand for 30 minutes. Perform the test with all solutions, using water as the control solution, as directed under the Ultraviolet-visible Spectroscopy and determine the absorbance of these solutions at 660 nm; the absorbance of the test solution is not greater than that of the control solution.

(6) ***Nucleic acid***—Weigh Sodium Hyaluronate, equivalent to 0.10 g, calculated on the dried basis, add 30 mL of 0.9 w/v% sodium chloride solution, shake gently for 12 hours until the solution becomes transparent and clear liquid, perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at 260 nm is NMT 0.5.

(7) ***Protein***—Weigh accurately an amount of Sodium Hyaluronate equivalent to 0.1 g, calculated on the dried basis, dissolve in water to make exactly 10 mL, and use this solution as the test solution (1). Mix the test solution (1) and water in the same volume ratio to prepare the test solution (2). Weigh accurately 50 mg of bovine serum albumin, dissolve in water to make exactly 100 mL, take 1.0, 3.0, 5.0, 7.0 and 10.0 mL of this solution, add water to make each 100 mL, and use these solutions as the standard solutions. Select an appropriate test solution considering the permitted limit and the calibration curve. Pipet 2.5 mL each of water (blank test solution), the test solution (1), and (2), and standard solutions into a test tube, add 2.5 mL of newly prepared Copper(II) tartrate TS in each tube, mix for 10 minutes, add each 0.5 mL of a mixture of water-phosphomolybdic acid TS (1 : 1), previously prepared, and allow to stand for 30 minutes. Determine the absorbances of these solutions at 750 nm as directed under the Ultraviolet-visible Spectroscopy, using the blank test solution as the control solution, and determine the protein content of the test solution from the calibration curve prepared with the absorbance of the standard solution (NMT 0.3%, and NMT 0.1% for injection).

Loss on drying NMT 20.0% (0.50 g, 105 ℃, 6 hours, phosphorus pentoxide(V)).

Sterility Meets the requirements (when prepared under aseptic conditions).

Bacterial endotoxins It is NMT 0.5 EU for each mg (when used for the manufacturing of parenteral preparations without any process to remove endotoxin). It is NMT 0.05 EU for each mg (when used for the manufacturing of intraocular or intra-articular preparations without any process to remove endotoxin).

Microbiological examination of non-sterile products The total aerobic microbial count is NMT 100 CFU per g of Sodium Hyaluronate.

Determination Determine the glucuronic acid content by reacting with carbazole. Weigh accurately about 0.170 g of Sodium Hyaluronate, dissolve in water to make ex-

actly 100 g, weigh accurately 10 g of this solution, add water to make exactly 200 g, and use this solution as the test solution. Repeat the same operation to prepare 3 test solutions. Weigh accurately about 0.1 g of D-Glucuronic acid, previously dried in vacuum to a constant mass, add water to make exactly 100 g, take a certain amount of this solution, add water to make 5 solutions containing between 6.5 μg and 65 μg per g, and use these solutions as the standard solutions. Prepare 25 test tubes, label from 1 to 25, and place in an ice bath. Take 1.0 mL of each of the 5 standard solutions 3 times for each concentration, place into test tubes and indicate as the standard solution tubes (1 - 15). Then, take 1.0 mL of each of the 3 test solutions 3 times, place into 9 test tubes, and indicate as the test solution tubes (16 - 24). Put water into the last tube, and indicate as the blank test solution tube (25). To each test tube, add 5 mL of sulfuric acid solution of 0.95 w/v% sodium tetraborate decahydrate, newly prepared, seal tightly with plastic caps, shake to mix, allow to stand on a steam bath for 15 minutes, and cool in an ice bath. To each test tube, add 0.2 mL of ethanol(95) solution of 0.125 w/v% carbazole, seal tightly with caps, shake to mix, allow to stand on a steam bath for 15 minutes, and cool to room temperature. Determine the absorbance of these solutions at the wavelength of 530 nm as directed under the Ultraviolet-visible Spectrophotometry, using the blank test solution as the control solution. Determine the mean concentration of D-Glucuronic acid in the test solutions with the calibration curve created from the mean absorbance of the standard solution.

$$\text{Amount (mg) of sodium hyaluronate } [(C_{14}H_{20}NNaO_{11})n] = \frac{C_g}{C_S} \times Z \times \frac{100}{100 - h} \times \frac{401.3}{194.1}$$

C_g: The mean concentration (mg/g) of D-Glucuronic acid in the test solutions

C_S: Concentration (mg/g) of Sodium Hyaluronate in the test solutions

Z: Content (%) of D-Glucuronic acid

h: Loss on drying (%)

401.3: Relative molecular weight of disaccharides

194.1: Relative molecular weight of glucuronic acid

Packaging and storage Preserve in light-resistant, tight containers.

Sodium Hyaluronate Ocular Injection
히알루론산나트륨 안과용주사액

Sodium Hyaluronate Ocular Injection, as used for ophthalmological surgery, contains NLT 90.0% and NMT 110.0% of the labeled amount of sodium hyaluronate $[(C_{14}H_{20}O_{11}NNa)_n]$.

Method of preparation Prepare as directed under Injections, with Sodium Hyaluronate.

Identification (1) ***Glucuronic acid*—**To 0.3 g of Sodium Hyaluronate Ocular Injection, add 50 mL of isotonic sodium chloride injection, and dissolve by shaking to mix. Carefully place 1 mL of this solution in a stoppered test tube containing previously cooled 5 mL of borax-sulfuric acid TS (0.95 in 100), and cool with care to maintain the temperature of the solution at not higher than the room temperature. While cooling, slowly shake initially and shake hard afterwards to mix. Heat in a boiling water bath for 10 minutes, immediately cool to the room temperature with iced water, add 0.2 mL of carbazole-ethanol TS (0.125 in 100), and shake enough to mix. Heat in a boiling water bath for 15 minutes, and immediately cool to the room temperature with iced water; the solution exhibits a red color.

(2) ***N-acetylglucosamine*—**Transfer 4 mg of Sodium Hyaluronate Ocular Injection to a test tube, dissolve in 0.4 mL of isotonic sodium chloride injection, add 0.1 mL of hyaluronidase solution, shake to mix, and warm on a steam bath for 30 minutes. To this solution, add 0.1 mL of boric acid solution, stopper the tube with a glass stopper, and heat in a boiling water bath for 3 minutes. Immediately cool with iced water, add 3 mL of 4-dimethylaminobenzaldehyde TS, shake enough to mix, and warm in a 37 ℃ water bath for 20 minutes; the solution exhibits a reddish purple color.

(3) An aqueous solution of Sodium Hyaluronate Ocular Injection (1 in 100) responds to the Qualitative Analysis (1) for sodium salt. Additionally, an aqueous solution of Sodium Hyaluronate Ocular Injection (1 in 10000) responds to the Qualitative Analysis (2) for sodium salt.

pH Between 6.3 and 8.3.

Purity (1) ***Protein*—**Use Sodium Hyaluronate Ocular Injection as the test solution. Separately, weigh accurately 0.10 g of bovine serum albumin, as the standard protein, and add it to isotonic sodium chloride injection to make 100 mL. To 2.5 mL of this solution, add isotonic sodium chloride injection to make 50 mL, and use this solution as the standard solution. Take 0.5 mL of the test solution and 0.5 mL of the standard solution, add 2.5 mL of alkaline copper solution to each, shake enough to mix, and allow each to stand for 10 minutes. To each, add 0.25 mL of 1 mol/L Folin solution, shake enough to mix, and allow each to stand for 30 minutes. Determine the absorbances, A_T and A_S, of the solutions, respectively, using a solution obtained by proceeding with 0.5 mL of isotonic sodium chloride injection in the same manner, as a control solution, at the wavelength of 750 nm as directed under the Ultraviolet-visible Spectroscopy, and determine the amount of protein in the test solution according to the following formula; it is NMT 25 μg/g.

$$\text{Amount (μg /g) of protein in the test solution} = 50 \times \frac{A_T}{A_S}$$

(2) ***Other acidic mucopolysaccharide***—To Sodium Hyaluronate Ocular Injection in the amount equivalent to about 10 mg of sodium hyaluronate according to the labeled amount, add 10 mL of barbital buffer solution, pH 8.6, dissolve by shaking to mix, and use this solution as the test solution. Perform the test with this solution as directed under the Electrophoresis. Apply 2 μL of this solution to a cellulose acetate membrane, in about 1/6 of the entire length and in the width of 1 cm, starting from the left end of the membrane. Next, electrify both ends at the current of 0.5 mA per cm of the membrane with barbital buffer solution, pH 8.6, for 20 minutes for electrophoresis. Immediately after electrophoresis is finished, dry the membrane with hot air, immerse it in 0.5% toluidine blue O solution, previously filtered with a filter paper, to stain the membrane for 1 minute, and wash with water. Dry the membrane with hot air and spread it by placing it on the filter paper to remove wrinkles; no spots other than the principal spot appear.

Bacterial endotoxins Less than 0.5 EU per mL.

Intrinsic viscosity Weigh accurately about 0.22 g of Sodium Hyaluronate Ocular Injection, add it to 10 mL of 0.15 mol/L sodium chloride solution, shake enough for 1 hour to mix, and add 0.15 mol/L sodium chloride solution to make 20 mL. Dilute this solution with 0.15 mol/L sodium chloride solution to make solutions diluted exactly 1.5-, 2.0-, 3.0- and 6.0-fold, and use these solutions as the test solutions. Perform the test with these solutions as directed under the Intrinsic viscosity of sodium hyaluronate; the intrinsic viscosity (dL/g) is 30 to 55 (dL/g).

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet Sodium Hyaluronate Ocular Injection in the amount equivalent to 3 mg of sodium hyaluronate $[(C_{14}H_{20}O_{11}NNa)_n]$, add isotonic sodium chloride injection to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of glucuronolactone and dissolve in benzoic acid saturated solution to make 100 mL. Add 3.0 mL of this solution to 100 mL of isotonic sodium chloride injection and use this solution as the standard glucuronolactone solution. Place exactly 1 mL each of the test solution and the standard glucuronolactone solution in a respective stoppered test tube containing previously cooled 5 mL of borax-sulfuric acid TS (0.95 in 100), and cool with care to maintain the temperature of each solution at not higher than the room temperature. While cooling, slowly shake initially and shake hard afterwards to mix. Heat each in a boiling water bath for 10 minutes, immediately cool to the room temperature with iced water, add 0.2 mL of carbazole-ethanol TS (0.125 in 100) to each, and shake enough to mix. Heat each in a boiling water bath for 15 minutes and immediately cool to the room temperature with iced water. Determine the absorbances, A_T and A_S, of these solutions, respectively, using a solution obtained by proceeding with 1 mL of isotonic sodium chloride injection in the same manner, as a control solution, at the wavelength of 530 nm, and determine the amount of sodium hyaluronate, calculated on the dried basis, in Sodium Hyaluronate Ocular Injection according to the following formula.

$$\text{Amount (mg) of sodium hyaluronate } [(C_{14}H_{20}O_{11}NNa)_n] = \text{Amount (mg) of glucuronolactone RS} \times \frac{A_T}{A_S} \times \frac{3}{200} \times 2.28$$

$\frac{3}{200}$: *dilution factor*

$$2.28: \frac{\left|\text{Molar mass of 1 unit of sodium hyaluronate } [(C_{14}H_{20}O_{11}NNa)n]\right|}{\text{Molar mass of glucuronolactone } (C_6H_8O_6)} = \frac{[(C_{14}H_{20}O_{11}NNa)_n]}{(C_6H_8O_6)} = \frac{401.30}{176.12}$$

Packaging and storage Preserve in hermetic containers.

Sodium Iodide
요오드화나트륨

NaI: 149.89

Sodium iodide [*7681-82-5*]

Sodium Iodide, when dried, contains NLT 99.0% and NMT 101.0% of sodium iodide (NaI).

Description Sodium Iodide occurs as colorless crystals or a white crystalline powder, and is odorless.
It is very soluble in water and freely soluble in glycerin or ethanol(95).
It is deliquescent in humid air.

Identification An aqueous solution of Sodium Iodide (1 in 20) responds to the Qualitative Analysis for sodium and iodide.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Sodium Iodide in 2 mL of water; the solution is clear and colorless.

(2) ***Alkalinity***—Dissolve 1.0 g of Sodium Iodide in 10 mL of freshly boiled and cooled water, add 1.0 mL of 0.005 mol/L sulfuric acid and 1 drop of phenolphthalein TS; the solution is colorless.

(3) ***Chloride, bromide and thiosulfate***—Dissolve 0.20 g of Sodium Iodide in 5 mL of ammonia TS, add 15.0 mL of 0.1 mol/L silver nitrate shake to mix for 2 to 3 minutes, and filter. To 10 mL of the filtrate, add 15 mL

of dilute nitric acid; the solution does not turn brown. Also, the turbidity of the solution is not more intense than that of the following control solution.

Control solution—To 0.30 mL of 0.01 mol/L hydrochloric acid, add 2.5 mL of ammonia TS, 7.5 mL of 0.1 mol/L silver nitrate solution, and 15 mL of dilute nitric acid.

(4) ***Nitrate, nitrite or ammonium***—Take 1.0 g of Sodium Iodide in a 40 mL test tube, add 5 mL of water, 5 mL of sodium hydroxide TS and 0.2 g of aluminum, and cover with absorbent cotton and carefully heat for 15 minutes on a steam bath; the gas produced does not change a moistened red litmus paper to blue.

(5) ***Cyanide***—Dissolve 0.5 of Sodium Iodide in 10 mL of water, add 1 drop of iron(II) sulfate TS and 2 mL of sodium hydroxide TS to 5 mL of this solution, warm, and add 4 mL of hydrochloric acid; the solution does not turn green.

(6) ***Iodate***—Dissolve 0.5 g of Sodium Iodide in 10 mL of freshly boiled and cooled water, and add 2 drops of dilute sulfuric acid and 1 drop of starch TS; the solution does not turn blue immediately.

(7) ***Heavy metals***—Proceed with 2.0 g of Sodium Iodide as directed under Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(8) ***Barium***—Dissolve 0.5 g of Sodium Iodide in 10 mL of water, add 1 mL of dilute sulfuric acid and allow to stand for 5 minutes; no turbidity is produced.

(9) ***Potassium***—Dissolve 1.0 g of Sodium Iodide in water to make 100 mL. To 4.0 mL of this solution, add 1.0 mL of dilute acetic acid and shake to mix. Add 5.0 mL of sodium tetraphenylborate solution (1 in 30), shake to mix and allow to stand for 10 minutes; the turbidity of the solution is not more intense than that of the following control solution.

Control solution—Dissolve 9.5 mg of potassium chloride in water to make 1000 mL. Add 1.0 mL of dilute acetic acid to 4.0 mL of this solution, shake to mix, and proceed in the same manner as the following.

(10) ***Arsenic***—Proceed with 0.40 g of Sodium Iodide as directed under Method 1 and perform the test (NMT 5 ppm).

Loss on drying NMT 5.0% (2 g, 120 ℃, 2 hours).

Assay Weigh accurately about 0.4 g of Sodium Iodide, previously dried, place in an iodine bottle and add 10 mL of water to dissolve. Add 35 mL of hydrochloric acid and 5 mL of chloroform and shake vigorously to mix; titrate with 0.05 mol/L potassium iodate VS until the purple color of the chloroform layer disappears. The endpoint is when the purple color of the chloroform layer does not reappear within 5 minutes after it is decolorized.

Each mL of 0.05 mol/L potassium iodate VS

= 14.989 mg of NaI

Packaging and storage Preserve in light-resistant, tight containers.

Sodium Iodide (^{123}I) Injection
요오드화나트륨(^{123}I) 주사액

Sodium Iodide (^{123}I) Injection contains iodine-123 in sodium iodide form.

Sodium Iodide (^{123}I) Injection contains, on the test date, NLT 90.0% and NMT 110.0% of the labeled amount of radioactivity of iodine-123.

Method of preparation (1) Isolate the iodine-123 created by bombarding telerium-124 with protons, prepare in the form of sodium iodide (^{123}I), purify, and prepare as directed under Injections.

(2) Isolate iodine-123 obtained from the decay of cesium-123 and xenon-123 created by bombarding xenon-124 with protons, prepare in the form of sodium iodide (^{123}I), purify, and prepare as directed under Injections.

Description Sodium Iodide (123I) Injection occurs as a clear, colorless and odorless liquid.

Identification (1) Place ^{123}I standard gamma ray radioactive source at a certain distance from the gamma-ray detector, and measure the gamma-ray spectrum. Find the relationship between the spectrum peak due to the photoelectric effect and gamma-ray energy from low energy to high energy at appropriate intervals to prepare the energy calibration curve for the spectrometer. Measure the gamma-ray spectrum for an appropriate amount of Sodium Iodide (123I) Injection; the test solution exhibits a maximum at 0.159 MeV.

(2) Test as directed under the Purity (1); a radioactivity maximum is exhibited at the iodide spot.

pH Between 7.0 and 9.0.

Purity (1) ***Radiochemical impurity***—Develop an appropriate amount of Sodium Iodide (123I) Injection as directed under the Thin Layer Chromatography to a distance of about 1 cm using 75% methanol as the developing solvent; radioactivity other than that of the spot for sodium iodide (^{123}I) Injection must be NMT 5% of total radioactivity.

(2) ***Radionuclide***—Test Sodium Iodide (^{123}I) Injection as directed under the Identification (1), and find the radioactivity of the 0.159 MeV maximum of iodine-123 and the 0.603 MeV maximum of iodide-124; the radioactivity of iodine-123 to the sum of the radioactivity as of the test date and time is NLT 95%.

Sterility Meets the requirements.

Bacterial endotoxins NMT 175/V EU per mL of Sodium Iodide (^{123}I) Injection. Provided, the V is the maximum recommended amount per mL in the effective time.

Assay Measure and compare the ionization current or converted indication value (hereinafter referred to as "ionization current") by using an ionization chamber in γ-ray emitted from the sample and the reference standard under the same conditions. Weigh accurately the sample and the reference standard of which radioactivity is known, add a solvent, if necessary, and dilute them to make the test and standard solutions. Put the same amount of the test and standard solutions in a measuring container made of the same material and shape. Place the container at a certain position in an ionization chamber and measure each ionization current to calculate radioactivity in a certain amount of the sample according to the following equation:

$$\text{Radioactivity in a certain amount of sample} = S \times \frac{I}{I'} \times \frac{D}{D'} \times G$$

S: Radioactivity in a certain amount of reference standard

I: Ionization current of the test solution

I': Ionization current of the standard solution

D: Dilution factor of sample

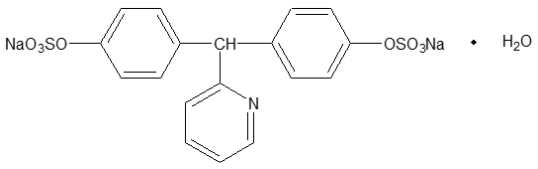
D': Dilution factor of reference standard

G: Correction terms such as geometric conditions of the position of test and standard solutions, etc.

However, use G = 1 as much as possible.

Expiration date Within 48 days of the test date.

Sodium Picosulfate Hydrate
피코설페이트나트륨수화물



Sodium Picosulfate $C_{18}H_{13}NNa_2O_8S_2 \cdot H_2O$: 499.42
Sodium 4,4'-(pyridin-2-ylmethylene)*bis*(4,1-phenylene) disulfate [*10040-45-6*, anhydride]

Sodium Picosulfate Hydrate contains NLT 98.5% and NMT 101.0% of sodium picosulfate ($C_{18}H_{13}N_2O_2S_2$), calculated on the anhydrous basis.

Description Sodium Picosulfate Hydrate occurs as a white, crystalline powder. It is odorless and tasteless.
It is very soluble in water, soluble in methanol, slightly soluble in ethanol(99.5) and practically insoluble in ether.
It is gradually colored by light.

Dissolve 1.0 g of Sodium Picosulfate Hydrate in 20 mL of water; the pH of the solution is between 7.4 and 9.4.

Identification (1) Add 10 mg of 1-chloro-2,4-dinitrobenzene to 5 mg of Sodium Picosulfate Hydrate to mix, and heat gently for 5 to 6 seconds to melt. After cooling, add 4 mL of potassium hydroxide-ethanol TS; the resulting solution exhibits an orange color.

(2) Add 5 mL of dilute hydrochloric acid to 0.2 g of Sodium Picosulfate Hydrate and boil the solution for 5 minutes. After cooling, add 1 mL of barium chloride; a white precipitate is produced.

(3) Determine the absorption spectra of aqueous solutions of Sodium Picosulfate Hydrate and sodium picosulfate hydrate RS (1 in 25000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared spectra of Sodium Picosulfate Hydrate and sodium picosulfate hydrate RS, previously dried at 105 °C for 4 hours, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(5) An aqueous solution of Sodium Picosulfate Hydrate (1 in 10) responds to the Qualitative Analysis for sodium salt.

Absorbance $E_{1cm}^{1\%}$ (263 nm): Between 120 and 130 (4 mg calculated on the anhydrous basis, water, 100 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Sodium Picosulfate Hydrate in 10 mL of water; the resulting solution is clear and colorless to pale yellow.

(2) ***Chloride***—Perform the test with 0.5 g of Sodium Picosulfate Hydrate. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid (NMT 0.028%).

(3) ***Sulfate***—Perform the test with 0.40 g of Sodium Picosulfate Hydrate. Prepare the control solution with 0.35 mL of 0.005 mol/L (NMT 0.042%).

(4) ***Heavy metals***—Proceed with 2.0 g of Sodium Picosulfate Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(5) ***Arsenic***—Proceed with 2.0 g of Sodium Picosulfate Hydrate according to Method 3 and perform the test (NMT 1 ppm).

(6) ***Related substances***—Dissolve 0.25 g of Sodium Picosulfate Hydrate in 5 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 500 mL, and use it as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of n-butanol, water and acetic acid(100) (74 : 20 : 19) as a developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 366 nm); any spot other than the principal spot obtained from the test solution is

not more intense than the spot from the standard solution.

Water Between 3.0% and 4.5% (0.5 g, volumetric titration, direct titration).

Assay Weigh accurately about 0.4 g of Sodium Picosulfate Hydrate, dissolve in 50 mL of methanol, add 7 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 48.14 mg of $C_{18}H_{13}NNa_2O_8S_2$

Packaging and storage Preserve in light-resistant, tight containers.

Sodium Polystyrene Sulfonate
폴리스티렌설폰산나트륨

Sodium poly (2-ethenylbenzenesulfonate) [*178955-71-0*]

Sodium Polystyrene Sulfonate is a sodium-type cation exchange resin produced by combining a sulfonic acid group with a copolymer of styrene and divinylbenzene.

Sodium Polystyrene Sulfonate contains 9.4% to 11.0% sodium (Na: 22.99), calculated on the anhydrous basis.

Each g of Sodium Polystyrene Sulfonatee, calculated on the anhydrous basis, exchanges with 0.110 to 0.135 g of potassium (K: 39.10).

Description Sodium Polystyrene Sulfonate occurs as a yellowish-brown powder. It is odorless and tasteless.
It is practically insoluble in water, ethanol(95), acetone or ether.

Identification (1) Determine the infrared spectra of Sodium Polystyrene Sulfonate and sodium polystyrene sulfonate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Add 10 mL of dilute hydrochloric acid to 1 g of Sodium Polystyrene Sulfonate, stir and mix, filter, and add ammonia TS to the filtrate to make it neutral. The solution responds to the Chemical identification reaction for sodium salt.

Purity (1) ***Ammonium***—Take 1.0 g of Sodium Polystyrene Sulfonate in a flask, add 5 mL of sodium hydroxide TS, cover the bottom with a watch glass with a wet red litmus test paper attached, and heat for 15 minutes; the gas produced does not change the red litmus test paper to blue.

(2) ***Heavy metals***—Proceed with 2.0 g of Sodium Polystyrene Sulfonate according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Prepare the test solution with 2.0 g of Sodium Polystyrene Sulfonate according to Method 2, and perform the test (NMT 1 ppm).

(4) ***Styrene***—Weigh 10.0 g of Sodium Polystyrene Sulfonate, add 10 mL of acetone, shake to mix for 30 minutes, and centrifuge. Use the clear supernatant as the test solution. Separately, weigh 10 mg of styrene and dissolve in acetone to make exactly 100 mL. Pipet 1 mL of this solution, add acetone to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area A_T and A_S of styrene in each liquid; A_T is not greater than A_S.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of water and acetonitrile (1 : 1).

Flow rate: Adjust the retention time so that the retention time of styrene is 7 to 8 minutes.

System suitability

System performance: Dissolve 20 mg each of styrene and butyl p-hydroxybenzoate in 100 mL of acetone. To 5 mL of this solution, add acetone to make 100 mL. Proceed with 20 mL of this solution according to the above operating conditions; butyl p-hydroxybenzoate and styrene are eluted in this order with the resolution being NLT 5.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of styrene is NMT 2.0%.

Water NMT 10.0% (0.2 g, volumetric titration, direct titration).

Assay (1) ***Sodium***—Weigh accurately about 1 g of Sodium Polystyrene Sulfonate, calculated on the anhydrous basis in a stoppered glass container, add exactly 50 mL of 3 mol/L hydrochloric acid TS, shake to mix for 60 minutes, and then filter. Discard the first 20 mL of the filtrate, pipet 5 mL of the subsequent filtrate, and add water to make 100 mL. Pipet 20 mL of this solution, add water to make exactly 1000 mL, and use this solution as the test solution. Separately, pipet an appropriate amount of sodium chloride standard stock solution, add water to dilute the solution so that each mL contains 1 to 3 μg of sodium (Na: 22.99), and use this solution as the standard solution. With the test and standard solutions, perform the test as directed under the Atomic Absorption Spectroscopy according to the following conditions, and determine

the sodium content in the test solution using the calibration curve obtained from the standard solution.

Gas: Air–acetylene
Lamp: Potassium hollow cathode lamp
Wavelength: 589.0 nm

(2) ***Potassium exchange capacity***—Weigh accurately about 1.5 g of Sodium Polystyrene Sulfonate, calculated on the anhydrous basis. in a stoppered glass container, add exactly 100 mL of potassium standard stock solution, shake to mix for 15 minutes, and then filter. Discard the first 20 mL of the filtrate, pipet 10 mL of the subsequent filtrate, and add water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make exactly 1000 mL, and use this solution as the test solution. Separately, take exactly an appropriate amount of potassium standard stock solution, add water to dilute the solution so that each mL contains 1 to 5 μg of potassium (K: 39.10), and use this solution as the standard solution. With the test and standard solutions, perform the test as directed under the Atomic Absorption Spectroscopy according to the following conditions, and determine the potassium content *Y* (mg) in 1000 mL of the test solution using the calibration curve obtained from the standard solution. Determine the potassium exchange amount per gram of Sodium Polystyrene Sulfonate, calculated on the anhydrous basis, using the following formula.

$$\text{Potassium (K) exchange rate (mg) per gram of Sodium Polystyrene Sulfonate, calculated on the anhydrous basis} = \frac{X - 100Y}{W}$$

X: Amount (mg) of potassium in 100 mL of potassium standard stock solution before exchange
W: Amount (mg) of Sodium Polystyrene Sulfonate taken, calculated on the anhydrous basis

Gas: Air–acetylene
Lamp: Potassium hollow cathode lamp
Wavelength: 766.5 nm

Packaging and storage Preserve in tight containers.

Sodium Pyrosulfite
피로아황산나트륨

Potassium Metabisulfite $Na_2S_2O_5$: 190.11
Disodiumpyrosulfite [*7681-57-4*]

Sodium Pyrosulfite contains NLT 95.0% and NMT 101.0% of sodium pyrosulfite ($Na_2S_2O_5$).

Description Sodium Pyrosulfite occurs as a white or almost white, crystalline power and has a sulfur dioxide-like odor.
It is freely soluble in water, very slightly solution in ethanol(95), and practically insoluble in ether.
An aqueous solution of Sodium Pyrosulfite (1 in 20) is acidity.
It is hygroscopic.
It gradually decomposes in air.

Identification An aqueous solution of Sodium Pyrosulfite (1 in 20) responds to the Qualitative Analysis for sodium salt and bisulfite.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Sodium Pyrosulfite in 10 mL of water; the solution is clear and colorless.

(2) ***Thiosulfate***—Dissolve 1.0 g of Sodium Pyrosulfite in 15 mL of water, add gradually 5 mL of dilute hydrochloric acid, shake and mix the solution, allow to stand for 5 minutes; the solution does not become turbid.

(3) ***Heavy metals***—Dissolve Sodium Pyrosulfite in 10 mL of water, add 5 mL of hydrochloric acid, and evaporate to dryness on a steam bath. Dissolve the residue in 10 mL of water, add 1 drop of phenolphthalein TS, add ammonia TS until the solution turn slightly red, and add 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by evaporating to dryness 5 mL of hydrochloric acid on a steam bath, adding 2 mL of dilute acetic acid, 2.9 mL of the lead standard solution and water to make 50 mL (NMT 20 ppm).

(4) ***Iron***—Prepare the test solution with 1.0 g of Sodium Pyrosulfite according to Method 1 and perform the test according to Method A. Prepare the control solution with 2.0 mL of the iron standard solution (NMT 20 ppm).

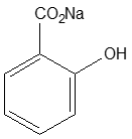
(5) ***Arsenic***—Dissolve Sodium Pyrosulfite in 10 mL of water, add 1 mL of sulfuric acid, heat in a sand bath until white fumes evolve, and add water to make 5 mL. Use this solution as the test solution and perform the test (NMT 4 ppm).

Assay Weigh accurately about 1.5 g of Sodium Pyrosulfite, and put in an iodine flask containing exactly 50 mL of 0.05 mol/L Iodine solution. Close the stopper of the flask, shake to mix, and allow to stand in a dark place for 5 minutes. Next, add 1 mL of hydrochloric acid, and titrate excess iodine with 0.1 mol/L sodium thiosulfate VS (indicator: 1 mL of starch TS). Perform a blank test in the same manner.

Each mL of 0.05 mol/L iodine VS
= 4.753 mg of $Na_2S_2O_5$

Packaging and storage Fill in a light-resistant, tight containers as full as possible, and preserve it at below 30 ℃.

Sodium Salicylate
살리실산나트륨



$C_7H_5NaO_3$: 160.10
Sodium 2-hydroxybenzoate [*54-21-7*]

Sodium Salicylate, when dried, contains NLT 98.0% and NMT 102.0% of sodium salicylate ($C_7H_5NaO_3$).

Description Sodium Salicylate occurs as white crystals or a crystalline powder.
It is very soluble in water, freely soluble in acetic acid(100) and soluble in ethanol(95).
It is gradually colored by light.

Identification (1) Determine the infrared spectra of Sodium Salicylate and sodium salicylate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Sodium Salicylate (1 in 20) responds to the Qualitative Analysis for sodium salt.

pH Dissolve 2.0 g of Sodium Salicylate in 20 mL of water; the pH of this solution is between 6.0 and 8.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Sodium Salicylate in 10 mL of water; the solution is clear. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at 420 nm is NMT 0.02.

(2) ***Chloride***—Dissolve 0.5 g of Sodium Salicylate in 15 mL of water and add 6 mL of dilute nitric acid and ethanol(95) to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 0.30 mL of 0.01 mol/L hydrochloric acid, 28 mL of ethanol(95), 6 mL of dilute nitric acid and water to make 50 mL (NMT 0.021%).

(3) ***Sulfate***—Dissolve 0.25 g of Sodium Salicylate in 5 mL of water, add 0.5 mL of barium chloride TS; the solution shows no change.

(4) ***Sulfite and thiosulfate***—Dissolve 1.0 g of Sodium Salicylate in 20 mL of water, add 1 mL of hydrochloric acid and filter it. Add 0.15 mL of 0.05 mol/L iodine solution to the filtrate; the color of the solution is yellow.

(5) ***Heavy metals***—Proceed with 1.0 g of Sodium Salicylate as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(6) ***Arsenic***—Put 1.0 g of Sodium Salicylate into a decomposition flask, add 5 mL of nitric acid and 2 mL of sulfuric acid, and heat carefully until white fumes are produced. After cooling, add 2 mL of nitric acid, heat, and cool it again. Then, add 2 mL of hydrogen peroxide water (30) and heat again until the solution becomes colorless to pale yellow. Repeat the procedure of adding nitric acid and hydrogen peroxide water (30) and heating, if necessary. After cooling, add 2 mL of saturated ammonium oxalate solution and heat again until white fumes are produced. After cooling, add water to make 5 mL and perform the test with this solution using as the test solution (NMT 2 ppm).

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

Assay Weigh accurately about 0.2 g each of Sodium Salicylate and sodium salicylate RS, previously dried, and dissolve by adding water to make exactly 100 mL. Pipet 10.0 mL each of these solutions, add 10.0 mL of the internal standard solution and water to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions and calculate the peak area ratios, Q_T and Q_S, of sodium salicylate to that of internal standard, respectively.

$$\text{Amount (mg) of sodium salicylate } (C_7H_5NaO_3) = \text{Amount (mg) of sodium salicylate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh 20 mg of anhydrous caffeine RS and dissolve in water to make 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

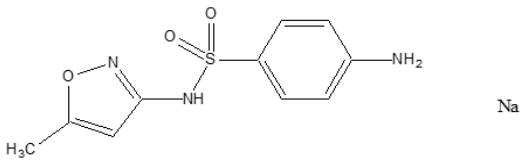
Mobile phase: A mixture of water, methanol and acetic acid(31) (50 : 50 : 1).

Flow rate: Adjust the flow rate so that the retention time of sodium salicylate is about 8.5 minutes.

Selection of column: Proceed with 10 μL of the standard solution according to the above conditions; internal standard and sodium salicylate are eluted in this order with the resolution between their peaks being NLT 4.0.

Packaging and storage Preserve in light-resistant, tight containers.

Sodium Sulfamethoxazole
설파메톡사졸나트륨



$C_{10}H_{11}N_3O_3S \cdot Na$: 275.26
4-Amino-*N*-(5-methyl-3-isoxazolyl)-benzenesulfonamide sodium salt (1:1), [*4563-84-2*]

Sodium Sulfamethoxazole, when dried, contains NLT 98.0% and NMT 101.0% of sodium sulfamethoxazole ($C_{10}H_{10}N_3NaO_3S$).

Description Sodium Sulfamethoxazole occurs as white crystals or a crystalline powder. It is odorless and has a bitter taste.
It is very soluble in water, slightly soluble in ethanol, and practically insoluble in ether.

Identification (1) Dissolve 0.4 g of Sodium Sulfamethoxazole in 10 mL of water, and add 1 mL of 1 mol/L hydrochloric acid TS to mix and separate crystals. Filter the precipitate, wash with a small amount of water, and dry at 105 ℃ for 2 hours. Dissolve 10 mg of the crystals in 1 mL of dilute hydrochloric acid and 4 mL of water; the solution responds to the Qualitative Analysis for primary aromatic amine.

(2) Dissolve 20 mg of the crystals obtained from (1) in 5 mL of water and 1 mL of *n*-butylamine, add 2 to 3 drops of copper sulfate TS, and shake well to mix. To this, add 5 mL of chloroform, shake to mix, and allow to stand; the chloroform layer exhibits a bluish green color.

(3) Determine the melting point of the crystals obtained from (1); the melting point is between 169 and 172 ℃.

(4) Determine the infrared spectrum of Sodium Sulfamethoxazole as directed in the paste method under the Mid-infrared Spectroscopy; it exhibits absorption at the wavenumbers of about 3505 cm^{-1}, 3400 cm^{-1}, 3220 cm^{-1}, 1625 cm^{-1}, 1595 cm^{-1}, 1315 cm^{-1} and 1170 cm^{-1}.

(5) An aqueous solution of Sodium Sulfamethoxazole (1 in 10) responds to the Qualitative Analysis for sodium salt.

pH Dissolve 2.0 g of Sodium Sulfamethoxazole in 20 mL of water; the pH of this solution is between 9.2 and 10.4.

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Sodium Sulfamethoxazole in 10 mL of water; the resulting solution is clear and colorless.

(2) ***Heavy metals*—**Proceed with 1.0 g of Sodium Sulfamethoxazole as directed under Method 3 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances*—**Weigh accurately 0.1 g of Sodium Sulfamethoxazole, dissolve in 5 mL of water, and use this solution as the test solution. Pipet 1 mL of this solution and add water to make exactly 20 mL. Pipet 1 mL of this solution, add water to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of tetrahydrofuran, acetonitrile, water and strong ammonia water (150 : 150 : 20 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

Assay Weigh accurately about 0.4 g of Sodium Sulfamethoxazole, previously dried, add 100 mL of water to dissolve, and titrate with 0.1 mol/L hydrochloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L hydrochloric acid VS
= 27.53 mg of $C_{10}H_{10}N_3NaO_3S$

Packaging and storage Preserve in tight containers.

Sodium Thiosulfate Hydrate
티오황산나트륨수화물

Sodium Thiosulfate $Na_2S_2O_3 \cdot 5H_2O$: 248.18
Sodium thiosulfate hydrate [*7772-98-7*, anhydrous]

Sodium Thiosulfate Hydrate, when dried, contains NLT 99.0% and NMT 101.0% of sodium thiosulfate ($Na_2S_2O_3$: 158.11).

Description Sodium Thiosulfate Hydrate occurs as colorless crystals or a crystalline powder and is odorless.
It is very soluble in water, very slightly soluble in ethanol(95) and practically insoluble in ether.
It effloresces in dry air and deliquesces in humid air.

Identification An aqueous solution of Sodium Thiosulfate Hydrate (1 in 10) responds to the Qualitative Analysis for sodium salt and thiosulfate.

pH Dissolve 1.0 g of Sodium Thiosulfate Hydrate in 10 mL of water; the pH of this solution is between 6.0 and 8.0.

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Sodium Thiosulfate Hydrate in 10 mL of water; the resulting solution is clear and colorless.

(2) ***Heavy metals***—Dissolve 1.0 g of Sodium Thiosulfate Hydrate in 10 mL of water, evaporate to dryness on a steam bath by slowly adding 5 mL of dilute hydrochloric acid. To the residue, add 15 mL of water, boil gently for 2 minutes, and then filter. Heat the filtrate to boiling, add bromine TS while it is hot, and when the solution becomes clear and there is a slight excess of bromine, boil it again to remove bromine. After cooling, add 1 drop of phenolphthalein TS and add sodium hydroxide TS one drop at a time until the solution exhibits a slight red color. Add 2 mL of dilute acetic acid, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 2 mL of dilute acetic acid and water to 2.0 mL of lead standard solution to make 50 mL (NMT 20 ppm).

(3) ***Calcium***—Dissolve 1.0 g of Sodium Thiosulfate Hydrate in 10 mL of water, add 2 mL of ammonium oxalate TS, and allow to stand for 4 minutes; the solution does not become turbid.

(4) ***Arsenic***—To 0.40 g of Sodium Thiosulfate Hydrate, add 3 mL of nitric acid and 5 mL of water, evaporate it to dryness on a steam bath. Proceed with the residue according to Method 2 and perform the test (NMT 5 ppm).

Loss on drying Between 32.0% and 37.0% (1 g, in vacuum, 40 ℃ to 45 ℃, 16 hours).

Assay Weigh accurately 0.4 g of Sodium Thiosulfate Hydrate, previously dried, dissolve in 30 mL of water, and titrate with 0.05 mol/L iodine VS (indicator: 1 mL of starch TS).

Each mL of 0.05 mol/L iodine VS
= 15.811 mg of $Na_2S_2O_3$

Packaging and storage Preserve in tight containers.

Sodium Thiosulfate Injection
티오황산나트륨 주사액

Sodium Thiosulfate Injection is an aqueous solution for injection. Sodium Thiosulfate Injection contains not less that 95.0% and NMT 105.0% of the labeled amount of sodium thiosulfate ($Na_2S_2O_3 \cdot 5H_2O$: 248.18).

Method of preparation Prepare as directed under Injections, with Sodium Thiosulfate Hydrate.

Description Sodium Thiosulfate Injection occurs as a clear, colorless liquid.

Identification Sodium Thiosulfate Injection responds to the Qualitative Analysis for sodium salt and thiosulfate.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.01 EU per mg of sodium thiosulfate.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

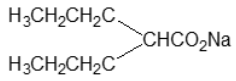
Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Sodium Thiosulfate Injection equivalent to 0.5 g of sodium thiosulfate ($Na_2S_2O_3 \cdot 5H_2O$), add water to make 30 mL, and titrate with 0.05 mol/L iodine VS (indicator : 1 mL of starch TS).

Each mL of 0.05 mol/L iodine VS
= 24.818 mg of $Na_2S_2O_3 \cdot 5H_2O$

Packaging and storage Preserve in hermetic containers.

Sodium Valproate
발프로산나트륨



$C_8H_{15}NaO_2$: 166.19
Sodium 2-propylpentanoate [*1069-66-5*]

Sodium Valproate, when dried, contains NLT 98.5% and NMT 101.0% of sodium valproate ($C_8H_{15}NaO_2$).

Description Sodium Valproate occurs as a white crystalline powder. It has a characteristic odor and a bitter taste.
It is very soluble in water, freely soluble in formic acid, ethanol(95), ethanol(99.5) or acetic acid(100) and practically insoluble in ether.
It is hygroscopic.

Identification (1) Add 4 mL of hydroxylamine perchlorate-ethanol (99.5) TS and 1 mL of *N,N'*-dicyclohexylcarbodiimide-ethanol (99.5) TS in 1 mL of a solution of Sodium Valproate in ethanol(99.5) (1 in 200), shake well to mix, and allow it to stand in lukewarm water for 20 minutes. After cooling, add 1 mL of iron(III) perchlorate hexahydrate-ethanol (99.5) TS, and shake well to mix; the resulting solution exhibits a violet color.

(2) Take 5 mL of an aqueous solution of Sodium Valproate (1 in 20), add 1 mL of cobalt nitrate solution (1 in 20), and warm on a steam bath; a violet precipitate is formed.

(3) Weigh 0.5 g each of Sodium Valproate and sodium valproate RS, dissolve in 5 mL of water, respectively, add 5 mL of chloroform and 1 mL of 2 mol/L hydrochloric acid TS, and shake strongly to mix. Allow it to stand, take the chloroform layer separately, dehydrate

with anhydrous sodium sulfate, and filter. Determine the infrared spectra of the residues as directed under the liquid membrane method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) An aqueous solution of Sodium Valproate (1 in 10) responds to the Qualitative Analysis for sodium salt.

pH Dissolve 1.0 g of Sodium Valproate in 20 mL of water; the pH of this solution is between 7.0 and 8.5.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Sodium Valproate in 10 mL of water; the resulting solution is clear and colorless.

(2) ***Chloride***—Dissolve 0.5 g of Sodium Valproate in 25 mL of ethanol(95), and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 0.70 mL of 0.01 mol/L hydrochloric acid, 25 mL of ethanol(95) and 6 mL of dilute nitric acid to make 50 mL (NMT 0.050%).

(3) ***Sulfate***—Dissolve 0.5 g of Sodium Valproate in 25 mL of ethanol(95), and add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 0.50 mL of 0.005 mol/L sulfuric acid, 25 mL of ethanol(95), 1 mL of dilute hydrochloric acid and water to make 50 mL (NMT 0.048%).

(4) ***Heavy metals***—Dissolve 2.0 g of Sodium Valproate in 44 mL of water, add 6 mL of dilute hydrochloric acid, shake well to mix, and allow it to stand for 5 minutes. Filter, discard 5 mL of the first filtrate, take 25 mL of the subsequent filtrate, neutralize with ammonia TS, and add 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 2 mL of lead standard solution and 2 mL of dilute acetic acid and water to make 50 mL (NMT 20 ppm).

(5) ***Arsenic***—Dissolve 2.0 g of Sodium Valproate in 10 mL of water, add 10 mL of dilute hydrochloric acid, shake well to mix, and allow it to stand for 5 minutes. Filter, discard 5 mL of the first filtrate, and take 10 mL of the subsequent filtrate. Use this solution as the test solution and perform the test (NMT 2 ppm).

(6) ***Related substances***—Dissolve 0.10 g of Sodium Valproate in 10 mL of a mixture of formic acid and chloroform (1 : 1), and use this solution as the test solution. Pipet 1 mL of this solution, add a mixture of formic acid and chloroform (1 : 1) to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 2 μL each of the test solution and standard solution as directed under the Gas Chromatography according to the following conditions. Determine the peak area of each solution as directed in the automatic integration method; the sum of peak areas other than the peak of valproic acid from the test solution is not greater than the peak area of valproic acid from the standard solution.

Operating conditions

Detector: A flame ionization detector.

Column: A column about 3 mm in internal diameter and about 2 m in length, packed with diethylene glycol adipic acid ester for gas chromatography and phosphoric acid covered with diatomaceous earth for gas chromatography with 5% and 1% ratio (between 150 and 180 μm in particle diameter).

Column temperature: A constant temperature of about 145 °C.

Carrier gas: Nitrogen

Flow rate: Adjust the flow rate so that the retention time of valproic acid is between 6 and 10 minutes.

System suitability

Detection sensitivity: Adjust the sensitivity so that the peak height of valproic acid obtained from 2 μL of the standard solution is between 4 and 10 mm.

System performance: Mix 1 mL of the test solution and 4 mL of a mixture of formic acid and chloroform (1 : 1) of *n*-valeric acid. Proceed with 2 μL of this solution according to the above conditions; *n*-valeric acid and valproic acid are eluted in this order with a resolution being NLT 3.

Time span of measurement: About 2 times the retention time of valproic acid after the solvent peak.

Loss on drying NMT 1.0% (1 g, 105 ℃, 3 hours).

Assay Weigh accurately about 0.2 g of Sodium Valproate, previously dried, dissolve in 80 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 16.619 mg of $C_8H_{15}NaO_2$

Packaging and storage Preserve in tight containers.

Sodium Valproate for Injection
주사용 발프로산나트륨

Sodium Valproate for Injection is an injection, which is dissolved before use, and contains NLT 95.0% and NMT 105.0% of the labeled amount of sodium valproate ($C_8H_{15}NaO_2$: 166.19).

Method of preparation Prepare as directed under Injections, with Sodium Valproate.

Identification (1) An aqueous solution of Sodium Valproate for Injection (1 in 10) responds to the Qualitative Analysis for sodium salt.

(2) To 1 mL of a solution of Sodium Valproate for Injection in ethanol(99.5) (1 in 200), add 4 mL of hydroxylamine perchlorate-anhydrous ethanol TS and 1 mL of *N*,*N*'-dicyclohexylcarbodiimide-ethanol (99.5) TS, shake well to mix, and allow it to stand in warm water for 20 minutes. After cooling, add 1 mL of iron(III) perchlo-

rate-ethanol (99.5) TS, and shake well to mix; the resulting solution exhibits a violet color.

(3) To 5 mL of an aqueous solution of Sodium Valproate for Injection (1 in 20), add 1 mL of cobalt nitrate solution (1 in 20), and warm on a steam bath; a violet precipitate is formed.

(4) Dissolve 0.5 g of Sodium Valproate for Injection in 5 mL of water, add 5 mL of chloroform and 1 mL of 2 mol/L hydrochloric acid TS, and shake strongly to mix for 1 minute. Allow it to stand, separately take the chloroform layer, dehydrate with anhydrous sodium sulfate, and filter. Remove the solvent from the filtrate, and determine the infrared spectrum of the residue as directed under the liquid film method under the Mid-infrared Spectroscopy; it exhibits absorption at the wavenumbers of about 1707 cm^{-1}, 1466 cm^{-1}, 1415 cm^{-1}, 1252 cm^{-1}, 1241 cm^{-1} and 938 cm^{-1}.

pH Between 6.8 and 8.5 (10% aqueous solution).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.125 EU per mg of sodium valproate.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Sodium Valproate for Injection in 10 mL of water; the resulting solution is clear and colorless.

(2) ***Related substances***—Dissolve 0.10 g of Sodium Valproate for Injection in 10 mL of a mixture of formic acid and chloroform (1 : 1), and use this solution as the test solution. Pipet 1.0 mL of the resulting solution, add a mixture of formic acid and chloroform (1 : 1) to make 200 mL, and use this solution as the standard solution. Perform the test with 2 μL each of the test solution and standard solution as directed under the Gas Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the sum of peak areas other than the peak of valproic acid from the test solution is not greater than the peak area of valproic acid from the standard solution (NMT 0.5%).

Operating conditions

Detector: A flame ionization detector.

Column: A column about 0.25 mm of internal diameter and 30.0 m of length, coated with polyethylene glycol nitroterephthalate in a thickness of 0.25 μm.

Column temperature: Maintain at 120 ℃ for the first 5 minutes, increase at a rate of 10 ℃ per minute up to 135 ℃, and maintain it for 5 minutes. Next, increase the temperature to 160 ℃ at a rate of 10 ℃ per minute, maintain it for 5 minutes, then increase the temperature to 180 ℃ at a rate of 10 ℃ per minute, and maintain it for 5 minutes. Then, increase the temperature to 230 ℃ at a rate of 50 ℃ per minute.

Sample injection port temperature: 240 ℃

Detector temperature: 250 ℃

Carrier gas: Nitrogen

Flow rate: 2.0 mL/min

System suitability

System performance: Mix 1 mL of the test solution and 4 mL of a solution of *n*-valeric acid in a mixture of formic acid and chloroform (1 : 1) (1 in 1000). Proceed with 2 μL of this solution according to the above conditions; *n*-valeric acid and valproic acid are eluted in this order with a resolution being NLT 3.

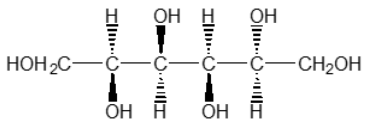
Loss on drying NMT 2.0% (2 g, 105 °C, 2 hours).

Assay Weigh accurately the mass of NLT 20 containers of Sodium Valproate for Injection. Weigh accurately an amount of Sodium Valproate for Injection, equivalent to about 0.2 g of sodium valproate ($C_8H_{15}NaO_2$), dissolve in 80 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 16.62 mg of $C_8H_{15}NaO_2$

Packaging and storage Preserve in hermetic containers.

D-Sorbitol
D-소르비톨



D-Sorbit

$C_6H_{14}O_6$: 182.17

(2*R*,3*R*,4*R*,5*S*)-Hexane-1,2,3,4,5,6-hexol [*50-70-4*]

D-Sorbitol, when dried, contains NLT 97.0% and NMT 101.0% of D-Sorbitol ($C_6H_{14}O_6$).

Description D-Sorbitol occurs as a white powder or grain or crystalline mass, is odorless and has a sweet taste with a cold sensation.
It is very soluble in water, sparingly soluble in ethanol(95) and practically insoluble in ether.
It is hygroscopic.

Identification (1) Add 2 mL iron(II) sulfate TS and 1 mL sodium hydroxide solution (1 in 5) to 1 mL of the aqueous solution of D-Sorbitol (7 in 10); the resulting solution exhibits a bluish green color but does not become cloudy.

(2) Add 1 mL of freshly prepared catechol solution (1 in 10) to 1mL of the aqueous solution of D-Sorbitol (1 in 20), shake well to mix, put quickly 2 mL of sulfuric acid, and shake to mix; the resulting solution soon exhibits a reddish purple to violet color.

(3) Add 10 mL acetic anhydride and 1 mL pyridine to 0.5 g of D-Sorbitol, attach a reflux condenser, and boil for 10 minutes. Cool, add 25 mL of water, shake to mix, and then allow to stand in a cold place. Transfer the resulting solution into a separatory funnel, add 30 mL of chloroform, and extract. Evaporate the extract on a steam bath, add 80 mL of water to the oily residue, heat on a steam bath for 10 minutes, and then filter when hot. Take the precipitate that forms after cooling by filtering through a glass filter (G3), wash with water, then recrystallize once with ethanol(95), and dry for 4 hours in a desiccator (in vacuum, silica gel) for 4 hours; the melting point is between 97 and 101 ℃.

Purity (1) ***Clarity and color of solution and acidity or alkalinity***—Dissolve 5 g of D-Sorbitol in 20 mL of water by shaking to mix while warming; the solution is colorless, clear and neutral.

(2) ***Chloride***—Perform the test with 2.0 g of D-Sorbitol. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.005%).

(3) ***Sulfate***—Perform the test with 4.0 g of D-Sorbitol. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid (NMT 0.006%).

(4) ***Heavy metals***—Proceed with 5.0 g of D-Sorbitol according to Method 1 and perform the test. Prepare the control solution with 2.5 mL of lead standard solution (NMT 5 ppm).

(5) ***Nickel***—Dissolve 0.5 g of D-Sorbitol in 5 mL of water, add 3 drops of dimethylglyoxime TS and 3 drops of ammonia TS, and allow to stand for 5 minutes; no red color is observed.

(6) ***Arsenic***—Proceed with 1.5 g of D-Sorbitol according to Method 1 and perform the test (NMT 1.3 ppm).

(7) ***Glucose***—Dissolve 20.0 g of D-Sorbitol in 25 mL of water, add 40 mL of Fehling's TS, and boil gently for 3 minutes. After cooling, filter the clear supernatant using a glass filter (G4), while taking cautions to ensure that the precipitate leaves in the flask. Wash the precipitate in the flask with warm water until the washings do not exhibit alkalinity, then filter the washings with the glass filter described above. Dissolve the precipitate in the flask in 20 mL of iron(III) sulfate TS, filter using the glass filter described above, wash with water, and combine the washings and the filtrate. Heat at 80 ℃ and titrate with 0.02 mol/L potassium permanganate VS; the consumed volume is NMT 6.3 mL.

(8) ***Sugars***—Dissolve 20.0 g of D-Sorbitol in 25 mL water, add 8 mL of dilute hydrochloric acid, and heat under a reflux condenser on a steam bath for 3 hours. Cool, then add 2 drops methyl orange TS, put sodium hydroxide TS until the resulting solution exhibits orange, and add water to make 100 mL. Take 10 mL of the resulting solution, add 10 mL of water and 40 mL of Fehling's TS, and then boil for 3 minutes over low heat. Proceed as directed in (7).

Loss on drying NMT 2.0% (0.5 g, in vacuum, phosphorus pentoxide, 80 ℃, 3 hours).

Residue on ignition NMT 0.02% (5 g).

Microbiological examination of non-sterile products The total aerobic microbial count is NMT 1000 CFU, and the total combined yeasts/molds count is NMT 100 CFU per g of D-Sorbitol. Also, *Escherichia coli* and *Salmonella* are not detected.

Assay Weight accurately about 0.2 g of D-Sorbitol, previously dried, and dissolve in water to make exactly 100 mL. Pipet 10 mL of the solution, put into an iodine bottle, add exactly 50 mL of potassium periodate TS, and heat for 15 minutes on a steam bath. After cooling, add 2.5 g of potassium iodide, immediately stopper tightly, and shake well to mix. Allow to stand for 5 minutes in a dark place and titrate the liberated iodine with 0.1 mol/L sodium thiosulfate VS (indicator: 3 mL of starch TS). Perform a blank test in the same manner.

Each mL of 0.1 mol/L sodium thiosulfate VS
= 1.8217 mg of $C_6H_{14}O_6$

Packaging and storage Preserve in tight containers.

D-Sorbitol Solution
D-소르비톨 액

D-Sorbit Solution

D-Sorbitol Solution contains NLT 97.0% and NMT 103.0% of the labeled amount of D-Sorbitol ($C_6H_{14}O_6$: 182.17).

Description D-Sorbitol Solution occurs as a clear, colorless liquid, is odorless, and have a sweet taste.
It is miscible with water, ethanol(95), glycerin or propylene glycol.
In some cases, it may precipitate crystalline masses.

Identification (1) Take an amount of D-Sorbitol Solution, equivalent to 0.7g of D-Sorbitol according to the labeled amount, and perform the test according to the Identification (1) of D-Sorbitol.

(2) Take an amount of D-Sorbitol Solution, equivalent to 1g of D-Sorbitol according to the labeled amount, add water to make 20 mL. Perform the test with 1 mL of the resulting solution according to the Identification (2) of D-Sorbitol.

Purity (1) ***Acidity or alkalinity***—D-Sorbitol Solution is neutral.

(2) ***Chloride***—Take an amount of D-Sorbitol Solution, equivalent to 2.0g of D-Sorbitol according to the

labeled amount, and perform the test according to the Purity (2) of D-Sorbitol (NMT 0.005%).

(3) ***Sulfate***—Take an amount of D-Sorbitol Solution, equivalent to 4.0g of D-Sorbitol according to the labeled amount, and perform the test according to the Purity (3) of D-Sorbitol (NMT 0.006%).

(4) ***Heavy metals***—Take an amount of D-Sorbitol Solution, equivalent to 5.0g of D-Sorbitol according to the labeled amount, and perform the test according to the Purity (4) of D-Sorbitol (NMT 5 ppm).

(5) ***Nickel***—Take an amount of D-Sorbitol Solution, equivalent to 0.5g of D-Sorbitol according to the labeled amount, and perform the test according to the Purity (5) of D-Sorbitol

(6) ***Arsenic***—Take an amount of D-Sorbitol Solution, equivalent to 1.5g of D-Sorbitol according to the labeled amount, dilute with water or concentrate on a steam bath as needed to make 5 mL, cool, and use this solution as the test solution (NMT 1.3 ppm).

(7) ***Glucose***—Take an amount of D-Sorbitol Solution, equivalent to 20.0 g of D-Sorbitol according to the labeled amount, dilute by adding water or concentrate on a steam bath as needed to make 40 mL, add 40 mL of Fehling's TS, and perform the test according to the Purity (7) of D-Sorbitol.

(8) ***Sugars***—Take an amount of D-Sorbitol Solution, equivalent to 20.0 g of D-Sorbitol according to the labeled amount, dilute by adding water or concentrate on a steam bath as needed to make 40 mL, add 8 mL of dilute hydrochloric acid, and perform the test according to the Purity (8) of D-Sorbitol.

(9) ***Ethylene glycol and diethylene glycol***—Weigh accurately about 2.0g of Cellulase II, transfer to a 25 mL volumetric flask, add 1 mL of diluent, and shake to mix for about 3 minutes. Add the remaining diluent in three portions while shaking to mix for about 3 minutes each time, and bring to the gauge line. Take the clear supernatant, filter through a membrane filter with pore diameter NMT 0.45 μm, discard the initial 2 mL of filtrate, take the remaining filtrate, and use this as the test solution. Separately, weigh an appropriate amount of diethylene glycol RS and ethylene glycol RS, dissolve in the diluent to make a solution containing 0.08 mg of each per mL, and use this solution as the standard solution. Perform the test with 1.0 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions. Determine the peak areas for each solution by the automatic integration method; the peak area of diethylene glycol obtained from the test solution is not greater than the peak area of diethylene glycol from the standard solution (NMT 0.10%), and the peak area of ethylene glycol from the test solution is not greater than the peak area of ethylene glycol from the standard solution (NMT 0.10%).

Operating conditions

Detector: A flame ionization detector

Column: A quartz glass column 0.32 mm in internal diameter and about 15 m in length, coated the inside with cyanopropylphenyl dimethylpolysiloxane for gas chromatography (6:94) in a 0.25 μm thickness.

Column temperature: Maintain at 70 ℃ for 2 minutes, then heat at a rate of 50 ℃ per min to 300 ℃, and hold for 5 minutes.

Sample injection port temperature: A constant temperature of about 240 ℃.

Detector temperature: A constant temperature of about 300 ℃.

Carrier gas: Helium

Flow rate: 3.0 mL/min

Split ratio: About 1 : 10.

System suitability

System performance: Proceed with 1 μL of the standard solution according to the above conditions; ethylene glycol and diethylene glycol are eluted in this order with the resolution being NLT 30.

Diluent—A mixture of acetone and· water (96 : 4).

Residue on ignition Accurately take an amount of D-Sorbitol Solution, equivalent to 5 g of D-Sorbitol according to the labeled amount, add 3 - 4 drops of sulfuric acid, evaporate by heating gently. Ignite and burn, cool, and perform the test with the residue; the resulting residue is NMT 1.0 mg.

Assay Take an amount of D-Sorbitol Solution, equivalent to about 5 g of D-Sorbitol ($C_6H_{14}O_6$), and add water to make exactly 250 mL. Pipet 10 mL of this solution and add water to make exactly 100 mL. Pipet 10 mL of this solution and place in an iodine bottle, and perform the test as directed under the Assay of D-Sorbitol.

Each mL of 0.1 mol/L sodium thiosulfate VS
= 1.8217 mg of $C_6H_{14}O_6$

Packaging and storage Preserve in tight containers.

D-Sorbitol and D-Mannitol Irrigation
D-소르비톨·D-만니톨 관류액

D-Sorbitol and D-Mannitol Irrigation contains NLT 90.0% and NMT 110.0% of the labeled amounts of D-Sorbitol ($C_6H_{14}O_6$: 182.17) and D-Mannitol ($C_6H_{14}O_6$: 182.17).

Method of preparation Prepared as directed under Irrigation, with D-Sorbitol and D-Mannitol.

Identification Perform the test as directed under the Assay; the retention times of D-Sorbitol and D-Mannitol peaks obtained from the test solution and the reference standard are the same.

pH Between 4.5 and 7.5.

Sterility Meets the requirements.

Pyrogen It meets the requirements when tested as directed under the Pyrogen.

Assay Weigh accurately an amount of D-Sorbitol and D-Mannitol Irrigation, equivalent to 0.135 g of D-Sorbitol ($C_6H_{14}O_6$) (27 mg of D-Mannitol) according to the labeled amount, add 4.0 mL of internal standard solution, and add water to make 25 mL. Filter, if necessary, and use the filtrate as the test solution. Separately, weigh accurately about 0.135 g of D-Sorbitol RS and about 27 mg of D-Mannitol RS, add 4.0 mL of internal standard solution, add water to make exactly 25 mL, and use this solution as the standard solution. Pipet 15 μL each of the test solution and the standard solution and perform the test as directed under the Liquid Chromatography. Determine the ratios Q_{T1}, Q_{S1}, Q_{T2} and Q_{S2} of the peak area of D-Sorbitol and D-Mannitol to the peak area of the internal standard from these solutions.

$$\text{Amount (g) of D-sorbitol } (C_6H_{14}O_6) = \text{Amount (mg) of D-sorbitol RS} \times \frac{Q_{T1}}{Q_{S1}}$$

$$\text{Amount (g) of D-mannitol } (C_6H_{14}O_6) = \text{Amount (mg) of D-mannitol RS} \times \frac{Q_{T2}}{Q_{S2}}$$

Internal standard solution—Weigh about 1.0 g of purified sucrose and dissolve in water to make 100.0 mL.

Operating conditions

Detector: A differential refractometer

Column: Sugar Pak I or equivalent column

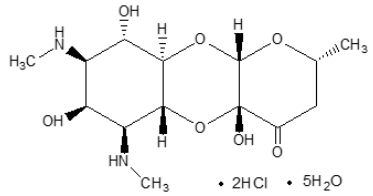
Column temperature: A constant temperature of about 90 °C.

Mobile phase: water

Flow rate: 0.6 mL/min

Packaging and storage Preserve in hermetic containers.

Spectinomycin Hydrochloride Hydrate
스펙티노마이신염산염수화물



Spectinomycin Hydrochloride

$C_{14}H_{24}N_2O_7 \cdot 2HCl \cdot 5H_2O$: 495.35

(1*R*,3*S*,5*R*,8*R*,10*R*,11*S*,12*S*,13*R*,14*S*)-8,12,14-trihydroxy-5-methyl-11,13-bis(methylamino)-2,4,9-trioxatricyclo[8.4.0.03,8]tetradecan-7-one hydrochloride pentahydrate [*22189-32-8*]

Spectinomycin Hydrochloride Hydrate is the hydrochloride of a compound having antibacterial activity produced by cultivating *Streptomyces spectabilis*.

Spectinomycin Hydrochloride Hydrate contains NLT 603 μg and NMT 713 μg (potency) of spectinomycin ($C_{14}H_{24}N_2O_7$: 332.35) per mg.

Description Spectinomycin Hydrochloride Hydrate occurs as a white to pale yellowish white crystalline powder.

It is freely soluble in water and practically insoluble in ethanol(95).

Identification (1) To 5 mL of an aqueous solution of Spectinomycin Hydrochloride Hydrate (1 in 100), add slowly anthrone TS; a blue to bluish green color is produced at the boundary layer.

(2) Determine the infrared spectra of Spectinomycin Hydrochloride Hydrate and spectinomycin hydrochloride RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) To 3 mL of an aqueous solution of Spectinomycin Hydrochloride Hydrate (1 in 150), add 1 drop of silver nitrate TS; a white turbidity is produced.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between +15° and +21° (2.1 g calculated on the anhydrous basis, water, 25 mL, 200 mm).

pH Dissolve about 0.1 g of Spectinomycin Hydrochloride Hydrate in 10 mL of water; the pH is between 4.0 and 5.6.

Water Between 16.0% and 20.0% (0.3 g, volumetric titration, direct titration).

Residue on ignition NMT 1.0% (1 g).

Sterility It meets the requirements when used in a sterile preparation. However, it is excluded when there is a terminal sterilization process in the manufacturing of a sterile preparation.

Bacterial endotoxins Less than 0.09 EU/mg (potency) of spectinomycin, when used in a sterile preparation.

Histamine It meets the requirements when used in a sterile preparation. Weigh an appropriate amount of Spectinomycin Hydrochloride Hydrate, dissolve it in isotonic sodium chloride injection to prepare a solution containing 15 mg (potency) per mL, and use this solution as the test solution.

Assay Weigh accurately about 30 mg (potency) each of Spectinomycin Hydrochloride Hydrate and spectinomycin hydrochloride RS, and add 10.0 mL of the internal standard solution and 1.0 mL of hexamethyldisilazane. Allow to react for 1 hour, shaking occasionally. Use them as the test solution and the standard solution, respectively. Perform the test with 0.5 μL each of these solutions as

directed under the Gas Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of the peak area of spectinomycin hydrochloride to that of the internal standard.

$$\text{Potency (μg) of spectinomycin hydrochloride } (C_{14}H_{24}N_2O_7) = \text{Potency (μg) of spectinomycin hydrochloride RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh 50 mg of triphenylantimony, add dimethylamide to dissolve, and make 25 mL.

Operating conditions

Detector: A flame ionization detector

Column: A glass column about 3 mm in internal diameter and about 60 cm in length, packed with column gas-chrom Q (80/100 mesh) coated with SE-52, equivalent to 5% of its mass.

Column temperature: A constant temperature of about 90 °C.

Carrier gas: Helium

Flow rate: 45 mL/min

Packaging and storage Preserve in tight containers.

Spectinomycin Hydrochloride for Injection
주사용 스펙티노마이신염산염

Spectinomycin Hydrochloride for Injection is a preparation, which is dissolved before use. Spectinomycin Hydrochloride for Injection contains NLT 90.0% and NMT 120.0% of the labeled amount of spectinomycin ($C_{14}H_{24}N_2O_7$: 332.35).

Method of preparation Prepare as directed under Injections, with Spectinomycin Hydrochloride Hydrate.

Description Spectinomycin Hydrochloride for Injection occurs as a white powder.

Identification (1) Determine the infrared spectra of Spectinomycin Hydrochloride for Injection and spectinomycin hydrochloride RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The relative retention time of the major peak to the internal standard from the test solution and the standard solution obtained under the Assay are the same.

Water Between 16.0% and 20.0% (0.1 g, volumetric titration, direct titration).

pH Dissolve Spectinomycin Hydrochloride for Injection according to the label; the pH of the resulting solution is between 4.0 and 7.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.09 EU per mg (potency) of spectinomycin.

Histamine Meets the requirements. Weigh an appropriate amount of Spectinomycin Hydrochloride for Injection, dissolve in isotonic sodium chloride injection to obtain a solution having known concentration of 15 mg of Spectinomycin Hydrochloride for Injection per mL, and use the solution as the test solution.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately an amount of Spectinomycin Hydrochloride for Injection, equivalent to 20 mg (potency) of spectinomycin according to the labeled potency, and dissolve in water to make exactly 100 mL. Pipet 1 mL of the solution, add 15 mL of acetone and evaporate to dryness under a stream of air. To the residue, add exactly 10 mL of the internal standard solution and 1 mL of hexamethyldisilazane, allow to react by shaking occasionally, and use this solution as the test solution. Separately, weigh accurately about 22 mg (potency) of spectinomycin hydrochloride RS and add water to make exactly 100 mL. Pipet 1 mL of the solution, add 15 mL of acetone, and evaporate to dryness under a stream of air. Add 10.0 mL of the internal standard solution and 1.0 mL of hexamethyldisilazane, allow to react by shaking occasionally, and use this solution as the standard solution. Perform the test with each 0.5 μL of the test solution and the standard solution as directed under the Gas Chromatography according to the following operating conditions and determine the ratios, Q_T and Q_S, of the peak area of spectinomycin to that of the internal standard.

$$\text{Potency (μg) of spectinomycin } (C_{14}H_{24}N_2O_7) = \text{Potency (μg) of spectinomycin RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh 50 mg of triphenylantimony and dissolve in dimethylamide to make 25 mL.

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A column, about 3 mm in internal diameter and about 60 cm in length, packed with 80 to 100 mesh diatomaceous earth for gas chromatography coated with methyl silicone polymer for gas chromatography at a rate of 5%.

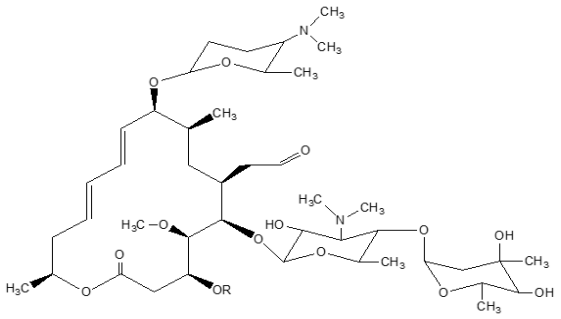
Column temperature: A constant temperature of about 90 °C.

Carrier gas: Helium

Flow rate: 45 mL/min

Packaging and storage Preserve in hermetic containers.

Spiramycin
스피라마이신



Spiramycin I : R = H $C_{43}H_{74}N_2O_{14}$: 843.06
Spiramycin II : R = $COCH_3$ $C_{45}H_{76}N_2O_{15}$: 885.09
Spiramycin III : R = $COCH_2CH_3$ $C_{46}H_{78}N_2O_{15}$: 899.12
Spiramycin I : (4*R*,5*S*,6*R*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-10-{[(2*R*,5*S*,6*R*)-5-(Dimethylamino)-6-methyl-tetrahydro-2*H*-pyran-2-yl]oxy}-4-hydroxy-9,16-dimethyl-5-methoxy-2-oxo-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-6-yl 3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-ribo-hexopyranosyl)-3-(dimethylamino)-α-D-glucopyranoside
Spiramycin II : (4*R*,5*S*,6*R*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-4-Acetyloxy-10-{[(2*R*,5*S*,6*R*)-5-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl]oxy}-9,16-dimethyl-5-methoxy-2-oxo-7-(2-oxoethyl)oxa-cyclohexadeca-11,13-dien-6-yl 3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-ribo-hexopyranosyl)-3-(dimethylamino)-α-D-glucopyranoside
Spiramycin III : (4*R*,5*S*,6*R*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-10-{[(2*R*,5*S*,6*R*)-5-(dimethylamino)-6-methyl-tetrahydro-2*H*-pyran-2-yl]oxy}-9,16-dimethyl-5-methoxy-2-oxo-4-propanoyloxy-7-(2-oxo-ethyl)oxacyclohexadeca-11,13-dien-6-yl 3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-ribo-hexopyranosyl)-3-(dimethylamino)-α-D-glucopyranoside

Spiramycin is a mixture of spiramycin I, spiramycin II and spiramycin III. Spiramycin contains NLT 3200 units (potency) of spiramycin I ($C_{43}H_{74}N_2O_{14}$: 843.06) per mg, calculated on a dried basis.

Description Spiramycin occurs as a white to pale yellowish white powder and has a bitter taste.
It is very soluble in methanol, in ethanol(95) or in acetone, sparingly soluble in ether and very slightly soluble in water.

Identification (1) Dissolve 0.5 g (potency) of Spiramycin in 10 mL of 0.1 mol/L sulfuric acid TS, add 25 mL of water and mix. Adjust the pH to 8.0 with 0.1 mol/L sodium hydroxide TS and add water to make 50 mL. To 5 mL of this solution, add 2 mL of a mixture of sulfuric acid and water (2 : 1); the resulting solution exhibits a brown color.

(2) Dissolve 0.1 g (potency) of Spiramycin in methanol to make 100 mL. Pipet 1 mL of this solution, add methanol to make 100 mL and determine the absorption spectrum of this solution at between 220 nm and 350 nm as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima at around 232 nm and at around 340 nm.

(3) Proceed with Spiramycin as directed under the Purity (2); the Rf values and the color of the principal spot obtained from the test solution are the same as those from the standard solution S1, and the spots other than the principal spot obtained from the test solution are similar to the spots other than the principal spot from the standard solution S1, but different from the principal spot from the standard solution S5.

Optical rotation $[\alpha]_D^{20}$: Between -80° and -85° (1.0 g, calculated on the anhydrous basis, 10% acetic acid, 50 mL).

pH Dissolve about 0.5 g (potency) of Spiramycin in 5 mL of methanol and add water to make 100 mL; the pH of this solution is between 8.5 and 10.5.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Spiramycin according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Weigh accurately about 40 mg of Spiramycin, dissolve in methanol to make exactly 10 mL, and use this solution as the test solution. Separately, weigh accurately about 40 mg of spiramycin RS and dissolve in methanol to make exactly 10 mL (S1). To 1 mL of this solution, add methanol to make exactly 10 mL (S2). To 5 mL and 2 mL each of the standard solution S2, dilute with methanol and make 10 mL each (S3 and S4, respectively). Dissolve 40 mg (potency) of erythromycin RS in methanol to make exactly 10 mL (S5). Perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solutions and the standard solutions S1, S2, S3, S4 and S5 on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with the clear supernatant of a mixture of 2-propanol, 15% ammonium acetate (adjust the pH to 9.6 with 1 mol/L sodium hydroxide TS) and ethyl acetate (4 : 8 : 9) as the developing solution to a distance of about 15 cm. Air-dry the plate, and to 10 mL of anisaldehyde, add 90 mL of ethanol(95) and mix well. Add 10 mL of sulfuric acid, mix well, and spray evenly this solution on the air-dried plate and heat at 110 ℃ for 5 minutes; the standard solution S1 shows the principal spot, and the spots of spiramycin II and spiramycin III appear slightly above and slightly further above the principal spot, respectively. The spots of spiramycin II obtained from the test solution are not more intense than the spots from the standard solution S2, and the spots of spiramycin III obtained from the test solution are not more intense than the spots from the standard solution S3. Any spot other than the principal spot obtained from the test solution is not more intense than the

spots from the standard solution S4.

Loss on drying NMT 3.5% (0.5 g, in vacuum, phosphorus pentoxide, 80 ℃, 6 hours).

Residue on ignition NMT 0.1% (1 g).

Assay ***The cylinder-plate method***—(1) Agar media for seed and base layer: Use the culture medium (A) (2) (a) ① ⓐ under the Microbial Assays for Antibiotics. Adjust the pH of the medium to between 7.8 and 8.0.

(2) Test organism: Use *Bacillus subtilis* ATCC 6633 as the test microorganism.

(3) Weigh accurately about 75000 units (potency) of Spiramycin, dissolve in 5 mL of methanol, dilute with 0.1 mol/L phosphate buffer solution (pH 8.0) to obtain solutions having known concentrations of 120 units (potency) and 30 units (potency) per mL, and use these solutions as the high concentration test solution and the low concentration test solution, respectively. Separately, weigh accurately about 75000 units (potency) of spiramycin RS, dissolve in 5 mL of methanol, add 0.1 mol/L phosphate buffer solution (pH 8.0) to obtain a solution having a known concentration of 7500 units (potency) per mL, and use this solution as the standard stock solution. Keep the standard stock solution at a temperature not exceeding 5 ℃ and use it within 7 days. Pipet an appropriate amount of the standard stock solution, add 0.1 mol/L phosphate buffer solution (pH 8.0) to obtain solutions having known concentrations of 120 units (potency) and 30 units (potency) per mL, and use these solutions as the high concentration standard solution and the low concentration standard solution, respectively. Perform the test as directed in (A) (8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in tight containers.

Spiramycin Tablets
스피라마이신 정

Spiramycin Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of spiramycin.

Method of preparation Prepare as directed under Tablets, with Spiramycin.

Identification Dissolve 0.1 g (potency) of Spiramycin Tablets in methanol to make 100 mL. To 1 mL of this solution, add methanol to make 100 mL and determine the absorption spectrum of this solution at the wavelength of between 220 nm and 350 nm as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima at around 232 nm and at around 340 nm.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Loss on drying NMT 5.0% (0.1 g, 0.7 kPa, 60 ºC, 3 hours).

Assay ***Cylinder plate method***—(1) Culture medium: Agar media for seed and base layer Use the culture medium A) (2) (A) ③ (a) under the Microbial Assays for Antibiotics. Adjust the pH to 7.8 to 8.0.

(2) Test organism: Use *Bacillus subtilis* ATCC 6633 as the test organism.

(3) Weigh accurately NLT 20 tablets of Spiramycin Tablets and powder. Weigh accurately about 750000 units (potency) of the powder according to the labeled potency, dissolve in methanol, shake vigorously to make exactly 50 mL. Filtrate or centrifuge, if necessary. Pipet an appropriate amount of this solution, dilute with 0.1 mol/L phosphate buffer solution (pH 8.0) to make solutions know concentrations of 120 and 30 units (potency) per mL, and use these solutions as the high concentration test solution and the low concentration test solution, respectively. Separately, weigh accurately about 75000 units (potency) of spiramycin RS, dissolve in 5 mL of methanol, add 0.1 mol/L phosphate buffer solution (pH 8.0) to obtain a solution having known concentration of 7500 units (potency) per mL, and use this solution as the standard stock solution. Keep the standard stock solution at a temperature not exceeding 5 ℃ and use it within 7 days. Pipet an appropriate amount of the standard stock solution, dilute with 0.1 mol/L phosphate buffer solution (pH 8.0) to obtain solutions having known concentrations of 120 and 30 units (potency) per mL, and use these solutions as the high concentration standard solution and the low concentration standard solution, respectively. With these solutions, perform the test according to A) (8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in tight containers.

Spiramycin and Metronidazole Tablets
스피라마이신·메트로니다졸 정

Spiramycin and Metronidazole Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of spiramycin ($C_{43}H_{74}N_2O_{14}$: 843.06) and NLT 90.0% and NMT 110.0% of the labeled amount of metronidazole ($C_6H_9N_3O_3$: 171.15).

Method of preparation Prepare as directed under Tablets, with Spiramycin and Metronidazole.

Identification Weigh an amount, equivalent to about 250 mg of spiramycin and 125 mg of metronidazole according to the labeled amount, add 25 mL of water, filter, and use the filtrate as the test solution. Weigh 250 mg of spiramycin RS and 125 mg of metronidazole RS, dissolve in 25 mL of methanol, and use these solutions, respectively as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chroma-

tography. Spot each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ether, diethylamine and methanol (97 : 2 : 1) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the color and R_f values of the spots obtained from the test solution and the standard solution are the same. Spray the titanium chloride solution on the plate, dry at 130 °C for several minutes, cool to room temperature, and spray 1% fast blue B salt solution; the metronidazole test solution and the standard solution exhibit pink spots at the same R_f value.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Spiramycin***—(i) Cylinder plate method

(a) Medium Agar media for seed and base layer Use the culture medium in (i) (2) (a) ③ ⓐ under the Microbial Assays for Antibiotics. Adjust the pH to 7.8 to 8.0.

(b) Test organism: Use Bacillus subtilis ATCC 6633 as the test organism.

(c) Weigh accurately about 75000 units (potency) of Spiramycin and Metronidazole Tablets, dissolve in 5 mL of methanol, dilute with 0.1 mol/L phosphate buffer solution (pH 8.0) to obtain solutions having known concentrations of 120 units (potency) and 30 units (potency) per mL, and use these solutions as the high concentration test solution and the low concentration test solution, respectively. Separately, weigh accurately about 75000 units (potency) of spiramycin RS, dissolve in 5 mL of methanol, add 0.1 mol/L phosphate buffer solution (pH 8.0) to obtain a solution having known concentration of 7500 units (potency) per mL, and use this solution as the standard stock solution. Keep the standard stock solution below 5 °C and use it within 7 days. Pipet an appropriate amount of the standard stock solution, add 0.1 mol/L phosphate buffer solution (pH 8.0) to obtain solutions having known concentrations of 120 units (potency) and 30 units (potency) per mL, and use these solutions as the high concentration standard solution and the low concentration standard solution, respectively. Perform the test as directed under the Microbial Assays for Antibiotics (i) with the test solution standard solution.

(ii) Turbidimetric assay (a) Culture medium: Use the culture medium described in (iii) (b) (ii) under the Microbial Assays for Antibiotics.

(b) Test organism: Use *Staphylococcus aureus* ATCC 6538P as the test organism.

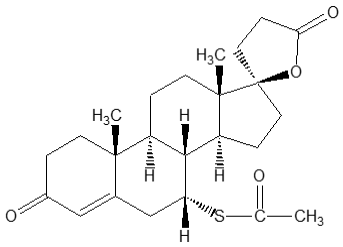
(c) Weigh accurately about 75000 units (potency) of Spiramycin and Metronidazole Tablets, dissolve in 5 mL of methanol, dilute with 0.05 mol/L phosphate buffer solution (pH 7.0) to obtain a solution having known concentration of 11.7 units (potency) per mL, and use this solution as the test solution. Separately, weigh accurately about 75000 units (potency) of spiramycin RS, dissolve in 5 mL of methanol, add 0.05 mol/L phosphate buffer solution (pH 7.0) to obtain a solution having known concentration of 7500 units (potency) per mL, and use per solution as the standard stock solution. Keep the standard stock solution at below 5 °C and use it within 7 days. Pipet an appropriate amount of the standard stock solution, dilute with 0.05 mol/L phosphate buffer solution (pH 7.0) to obtain solutions having known concentrations of 17.5, 14.3, 11.7, 9.59 and 7.86 units (potency) per mL, and use these solutions as the test solutions. With these solutions, perform the test according to C) under the Microbial Assays for Antibiotics.

(2) ***Metronidazole***—Weigh accurately the mass of NLT 20 tablets of Spiramycin and Metronidazole Tablets, and powder. Weigh accurately an amount, equivalent to about 100 mg of metronidazole ($C_6H_9N_3O_3$) and add 20 mL of 1 mol/L hydrochloric acid, shake to mix, allow to stand for 5 minutes, add water to make exactly 200 mL, and then filter. Pipet 2 mL of this solution, add 1 mol/L hydrochloric acid to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 100 mg of metronidazole RS, dissolve in 20 mL of 1 mol/L hydrochloric acid, and add water to make exactly 200 mL. To 2 mL of this solution, add 0.1 mol/L hydrochloric acid to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution at the wavelength of 276 nm as directed under the Ultraviolet-visible Spectroscopy, using 0.1 mol/L hydrochloric acid as a control solution.

$$\text{Amount (mg) of metronidazole } (C_6H_9N_3O_3) = \text{Amount (mg) of metronidazole RS} \times (A_T / A_S)$$

Packaging and storage Preserve in tight containers.

Spironolactone
스피로노락톤



$C_{24}H_{32}O_4S$: 416.57

7α-Acetylthio-3-oxo-17α-pregn-4-ene-21,17-carbolactone [*52-01-7*]

Spironolactone, when dried, contains NLT 97.0% and NMT 103.0% of spironolactone ($C_{24}H_{32}O_4S$).

Description Spironolactone occurs as a white to pale yellowish brown, very fine powder.

It is freely soluble in chloroform, soluble in ethanol(95), slightly soluble in methanol and practically insoluble in

water.

Melting point—Between 198 and 207 ℃. Continue heating on a steam bath at about 125 ℃ so that the temperature rises at a rate of about 10 ℃ per minute in the range between 140 and 185 ℃, and then, when the temperature is not within the above melting range, adjust the heating so that the temperature rises at a rate of about 3 ℃ per minute.

Identification (1) Determine the absorption spectra of solutions of Spironolactone and spironolactone RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Spironolactone and spironolactone RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If there is any difference between the spectra, dissolve each of Spironolactone and spironolactone RS in methanol, then evaporate methanol to dryness, and repeat the test on the residues.

Optical rotation $[\alpha]_D^{20}$: Between -33° and -37° (0.25 g, after drying, chloroform, 25 mL, 200 mm).

Purity (1) ***Mercapto compounds***—To 2.0 g of Spironolactone, add 20 mL of water, shake to mix, and filter. To 10 mL of the filtrate, add 1 mL of starch TS and 0.05 mL of 0.01 mol/L iodine VS and mix; the resulting solution exhibits a blue color.

(2) ***Related substances***—Dissolve 0.20 g of Spironolactone in 10 mL of ethanol(95) and use this solution as the test solution. Pipet 1 mL of this solution, add ethanol(95) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate using n-butyl acetate as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray evenly a solution of sulfuric acid in methanol (1 in 10) on the plate and heat the plate at 105 ℃ for 10 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1%. (1 g).

Assay Weigh accurately about 50 mg each of Spironolactone and spironolactone RS, previously dried for 2 hours at 105 ℃, and dissolve each in ethanol to make exactly 250 mL. Pipet 5 mL each of these solutions, add methanol to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with these solutions as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbances, A_T and A_S, at 238 nm.

$$\text{Amount (mg) of spironolactone } (C_{24}H_{32}O_4S) = \text{Amount (mg) of spironolactone RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in light-resistant, tight containers.

Stannous Fluoride
플루오르화석

SnF_2 : 156.71

Difluorotin [*7783-47-3*]

Stannous Fluoride contains NLT 71.2% of tin(II) (Sn^{2+}: 118.71) and NLT 22.3% and NMT 25.5% of fluorine (F: 19.00), calculated on the dried basis.

Description Stannous Fluoride occurs as a white crystalline powder, which has bitter and salty taste.
It is freely soluble in water and practically insoluble in ethanol(95), ether or chloroform.

Melting point—About 213 °C.

Identification (1) To 5 mL of an aqueous solution of Stannous Fluoride (1 in 100), add 2 mL of calcium chloride TS; a white crystalline precipitate of calcium fluoride is formed.

(2) Put 2 drops of the aqueous solution (1 in 100) of Stannous Fluoride on a white drip plate and add 2 drops of silver nitrate TS; a dark brown precipitate is formed.

(3) To 2 mL of an aqueous solution of Stannous Fluoride (0.8 in 100), add 5 mL of acidic potassium permanganate TS; a violet solution turns colorless.

pH Dissolve 0.1 g of Stannous Fluoride in freshly boiled and cooled water to make 25 mL. The pH of this solution is between 2.8 and 3.5.

Purity (1) ***Water insoluble matter*—**Weigh accurately about 10 g of Stannous Fluoride, put in a plastic beaker, add 200 mL of water, and stir with a plastic rod for 3 minutes or until the solid is not disintegrated anymore. Filter the resulting solution by a Gooch crucible, weighed previously and filled with asbestos, wash with ammonium fluoride solution (1 in 100) first, and then wash with water thoroughly. Dry the residue at 105 °C for 4 hour; the amount is NMT 0.2%.

(2) ***Antimony***—(i) Rhodamine B solution: Dissolve about 0.5 g of rhodamine B in 200 mL of 0.5 mol/L hydrochloric acid.

(ii) Standard solution: Weigh accurately about 55.0 mg of antimony potassium tartrate, dissolve in water to make exactly 200 mL, pipet 5 mL of the resulting solution, and add 6 mol/L hydrochloric acid to make exactly 500 mL. Use this solution as the standard solution.

(iii) Test solution: Weigh accurately about 1.0 g of Stannous Flouride, and add 6 mol/L hydrochloric acid

to make 50 mL. Use this solution as the test solution.

(iv) Procedure: Pipet 5 mL each of the test solution and standard solution, put them in the separatory funnel, add 15 mL of hydrochloric acid and 1 g of cerium sulfate, shake from time to time for mixing, and allow to stand for 5 minutes. To this solution, add 0.5 g of hydroxylamine hydrochloride, shake for 1 minute, add 15 mL of isopropyl ether, shake for 30 seconds, then add 7 mL of water to shake for mixing. After cooling for 10 minutes at room temperature, shake for 30 seconds, allow it stand to separate into two layers, and discard the aqueous layer. To the resulting solution, add 20 mL of rhodamine B solution, shake to mix for 30 minutes, and discard the aqueous layer again. Tilt the separatory funnel to take the isopropyl ether layer from the top, and centrifuge, if necessary, to make it a transparent solution. Determine the absorption spectra of the isopropyl ether layers obtained from test solution and standard solution as directed under Ultraviolet-visible Spectroscopy at the absorbance maximum wavelength (λmax) of around 550 nm with water as a control; the absorbance of the test solution is not greater than that of the standard solution (NMT 0.005%).

Loss on drying NMT 0.5% (1 g, 105 °C, 4 hours).

Assay (1) ***Tin***—Weigh accurately about 0.25 g of Stannous Fluoride, put in the Erlenmeyer flask, and add 300 ml of 3 mol/L hydrochloric acid which has been heated and started boiling. Shake the flask while passing oxygen-free inert gas to the surface of the solution to dissolve stannous fluoride, then cool to room temperature. Add 5 mL of potassium iodide TS, pass through the inert gas, and titrate with 0.05 mol/L potassium iodate VS. To the resulting solution, add 3 mL of starch TS around the endpoint.

Each mL of 0.05 mol/L potassium iodate
= 5.935 mg of Sn^{2+}

(2) ***Fluorine***—Weigh accurately about 0.1 g of Stannous Fluoride, add 50 mL of water to dissolve, shake vigorously for 5 minute to mix, and add water to make exactly 250 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of stannous fluoride RS, dissolve in water to make a solution containing about 10 μg of fluorine per mL, and use this solution as the standard solution. Take 1.0 mL, 2.0 mL, 3.0 mL and 4.0 mL each of the standard solution, put them in the 100-mL volumetric flasks, respectively, add 10.0 mL of the solution D to each flask, add water up to the gauge line of each flask, and mix well. Determine the absorption spectra of the respective solutions and solution E as directed under Ultraviolet-visible Spectroscopy at the absorbance maximum wavelength (λmax) of around 590 nm with the solution C as a control solution. Subtract the absorbance of each solution from the absorbance of the solution E to obtain absorbance differences, based on which the standard curve of the fluorine content (μg) is drawn. Separately, take 5.0 mL of the test solution, proceed with it in the same manner stated above, and obtain the amount (μg) of fluorine (F) contained in 5 mL of the test solution from the standard curve.

Solution A—Dissolve 3.16 g of 4,5-dihydroxy-3-(p-sulfophenylazo)-2,7-naphthalenedisulfonic acid trisodium salt in 550 mL of water.

Solution B—Dissolve 0.113 g of oxychlorzirconium in 50 mL of water, then add 350 mL of hydrochloric acid and water to make exactly 500 mL.

Solution C—Dilute 50 mL of the solution A by adding 500 mL of water and 35 mL of hydrochloric acid.

Solution D—Mix equal amounts of the solution A and solution B in a brown bottle.

Solution E—Add water to 10.0 mL of the solution D to make exactly 100 mL.

Packaging and storage Preserve in well-closed containers.

Streptokinase and Streptodornase
스트렙토키나제·스트렙토도르나제

Streptokinase and Streptodornase is an enzyme, obtained by purifying the culture products of *Enterococcus hemolyticus* H 46 A strain.

Streptokinase and Streptodornase contains NLT 1000 units of streptokinase and NLT 250 units of streptodornase.

Description Streptokinase and Streptodornase occurs as a white or pale brown powder and is odorless.

Dissolve Streptokinase and Streptodornase in 20 mL of physiological saline solution containing 50,000 units of streptokinase; the solution becomes clear or slightly turbid in 5 hours.

Identification Dissolve 50 mg of Streptokinase and Streptodornase in 20 mL of physiological saline solution. Add dilute gelatin TS to 1 mL of this solution so that the resulting solution contains 10 units of streptokinase per mL, and use this solution as the test solution. Transfer 0.2 mL each of the test solution and dilute gelatin TS (control solution) to separate test tubes, put into a water bath at 25 ± 0.1 ℃, add 0.2 mL of plasminogen TS to each test tube, and shake to mix. Add 0.4 mL of fibrinogen TS after 4 minutes, add again plasminogen TS, put 0.1 mL of thrombin TS after 5 minutes, and shake to mix; the test solution coagulates but do not dissolve in 15 minutes. The control solution also coagulates and do not dissolve within 1 hour.

pH Dissolve about 0.25 g of Streptokinase and Strep-

todornase in 100 mL of isotonic sodium chloride injection; the pH of the solution is between 6.5 and 8.5.

Loss on drying 6.0% (0.1 g in vacuum, phosphorus oxide (V), constant mass)

Assay (1) ***Streptokinase***—Weigh accurately about 0.5 g of Streptokinase and Streptodornase, add physiological saline solution to dissolve by gently shaking, and make exactly 200 mL. To the resulting solution, add dilute gelatin TS, make solutions with a concentration of 1 in 500, 1 in 750, 1 in 1000, 1 in 1500, 1 in 2000, and 1 in 3000, respectively, and use them as the test solutions. Separately, put an appropriate amount of streptokinase RS into the physiological saline solution to gently shake to mix so that 1 mL of the solution contains 10,000 units of streptokinase. Add dilute gelatin TS to achieve equivalent concentrations to those of the test solutions and use these solutions as the standard solutions. Transfer 0.2 mL each of the six test and standard solutions to separate test tubes (100 mm in length x 10 mm in diameter), put them into a water bath maintained at 25 ± 0.1 ℃, add 0.2 mL of plasminogen TS to each test tube, and shake to mix. Add 0.4 mL of fibrinogen TS after 4 minutes. Add 0.1 mL of thrombin TS in 5 minutes after putting plasminogen TS, and record the time (second) required for the thrombin-induced coagulates to dissolve. Tilt the test tube; if the surface of the solution in the test tube is horizontal and little residue is observed, the coagulates are considered to be dissolved. Plot the dissolution time for the standard and test solutions on the vertical axis and the dilution factor on the horizontal axis of a log-log graph to construct two straight lines. Determine the dilution factor for the test solution and the standard solution at the point where the respective straight line intersects with the horizontal line representing the dissolution time of 10 minutes.

Unit of Streptokinase per mg =
Unit of standard solution (10,000) × (dilution factor of sample / dilution factor of the standard solution) × [200 / amount of sample taken (mg)]

(2) ***Streptodornase***—Weigh accurately about 0.1 g of Streptokinase and Streptodornase and dissolve in the physiological saline solution to make exactly 100 mL. To the solution, add mixed peptone so that 1 mL of the resulting solution contains 10 units of streptodornase, and use this solution as the test solution. Separately, dissolve an appropriate amount of streptodornase RS in the physiological saline solution so that 1 mL of the solution contains 5,000 units of streptodornase. Add mixed peptone TS to achieve equivalent concentrations to those of the test solution and use this solution as the standard solution. Immerse a viscometer in the upright position on a steam bath at 30 ± 0.1 ℃ up to about 10 mm above the gauge line. Remove the stopper with a platinum electrode, add 3.5 mL of deoxyribonucleic acid TS into the upper room, install the stopper with a platinum electrode, and allow to stand. Wait for 30 minutes until the deoxyribonucleic acid TS reaches thermal equilibrium with the water bath. Connect the viscometer with a vacuum pump, suck the deoxyribonucleic acid TS traveled down to the lower room up to the gauge line indicated on the upper room. Measure travel time 2 to 3 times; travel time is defined as the time required for the liquid level to drop from the short needle to the long needle of the platinum electrode. In consecutive measurements, gradually decreasing travel time indicates potential contamination of deoxyribonucleic acid TS; repeat the procedure. Once the travel time of the deoxyribonucleic acid TS becomes constant, accurately add 0.1 mL of the test solution to the upper room and shake well to mix. Measure the travel time B (second). Measure travel time 5, 10, 15, 20, 25, and 30 minutes after adding the test solution to the upper room. Assign the respective measurements to B_1, B_2, B_3, B_4, B_5, and B_6. Determine the viscometer constant, A (second), in advance by measuring the time required for the liquid level to drop from the short needle to the long needle of the platinum electrode with 3 mL of mixed peptone TS. Divide A by B_1, B_2, B_3, B_4, B_5 and B_6, resulting in X_1, X_2, X_3, X_4, X_5 and X_6, respectively. Plot X values versus time (5, 10, 15, 20, 25, and 30 minutes) to construct a straight line. From the straight line, determine the values at 0 minute (C) and 25 minutes (D), subtract the value C from the value D, and the resulting value becomes K_{25} of the test solution. Separately, repeat the above procedure for the standard solution to determine K_{25} of the standard solution.

Unit of streptodornase per mg =
Unit of the standard solution (10) × (K_{25} test solution / K_{25} standard solution) × [1 / amount of sample taken (mg)]

Packaging and storage Preserve in tight containers (at 2 to 10 ℃).

Streptokinase and Streptodornase Tablets
스트렙토키나제·스트렙토도르나제 정

Streptokinase and Streptodornase Tablets contain NLT 90.0% and NMT 150.0% of the labeled amount (potency) of streptokinase and NLT 100.0% of the labeled amount (potency) of streptodornase.

Method of preparation Prepare as directed under Tablets, with Streptokinase and Streptodornase.

Identification (1) Weigh an amount of Streptokinase and Streptodornase Tablets, equivalent to 50 mg of streptokinase, dissolve in 20 mL of normal saline solution, and add dilute gelatin TS to 1 mL of this solution so that the resulting solution contains 10 units of streptokinase per mL. Use this solution as the test solution. Transfer 2 mL of the test solution and 0.2 mL of dilute gelatin TS (control solution) to test tubes, respectively, put into a water bath at 25 ± 0.1 ℃, add 0.2 mL of plasminogen TS to

each test tube, and shake to mix. Add 0.2 mL of fibrinogen TS after 4 minutes, add again plasminogen TS, add 0.1 mL of thrombin TS after 5 minutes, and shake to mix; the test solution coagulates but dissolves in 15 minutes. The control solution also coagulates but do not dissolve within 1 hour.

(2) ***Streptodornase***—Dissolve Streptokinase and Streptodornase Tablets in normal saline solution so that the resulting solution contains 5000 units of streptodornase per mL. To this solution, add mixed peptone TS so that the resulting solution contains 10 units of streptodornase per mL, and use this solution as the test solution. When tested as directed under the Assay, the velocity of substrate increases over time.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Streptokinase***—Weigh accurately the mass of NLT 20 tablets of Streptokinase and Streptodornase Tablets, and powder. Weigh accurately an amount, equivalent to 0.125 g of streptokinase, dissolve in normal saline solution by shaking gently to make 50 mL. To the resulting solution, add dilute gelatin solution to obtain a concentration of 1 in 500, 1 in 750, 1 in 1000, 1 in 1500, 1 in 2000, and 1 in 3000, respectively, and use these solutions as the test solutions. Separately, add the physiological saline solution to an appropriate amount of streptokinase RS, shake gently to mix so that the solution contains 10000 units of streptokinase per mL, add dilute gelatin TS to obtain the same concentrations as those of the test solutions and use these solutions as the standard solutions. Perform the test as directed under the Assay of streptokinase in Streptokinase and Streptodornase.

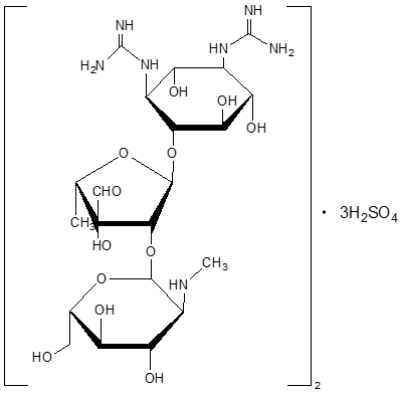
$$\begin{aligned}&\text{Streptokinase unit in 1 tablet}\\&= \text{Unit (10,000) of standard solution}\\&\times \frac{Dilution\ factor\ of\ sample}{Dilution\ factor\ of\ standard\ solution}\\&\times \frac{50}{Amount\ (mg)\ of\ sample\ taken}\\&\times Average\ mass\ (mg)\ of\ 1\ tablet\end{aligned}$$

(2) ***Streptodornase***—Weigh accurately the mass of NLT 20 tablets of Streptokinase and Streptodornase Tablets, and powder. Weigh accurately an amount, equivalent to 0.1 g of streptodornase, and dissolve in normal saline solution to make 100 mL. To the solution, add mixed peptone so that 1 mL of the resulting solution contains 10 units of streptodornase, and use this solution as the test solution. Separately, dissolve an appropriate amount of streptodornase RS in the physiological saline solution so that the solution contains 5000 units of streptodornase per mL. Add mixed peptone TS to obtain the same concentrations as those of the test solution and use this solution as the standard solution. Perform the test as directed under Assay of streptodornase in Streptokinase and Streptodornase.

$$\begin{aligned}&\text{Streptodornase unit in 1 tablet}\\&= \text{Unit (10) of standard solution}\\&\times \frac{K_{25}\ test\ solution}{K_{25}\ standard\ solution}\\&\times \frac{Average\ mass\ (mg) of\ 1\ tablet}{Amount\ (mg)\ of\ sample\ taken}\\&\times Dilution\ factor\ of\ test\ solution\end{aligned}$$

Packaging and storage Preserve in tight containers (at 2 to 10 °C).

Streptomycin Sulfate
스트렙토마이신황산염



$(C_{21}H_{39}N_7O_{12})_2 \cdot 3H_2SO_4$: 1457.38

2-[(1*S*,2*S*,3*R*,4*S*,5*S*,6*R*)-3-(Diaminomethylideneamino)-4-[(2*R*,3*R*,4*R*,5*S*)-3-[(2*S*,3*S*,4*S*,5*R*,6*S*)-4,5-dihydroxy-6-(hydroxymethyl)-3-(methylamino) oxan-2-yl]oxy-4-formyl-4-hydroxy-5-methyloxolan-2-yl]oxy-2,5,6-trihydroxycyclohexyl]guanidine sulfate [*3810-74-0*]

Streptomycin Sulfate is the sulfate of an aminoglycoside substance having antibacterial activity and obtained from *Streptomyces griseus* culture.

Streptomycin Sulfate contains NLT 740 μg (potency) and NMT 820 μg (potency) of streptomycin ($C_{21}H_{39}N_7O_{12}$: 581.57) per mg, calculated on the dried basis.

Description Streptomycin Sulfate occurs as a white to pale yellowish white powder.
It is freely soluble in water and very slightly soluble in ethanol(95).

Identification (1) Dissolve 50 mg of Streptomycin Sulfate in 5 mL of water, add 1 mL of ninhydrin TS and 0.5 mL of pyridine, and heat for 10 minutes; a purple color develops.

(2) Dissolve 10 mg each of Streptomycin Sulfate and streptomycin sulfate RS in 10 mL of water, and use these solutions as the test solution and standard solution. Perform the test directed under the Thin Layer Chromatography. Spot 10 μL each of these solutions on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a solution

of potassium dihydrogen phosphate (7 in 100) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Spray evenly a mixture of a solution of 1,3-dihydroxynaphthalene in ethanol(95) (1 in 500) and diluted sulfuric acid (1 in 5) (1 : 1) on the plate, and heat at about 150 °C for about 5 minutes; the principal spots obtained from the test solution and standard solution show the same color and R_f value.

(3) A solution of Streptomycin Sulfate (1 in 5) responds to the Qualitative Analysis for sulfate.

Optical rotation $[\alpha]_D^{20}$: Between -79° and -88° (0.5 g calculated on the dried basis, water, 50 mL, 100 mm).

pH Dissolve about 2 g of Streptomycin Sulfate in 10 mL of water; the pH of the solution ranges between 4.5 and 7.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Streptomycin Sulfate in 5 mL of water; the resulting solution is colorless to pale yellow and clear.

(2) ***Heavy metals***—Proceed with 2.0 g of Streptomycin Sulfate according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Prepare the test solution with 2.0 g of Streptomycin Sulfate according to Method 3 and perform the test (NMT 1 ppm).

(4) ***Related substances***—Weigh accurately 0.20 g of Streptomycin Sulfate, dissolve in a mixture of methanol and sulfuric acid (97 : 3) to make 5 mL, and heat under a reflux condenser for 1 hour. Cool, wash the inside of the condenser with an appropriate amount of a mixture of methanol and sulfuric acid (97 : 3), add a mixture of methanol and sulfuric acid (97 : 3) to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately 36 mg of D(+)-mannose, dissolve in a mixture of methanol and sulfuric acid (97 : 3) to make 5 mL, and heat with a reflux condenser for 1 hour. After cooling, wash the inside of the condenser with an appropriate amount of a mixture of methanol and sulfuric acid (97 : 3), and add a mixture of methanol and sulfuric acid (97 : 3) to make exactly 50 mL. Pipet 5 mL of this solution and mix with a mixture of methanol and sulfuric acid (97 : 3) to make exactly 50 mL and use this solution as the standard solution. Perform the test directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of toluene, methanol and acetic acid(100) (2 : 1 : 1) to a distance of 13 to 15 cm, and air-dry the plate. Spray evenly a mixture of 1,3-dihydroxynaphthalene in ethanol(95) (1 in 500) and diluted sulfuric acid (1 in 5) (1 : 1) on the plate, and heat at 110 °C for 5 minutes; the spot from the test solution corresponding to the spot from the standard solution is not more intense than the spot from the standard solution.

Loss on drying NMT 5.0% (0.5 g, not exceeding 0.67 kPa, 60 °C, 3 hours).

Residue on ignition NMT 1.0% (1 g).

Sterility It meets the requirements when used in a sterile preparation. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of a sterile preparation.

Bacterial endotoxins Less than 0.10 Eu/mg (potency) of streptomycin, when used in a sterile preparation.

Abnormal toxicity Dissolve 1 mg of Streptomycin Sulfate in 0.5 mL of water for injection, and inject intravenously for 15 to 30 seconds to each of 5 healthy mice weighing 17 to 24 g. Use the animals without any sign of abnormality for at least 5 days before the test. No animals die for the first 24 hours after injection. If 1 animal dies, repeat the test with 5 animals, and make sure that no animal dies for the first 24 hours.

Histamine It meets the requirements when used in a sterile preparation. Weigh an appropriate amount of Streptomycin Sulfate, dissolve it in isotonic sodium chloride injection so that the solution contains 3.0 mg (potency) of the Streptomycin sulfate per mL, and use the solution as the test solution.

Assay ***Cylinder plate method*** (1) Agar media for seed and base layer: Use the medium in (A) (2) (a) ① ⓐ under the Microbial Assays for Antibiotics.

(2) Test organism: *Bacillus subtilis* ATCC 6633

(3) Weigh accurately about 20 mg (potency) of Streptomycin Sulfate, dissolve in water to make exactly 50 mL, and use this solution as the test stock solution. Pipet an appropriate amount of the test stock solution, add 0.1 mol/L phosphate buffer solution (pH 8.0) to dilute so that the resulting solutions contain 8.0 μg (potency) and 2.0 μg (potency) per mg, and use these solutions as the high-concentration test solution and low-concentration test solution, respectively. Separately, weigh accurately about 20 mg (potency) of streptomycin sulfate RS, previously dried, dissolve in diluted pH 6.0 phosphate buffer solution (1 in 2) to make exactly 50 mL, and use this solution as the standard stock solution. Keep the standard stock solution between 5 and 15 °C and use within 30 days. Pipet an appropriate amount of the standard stock solution, dilute with 0.1 mol/L phosphate buffer solution (pH 8.0) so that the resulting solutions contain 8.0 μg (potency) and 2.0 μg (potency) per mL, and use these solutions as the high-concentration standard solution and low-concentration standard solution, respectively. Perform the test with these solutions as directed in (A) (8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in tight containers.

Streptomycin Sulfate for Injection
주사용 스트렙토마이신황산염

Streptomycin Sulfate for Injection is a preparation for injection, which is dissolved before use. Streptomycin Sulfate for Injection contains NLT 90.0% and NMT 110.0% of the labeled amount of streptomycin ($C_{21}H_{39}N_7O_{12}$: 581.57).

Method of preparation Prepare as directed under Injections, with Streptomycin Sulfate.

Description Streptomycin Sulfate for Injection occurs as a white to pale yellow mass or a powder.

Identification Perform the test as directed under the Identification (2) under Streptomycin Sulfate.

pH Dissolve an amount of Streptomycin Sulfate for Injection, equivalent to 2.0 g (potency) of streptomycin, in water; the pH of the solution is between 5.0 and 7.0.

Purity ***Clarity and color of solution***—Dissolve an amount of Streptomycin Sulfate for Injection, equivalent to 1.0 g (potency) of streptomycin sulfate according to the labeled amount, in 3 mL of water; the resulting solution is clear. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at a wavelength of 400 nm is NMT 0.50.

Loss on drying NMT 4.0% (0.5 g, not exceeding 0.67 kPa, 60 ℃, 3 hours)

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.10 EU per mg (potency) of streptomycin.

Particulate contamination: Visible particles Meets the requirements.

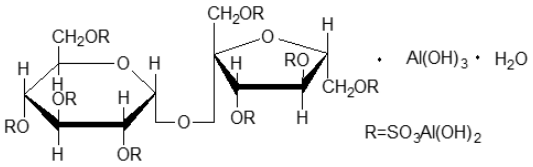
Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Proceed as directed under the Assay under Streptomycin Sulfate. Weigh accurately an amount of Streptomycin Sulfate for Injection, equivalent to about 1.0 g (potency) according to the labeled potency, and add water to make exactly 200 mL. Pipet an appropriate amount of this solution, add 0.1 mol/L phosphate buffer solution (pH 8.0) to obtain a solution having known concentration of 8.0 μg and 2.0 μg (potency) per mL, and use them as the high-concentration test solution and low-concentration test solution, respectively.

Packaging and storage Preserve in hermetic containers.

Sucralfate Hydrate
수크랄페이트수화물



Sucrose Sulfate Aluminum Salt

Sucralfate $C_{12}H_{30}Al_8O_{51}S_8 \cdot x\mathrm{Al(OH)_3} \cdot yH_2O$

Aluminum;[(2*R*,3*R*,4*S*,5*R*,6*R*)-2-[(2*R*,3*R*,4*S*,5*S*)-3,4-*bis*(λ1-alumanyloxysulfonyloxy)-2,5-*bis*(λ1-alumanyloxysulfonyloxymethyl)oxolan-2-yl]oxy-3,5-bis(λ1-alumanyloxysulfonyloxy)-6-(λ1-alumanyloxysulfonyloxymethyl)oxan-4-yl]oxysulfonyloxyaluminum;tetracontahydrate [*54182-58-0*]

Sucralfate Hydrate contains NLT 17.0% and NMT 21.0% of aluminum (Al: 26.98) and NLT 34.0% and NMT 43.0% of sucrose octasulfate ($C_{12}H_{22}O_{35}S_8$: 982.80), calculated on the dried basis.

Description Sucralfate Hydrate occurs as a white powder and is odorless and tasteless.
It is practically insoluble in water, hot water, ethanol(95) or ether.
It dissolves in dilute hydrochloric acid or sulfuric acid-sodium hydroxide TS.

Identification (1) Transfer 50 mg of Sucralfate Hydrate to a small test tube, add 50 mg of freshly cut pieces of sodium metal, and melt by careful heating. Immerse the test tube immediately in 100 mL of water, break the test tube, shake well to mix, and filter. To 5 mL of the filtrate, add 1 drop of sodium pentacyanonitrosylferrate(III) TS; the solution exhibits a purple color.

(2) Dissolve 40 mg of Sucralfate Hydrate in 2 mL of dilute sulfuric acid, and add gently 2 mL of anthrone TS to make 2 layers; the boundary layer exhibits a blue color, and gradually changes to bluish green.

(3) Dissolve 0.5 g of Sucralfate Hydrate in 10 mL of dilute hydrochloric acid; the solution responds to the Qualitative Analysis for aluminum salt.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Sucralfate Hydrate in 10 mL of dilute sulfuric acid; the resulting solution is clear and colorless.

(2) ***Chloride***—Dissolve 0.5 g of Sucralfate Hydrate in 30 mL of dilute nitric acid, and heat gently to boiling. After cooling, add water to make 100 mL, and to 10 mL of this solution, add 3 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.70 mL of 0.01 mol/L hydrochloric acid (NMT 0.50%).

(3) ***Heavy metals***—Dissolve 1.0 g of Sucralfate Hydrate in 20 mL of sodium chloride solution (1 in 5) and 1 mL of dilute hydrochloric acid, and to this solution,

add 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by evaporating 1 mL of dilute hydrochloric acid on a steam bath to dryness, and adding 20 mL of sodium chloride solution (1 in 5), 2 mL of dilute acetic acid, 2.0 mL of lead standard solution and water to make 50 mL (NMT 10 ppm).

(4) ***Free aluminum***—To 3.0 g of Sucralfate Hydrate, add 50 mL of water, heat on a steam bath for 5 minutes, cool, and filter. Wash the residue with four 5-mL portions of water, combine the filtrate with the washings, add 2 mL of dilute hydrochloric acid, and heat on a steam bath for 30 minutes. After cooling, neutralize with sodium hydroxide TS, add water to make exactly 100 mL, and use this solution as the test solution. Pipet 50 mL of the test solution, add exactly 25 mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt and 20 mL of acetic acid-ammonium acetate buffer solution, pH 4.5, and boil for 5 minutes. After cooling, add 50 mL of ethanol(95) and titrate the excess ethylenediaminetetraacetic acid disodium salt with 0.05 mol/L zinc acetate VS (indicator: 3 mL of dithizone TS). The endpoint of the titration is when this solution changes from greenish purple through violet to red. Perform a blank test in the same manner (NMT 0.2%).

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt
= 1.3491 mg of Al

(5) ***Arsenic***—Dissolve 1.0 g of Sucralfate Hydrate in 5 mL of dilute hydrochloric acid, use this solution as the test solution, and perform the test (NMT 2ppm).

(6) ***Related substances***—With 50 μL of the test solution obtained in the Assay (2) Sucrose octasulfate ester, perform the test as directed under the Liquid Chromatography according to the Assay (2) Sucrose octasulfate ester. Determine the peak area of sucrose octasulfate and the peak area of related substances having the relative retention time to the peak of sucrose octasulfate of about 0.7 from the test solution by the automatic integration method, and determine the ratio of the peak area of the related substances to that of sucrose octasulfate; it is NMT 0.1.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of sucrose octasulfate ester obtained from 50 μL of the standard solution in the Assay (2) Sucrose octasulfate ester is between 60% and 100% of the full scale.

Loss on drying NMT 14.0% (1 g, 105 °C, 3 hours).

Acid-neutralizing capacity Weigh accurately about 0.25 g of Sucralfate Hydrate, previously dried, and perform the test; the amount of 0.1 mol/L hydrochloric acid VS consumed per g of Sucralfate Hydrate is NLT 130 mL.

Assay (1) ***Aluminum***—Weight accurately about 1 g of Sucralfate Hydrate, dissolve in 10 mL of dilute hydrochloric acid by warming, cool, and add water to make exactly 250 mL. Pipet 25 mL of this solution, add exactly 25 mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt and 20 mL of acetic acid-ammonium acetate buffer solution, pH 4.5, and boil for 5 minutes. After cooling, add 50 mL of ethanol(95), and titrate the excess ethylenediaminetetraacetic acid disodium salt with 0.05 mol/L zinc acetate VS (indicator: 3 mL of dithizone TS). The endpoint of the titration is when this solution changes from greenish purple through violet to red. Perform a blank test in the same manner.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt
= 1.3491 mg of Al

(2) ***Sucrose octasulfate ester***—Weigh accurately about 0.55 g of Sucralfate Hydrate, add exactly 10 mL of sulfuric acid-sodium hydroxide TS, shake vigorously to mix, and dissolve by sonicating at below 30 °C for 5 minutes. Add 0.1 mol/L sodium hydroxide to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately about 0.25 g of potassium sucrose octasulfate RS, add the mobile phase to make exactly 25 mL, and use this solution as the standard solution. Prepare rapidly the test solution and the standard solution, and perform the test immediately. Pipet 50 μL each of the test solution and the standard solution, and perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas, A_T and A_S, of sucrose octasulfate ester from these solutions.

Amount (mg) of sucrose octasulfate ester ($C_{12}H_{22}O_{35}S_8$)
= Amount (mg) of potassium sucrose octasulfate RS, calculated on the dried basis $\times \frac{A_T}{A_S} \times 0.7633$

Operating conditions

Detector: A differential refractometer

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with aminopropylsilyl silica gel for liquid chromatography (about 8 μm in particle diameter).

Mobile phase: Dissolve an appropriate amount (26 g to 132 g) of ammonium sulfate in 1000 mL. of water, and adjust the pH to 3.5 with phosphoric acid. Allow a solution of potassium sucrose sctasulfate RS in dilute hydrochloric acid (1 in 100) to stand at 60 °C for 10 minutes, cool, and perform the test immediately. Adjust the amount of ammonium sulfate so that the peak of a related substance, having the relative retention time to that of sucrose octasulfate ester of about 0.7, almost returns to the base line, and the peak of sucrose octasulfate ester elutes most rapidly.

Flow rate: Adjust the flow rate so that the retention time of sucrose octasulfate ester is between 6 and 11 minutes.

System suitability

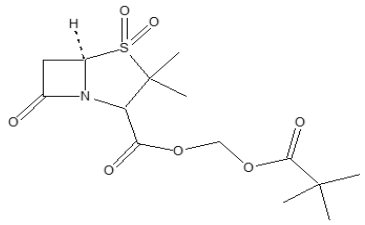
System performance: Allow a solution of potassi-

um sucrose octasulfate RS in dilute hydrochloric acid (1 in 100) to stand at 60 °C for 10 minutes, cool, and proceed immediately with 50 μL of this solution according to the above operating conditions; the resolution between sucrose octasulfate ester and the related substance with the relative retention time being about 0.7 to sucrose octasulfate ester is NLT 1.5.

System repeatability: Repeat the test 6 times with 50 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak areas for sucrose octasulfate ester is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Sulbactam Pivoxil
설박탐피복실



$C_{14}H_{21}NO_7S$:347.38
(2,2-Dimethyl-1-oxopropoxy) methyl (2*S*-*cis*)-3,3-dimethyl-7-oxo-4,4-dioxide4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid ester, [*69388-79-0*]

Sulbactam Pivoxil contains NLT 620 μg and NMT 680 μg (potency) of sulbactam ($C_8H_{11}NO_5S$: 233.24) per mg, calculated on the anhydrous basis.

Description Sulbactam Pivoxil occurs as a milky white crystalline powder.
It is sparingly soluble in water and soluble in methanol, chloroform, and acetone.

Identification (1) Determine the infrared spectra of Sulbactam Pivoxil and sulbactam pivoxil RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Weigh about 100 mg (potency) of Sulbactam Pivoxil and sulbactam pivoxil RS, dissolve in 10 mL of methanol, and use these solutions as the test solution and standard solution, respectively. With the test and standard solutions, perform the test as directed under the Thin Layer Chromatography. Spot 1 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of diethyl ether-methanol-acetic acid (50:50:1), and air-dry the plate. Put the thin-layer chromatographic plate into a suitable container containing 2 to 4 g of iodine crystals, cover it with a lid, and allow to stand for 3 to 5 minutes; the R*f* values obtained from the test solution and the standard solution are the same.

Optical rotation $[\alpha]_D^{20}$: Between +162 ° and +170 ° (0.1 g, Methanol, 10 mL, 100 mm).

Melting point Between 103 and 106 ℃.

Purity ***Heavy metals***—Proceed with 1.0 g of Sulbactam Pivoxil according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Water NMT 1.0%.

Assay Weigh accurately about 75 mg each of Sulbactam Pivoxil and sulbactam pivoxil RS, add a mixture of water and methanol (1:1) to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of sulbactam in each solution.

$$\text{Potency (μg) of sulbactam } (C_8H_{11}NO_5S) = \text{Potency (μg) of sulbactam in sulbactam pivoxil RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 235 nm).

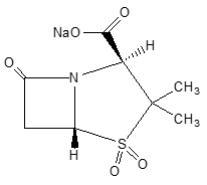
Column: A stainless steel column about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: A mixture of methanol and 1% acetic acid (65 : 35).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Sulbactam Sodium
설박탐나트륨



$C_8H_{10}NNaO_5S$: 255.22
Sodium (3*S*)-2,2-dimethyl-1,1-dioxo-1λ6-penam-3-carboxylate [*69388-84-7*]

Sulbactam Sodium contains NLT 875 μg and NMT 941 μg (potency) per mg of sulbactam ($C_8H_{11}NO_5S$: 233.24), calculated on the anhydrous basis.

Description Sulbactam Sodium occurs as a white to yellowish white crystalline powder.
It is freely soluble in water, sparingly soluble in methanol, very slightly soluble in ethanol(99.5), and practically insoluble in acetonitrile.

Identification (1) Determine the infrared spectra of Sulbactam Sodium and sulbactam sodium RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

(2) Sulbactam Sodium responds to the Qualitative Analysis for sodium salt.

Crystallinity Meets the requirements.

Optical rotation $[\alpha]_D^{20}$: Between +219° and +233° (1.0 g, water, 100 mL, 100 mm).

pH Dissolve 1.0 g of Sulbactam Sodium in 20 mL of water. The pH of this solution is between 5.2 and 7.2.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Sulbactam Sodium in 20 mL of water; the solution is colorless to pale yellow color and is clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Sulbactam Sodium and perform the test as directed under Method 2. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Sulbactam Sodium according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Sulbactam penicillamine***—Weigh accurately about 0.2 g of Sulbactam Sodium, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, dissolve 40 mg of sulbactam sodium for sulbactam penicillamine, accurately weighed, in 2 mL of water, add 0.5 mL of sodium hydroxide TS, and allow it to stand for 10 minutes at room temperature. Then, add 0.5 mL of 1 mol/L hydrochloric acid TS, and add the mobile phase to make exactly 100 mL. Pipet 5 mL of the resulting solution, add the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Take exactly 10 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas A_T and A_S of sulbactam penicillamine for each solution; the amount of sulbactam penicillamine is NMT 1.0%.

$$\text{Content (\%) of sulbactam penicillamine} = \frac{W_S}{W_T} \times \frac{A_T}{A_S} \times 5$$

W_S: Amount (mg) taken of sulbactam sodium for sulbactam penicillamine

W_T: Amount (mg) taken of Sulbactam Sodium

Operating conditions

For the column, column temperature, mobile phase and flow rate, comply with the operating conditions as directed under the Assay.

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

System suitability

System performance: Proceed as directed under the system suitability under the Assay.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of sulbactam penicillamine is NMT 2.0%.

Water NMT 1.0% (0.5 g, volumetric titration, direct titration)

Sterility It meets the requirements when Sulbactam Sodium is used in a sterile preparation. However, it is excluded in cases where there is a final sterilization process in the manufacturing of a sterile preparation.

Bacterial endotoxins Less than 0.17 EU/mg (potency) when Sulbactam Sodium is used in a sterile preparation.

Assay Weigh accurately about 0.1 g (potency) each of Sulbactam Sodium and sulbactam sodium RS, dissolve each in the mobile phase, and add 10.0 mL of the internal standard solution. Add the mobile phase to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions and calculate the peak area ratios, Q_T and Q_S, of sulbactam to internal standard, respectively.

$$\text{Potency (μg) of sulbactam } (C_8H_{11}NO_5S) = \text{Potency (μg) of sulbactam RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of ethyl p-hydroxybenzoate in the mobile phase (7 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 35 ℃.

Mobile phase: Add 0.005 mol/L tetrabutylammonium hydroxide TS to 250 mL of acetonitrile to make exactly 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of sulbactam is about 6 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; sulbactam and internal standard are eluted in this order with resolution between their peaks being NLT 1.5.

System repeatability: Repeat the test 6 times with

10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of sulbactam is NMT 1.0%.

0.005 mol/L Tetrabutylammonium hydroxide TS— To 10 mL of tetrabutylammonium hydroxide TS, add phosphoric acid diluted with 700 mL of water (1 in 10) to adjust pH to 4.0. Add water to make 1000 mL.

Packaging and storage Preserve in tight containers.

Sulbactam Sodium·Amoxicillin Sodium for Injection
주사용 설박탐나트륨·아목시실린나트륨

Sulbactam Sodium·Amoxicillin Sodium for Injection, as an injection that is dissolved upon use, contains NLT 90.0% and NMT 120.0% of the labeled amount of sulbactam ($C_8H_{11}NO_5S$: 233.24) and amoxicillin ($C_{16}H_{19}N_3O_5S$: 365.41), respectively.

Method of preparation Prepare as directed under Injections, with Sulbactam Sodium and Amoxicillin Sodium.

Description Sulbactam Sodium·Amoxicillin Sodium for Injection occurs as a white to yellowish white powder.

Identification The major peaks obtained from the test solution and the standard solution under the Assay are the same in the retention time.

pH Dissolve Sulbactam Sodium·Amoxicillin Sodium for Injection in water to make a concentration of 0.1 g (potency)/mL as amoxicillin; the pH of this solution is between 7.0 and 9.0.

Sterility Meets the requirements.

Pyrogen Perform the test by injecting a solution, prepared by adding isotonic sodium chloride injection to make a known concentration of 40 mg (potency) of Sulbactam Sodium·Amoxicillin Sodium for Injection per mL, into a rabbit (1 mL of the solution per kg of the rabbit weight); it meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Water NMT 3.0% (0.2 g, volumetric titration, direct titration).

Assay Weigh accurately an amount of Sulbactam Sodium·Amoxicillin Sodium for Injection equivalent to about 0.14 g (potency) of amoxicillin, add the mobile phase to make exactly 200 mL, and use this solution as the test solution. Separately, weigh accurately each about 35 mg (potency) of sulbactam RS and about 70 mg (potency) of amoxicillin RS, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak areas of sulbactam and amoxicillin, A_{T1}, A_{S1}, A_{T2} and A_{S2}, in each solution.

$$\text{Potency (μg) of sulbactam } (C_8H_{11}NO_5S) = \text{Potency (μg) of sulbactam RS} \times \frac{A_{T1}}{A_{S1}}$$

$$\text{Potency (μg) of amoxicillin } (C_{16}H_{19}N_3O_5S) = \text{Potency (μg) of amoxicillin RS} \times \frac{A_{T2}}{A_{S2}}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of 0.01 mol/L phosphate buffer solution (pH 3.0) and methanol (95 : 5).

Packaging and storage Preserve in hermetic containers.

Sulbactam Sodium·Ampicillin Sodium
설박탐나트륨·암피실린나트륨

Sulbactam Sodium·Ampicillin Sodium is a mixture of Sulbactam Sodium and Ampicillin Sodium at a ratio of 1 to 2. It contains NLT 280 μg and NMT 340 μg (potency) of sulbactam ($C_8H_{11}NO_5S$: 233.24), and NLT 560 μg and NMT 680 μg (potency) of ampicillin ($C_{16}H_{19}N_3O_4S$: 349.41) per mg, calculated on the anhydrous basis.

Description Sulbactam Sodium·Ampicillin Sodium occurs as a white or milky white powder.
It is very soluble in water, sparingly soluble in methanol, and very slightly soluble in ethanol(95).

Identification (1) ***Sulbactam sodium***—The retention time of the major peak obtained from the test solution corresponds to that from the standard solution, as obtained in the Assay (1).

(2) ***Ampicillin sodium***—The retention time of the major peak obtained from the test solution corresponds to that from the standard solution, as obtained in the Assay (2).

pH Dissolve Sulbactam Sodium·Ampicillin Sodium in water to make 5 mg (potency)/mL as sulbactam ($C_8H_{11}NO_5S$); the pH of this solution is between 8.0 and

10.0.

Sterility It meets the requirements when Sulbactam Sodium·Ampicillin Sodium is used in sterile preparations. However, it is excluded in cases where there is a final sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins It meets the requirements when Sulbactam Sodium·Ampicillin Sodium is used in sterile preparations. However, Sulbactam Sodium·Ampicillin Sodium is less than 0.51 EU per mg (potency) as sulbactam ($C_8H_{11}NO_5S$).

Water NMT 2.0% (0.5 g, volumetric titration, direct titration)

Assay (1) ***Sulbactam sodium***—Weigh accurately an amount equivalent to about 0.1 g (potency) as sulbactam ($C_8H_{11}NO_5S$) according to the labeled potency of Sulbactam Sodium·Ampicillin Sodium, and dissolve by putting the mobile phase. Add 10.0 mL of the internal standard solution, put the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g (potency) of sulbactam RS, proceed in the same manner as in the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of sulbactam to the internal standard.

$$\text{Potency (μg) of sulbactam } (C_8H_{11}NO_5S) = \text{Potency (μg) of sulbactam RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of ethyl *p*-hydroxybenzoate in the mobile phase (7 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: Add 0.005 mol/L tetra-n-butylammonium hydroxide to 250 mL of acetonitrile to make exactly 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of sulbactam is about 6 minutes.

System suitability

System performance: Perform the test with 10 μL of the standard solution; sulbactam and the internal standard are eluted in this order with the resolution between these peaks being NLT 1.5.

(2) ***Ampicillin sodium***—Weigh accurately an amount equivalent to about 60 mg (potency) as ampicillin ($C_{16}H_{19}N_3O_4S$) according to the labeled potency of Sulbactam Sodium·Ampicillin Sodium and about 60 mg (potency) of ampicillin sodium RS, and add the mobile phase to make exactly 25 mL. Pipet 5 mL each of these solutions, add the mobile phase to make exactly 25 mL, and use these solutions as the test and standard solutions. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of ampicillin for each solution.

$$\text{Potency (μg) of ampicillin } (C_{16}H_{19}N_3O_4S) = \text{Potency (μg) of ampicillin sodium RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: Add 0.005 mol/L tetrabutylammonium hydroxide TS to 175 mL of acetonitrile to make exactly 1000 mL.

Flow rate: 2.0 mL/min

Packaging and storage Preserve in tight containers.

Sulbactam Sodium-Ampicillin Sodium for Injection
주사용 설박탐나트륨·암피실린나트륨

Sulbactam Sodium-Ampicillin Sodium for Injection, as an injection that is dissolved upon use, contains NLT 90.0% and NMT 120.0% of the labeled amount of sulbactam ($C_8H_{11}NO_5S$: 233.24) and ampicillin ($C_{16}H_{19}N_3O_4S$: 349.41), respectively.

Method of preparation Prepare as directed under Injections, with Sulbactam Sodium and Ampicillin Sodium at a ratio of 1 : 2 (potency).

Description Sulbactam Sodium-Ampicillin Sodium for Injection occurs as a white to grayish white crystalline powder.

Identification (1) ***Sulbactam sodium***—The retention time of the major peak of sulbactam obtained from the test solution is the same as that from the standard solution, as obtained in the Assay (1).

(2) ***Ampicillin sodium***—The retention time of the major peak of ampicillin obtained from the test solution is the same as that from the standard solution, as obtained in the Assay (2).

pH Dissolve an amount of Sulbactam Sodium·Ampicillin Sodium for Injection, equivalent to 1.0 g (potency) of ampicillin sodium, in 100 mL of water; the

pH of this solution is between 8.0 and 10.0.

Water NMT 2.0% (0.5 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.20 EU per mg (potency) of ampicillin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Dissolve an appropriate amount of Sulbactam Sodium and Ampicillin Sodium for Injection according to the labeled amount in water, pipet an appropriate amount of the resulting solution, dilute with the mobile phase to make a solution having a known concentration of 0.25 mg (potency) of sulbactam and 0.5 mg (potency) of ampicillin per mL, and use this solution as the test solution. Separately, weight accurately appropriate amounts of ampicillin RS and sulbactam RS, dissolve in the mobile phase to make a solution having a known concentration of 0.25 mg (potency) of sulbactam and 0.5 mg (potency) of ampicillin per mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak areas of sulbactam and ampicillin, A_{T_1}, A_{S_1}, A_{T_2} and A_{S_2}, in the test solution and the standard solution, respectively.

Potency (μg) of sulbactam ($C_8H_{11}NO_5S$)
= Concentration [potency (μg)/mL] of sulbactam in the standard solution × $\frac{A_{T1}}{A_{S1}}$ × dilution factor of the test solution

Potency (μg) of ampicillin ($C_{16}H_{19}N_3O_4$)
= Concentration [potency (μg)/mL] of ampicillin in the standard solution × $\frac{A_{T2}}{A_{S2}}$ × dilution factor of the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (1.5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of 0.005 mol/L tetrabutylammonium hydroxide TS and acetonitrile (1650 : 350).

Flow rate: 2.0 mL/min

0.005 mol/L Tetrabutylammonium hydroxide TS—To 6.6 mL of 40% tetrabutylammonium hydroxide solution, add water to make 1800 mL, adjust the pH to 5.0 ± 1 with 1 mol/L phosphoric acid, and then add water to make 2000 mL.

System suitability

System performance: Proceed with 10 μL of the system suitability solution under the above operating conditions; the relative retention time of ampicillin with respect to the alkaline degradation product of sulbactam is about 0.7, with the resolution between these peaks being NLT 4.0. Proceed with 10 μL of the standard solution according to the above operating conditions; the relative retention time of ampicillin with respect to sulbactam is about 0.35. The number of theoretical plates and the symmetry factor of sulbactam are NLT 3500 and NMT 1.5, respectively.

System repeatability: Repeat the test 5 times with 10 μL of the standard solution according to the above operating conditions; the relative standard deviation of the areas of sulbactam peaks is NMT 2.0%.

System suitability solution—Weigh about 30 mg of sulbactam RS and dissolve in 0.01 mol/L sodium hydroxide solution to make 100 mL, allow to stand for 30 minutes, and then adjust the pH to 5.0 ± 1 with 1 mol/L phosphoric acid. To 5 mL of this solution, add 4.25 mL of acetonitrile, and dilute with 0.005 mol/L tetrabutylammonium hydroxide TS to make 25 mL. To 1 mL of this solution, add 15 mg of ampicillin RS, and dilute with the mobile phase to make 25 mL.

Packaging and storage Preserve in hermetic containers.

Sulbactam Sodium·Cefoperazone Sodium for Injection
주사용 설박탐나트륨·세포페라존나트륨

Sulbactam Sodium·Cefoperazone Sodium for Injection, as an injection that is dissolved upon use, contains sulbactam sodium and cefoperazone sodium at a ratio of 1 : 1 (potency), and contains NLT 90.0% and NMT 120.0% of the labeled amount of sulbactam ($C_8H_{11}NO_5S$: 233.24) and cefoperazone ($C_{25}H_{27}N_9O_8S_2$: 645.67), respectively.

Method of preparation Prepare as directed under Injections, with Sulbactam Sodium and Cefoperazone Sodium.

Description Sulbactam Sodium·Cefoperazone Sodium for Injection occurs as a white to grayish white crystalline powder or a powder.

Identification (1) Dissolve 10 mg of Sulbactam Sodium·Cefoperazone Sodium for Injection with 2 mL of water, add 3 mL of hydroxylamine hydrochloride TS, allow it to stand for 5 minutes, add 1 mL of acidic am-

monium iron(III) sulfate TS, and shake well to mix; the resulting solution exhibits a reddish brown color.

(2) Dissolve 20 mg of Sulbactam Sodium·Cefoperazone Sodium for Injection with 1 mL of a mixture of water and methanol (1 : 1), spot 1 drop of the resulting solution on a filter paper, dry, spray hydroiodic acid TS, and dry at room temperature for 15 minutes in vacuum while protected from light; a brown color develop in the spot. Spay 5% starch TS on this brown spot; it turns purple.

(3) Dissolve 20 mg of Sulbactam Sodium·Cefoperazone Sodium for Injection in 20 mL of water, take 4 mL of the resulting solution, add 1 mL of sodium carbonate solution (1 in 100) and 1 mL of diazobenzenesulfonic acid TS, and shake well to mix; the resulting solution exhibits an orange color.

(4) Dissolve 20 mg of Sulbactam Sodium·Cefoperazone Sodium for Injection with 4 mL of 1 mol/L sodium hydroxide TS, heat on a steam bath for 20 minutes, cool it, neutralize with 6 mol/L hydrochloric acid TS, heat on a steam bath for 2 to 3 minutes, add 1 mL of potassium chloride TS, and then allow to stand for 30 minutes. Filter the produced precipitate using a glass filter (G_4), wash the precipitate with 5 mL of water 4 times, dissolve with 1 mL of 1 mol/L sulfuric acid TS, add about 10 mg of magnesium, and dissolve. Take 3 drops of the resulting solution, add 2 mL of 2,7-dihydroxynaphthalene TS, and heat on a steam bath for 10 minutes; the solution exhibits a magenta color.

pH Dissolve Sulbactam Sodium·Cefoperazone Sodium for Injection in water to make a concentration of 50 mg (potency)/mL as sulbactam; the pH of this solution is between 4.5 and 6.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.9 EU per mg (potency) of Sulbactam Sodium·Cefoperazone Sodium for Injection.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Water NMT 4.0% for crystalline powder (0.2 g, volumetric titration, direct titration), and NMT 1.0% for freeze-dried powder (1.0 g, volumetric titration, direct titration).

Assay Weigh accurately an amount of Sulbactam Sodium·Cefoperazone Sodium for Injection equivalent to about 500 mg of sulbactam ($C_8H_{10}NN_5S$) and about 500 mg of cefoperazone sodium ($C_{25}H_{26}N_9NaO_8SS$), dissolve in water to make 500 mL, and filter through a membrane filter with a pore size of 0.45 μm, and use this filtrate as the test solution. Separately, weigh accurately about 100 mg of sulbactam sodium RS and about 100 mg of cefoperazone sodium RS, add water to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak areas of sulbactam sodium and cefoperazone sodium, A_{T1}, A_{S1}, A_{T2} and A_{S2}, in each solution.

$$\text{Amount (mg) of sulbactam sodium } (C_8H_{11}NO_5S) = \text{Amount (mg) of sulbactam sodium RS} \times \frac{A_{T1}}{A_{S1}} \times 5$$

$$\text{Amount (mg) of cefoperazone sodium } (C_{25}H_{27}N_9O_8S_2) = \text{Amount (mg) of cefoperazone sodium RS} \times \frac{A_{T1}}{A_{S1}} \times 5$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Add 0.005 mol/L tetra n-butylammonium bromide solution containing 0.1% acetic acid to 350 mL of methanol to make exactly 1000 mL.

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; sulbactam sodium and cefoperazone sodium are eluted in this order with the resolution between these peaks being NLT 9.0.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of sulbactam sodium and cefoperazone sodium is NMT 1.0%.

Packaging and storage Preserve in hermetic containers.

Sulbactam Sodium·Piperacillin Sodium for Injection
주사용 설박탐나트륨·피페라실린나트륨

Sulbactam Sodium·Piperacillin Sodium for Injection, as an injection that is dissolved upon use, contains NLT 90.0% and NMT 120.0% of the labeled amount of sulbactam ($C_8H_{11}NO_5S$: 233.24) and piperacillin ($C_{23}H_{27}N_5O_7S$: 517.56), respectively.

Method of preparation Prepare as directed under Injections, with Sulbactam Sodium and Piperacillin Sodium.

Description Sulbactam Sodium·Piperacillin Sodium for

Injection occurs as a white to pale yellow powder or a mass.

Identification (1) *Sulbactam sodium*—The retention time of major peak of the test solution and the standard solution for Assay (1) is the same.

(2) ***Piperacillin sodium***—The retention time of major peak of the test solution and the standard solution for Assay (2) is the same.

pH Dissolve Sulbactam Sodium·Piperacillin Sodium for Injection in water to make 0.1 g (potency)/mL as piperacillin; the pH of the solution is between 7.0 and 9.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 6.67 EU per 100 mg of sulbactam sodium·piperacillin sodium.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets requirements.

Water NMT 1.0% (1.0 g, volumetric titration, direct titration)

Assay (1) *Sulbactam sodium*—Weigh accurately an amount of Sulbactam Sodium·Piperacillin Sodium for Injection equivalent to about 25 mg (potency) of sulbactam ($C_8H_{11}NO_5S$: 233.24) and about 25 mg (potency) of sulbactam RS, add the mobile phase to make exactly 100 mL, respectively, and use these solutions as the test solution and the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak areas of sulbactam, A_T and A_S, in each solution.

$$\text{Potency (μg) of sulbactam } (C_8H_{11}NO_5S) = \text{Potency (μg) of sulbactam RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: A mixture of methanol, water, 0.2 mol/L sodium dihydrogen phosphate solution and 0.4 mol/L tetrabutylammonium hydroxide solution (450: 447 : 100 : 3).

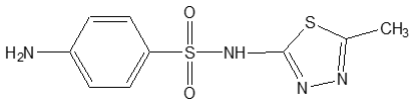
Flow rate: About 1.0 mL/min

(2) ***Piperacillin sodium***—Weigh accurately an amount of Sulbactam Sodium·Piperacillin Sodium for Injection equivalent to about 50 mg (potency) of piperacillin sodium ($C_{23}H_{27}N_5O_7S$) and about 50 mg (potency) of piperacillin sodium RS, add the mobile phase to make exactly 100 mL, respectively, and use these solutions as the test solution and the standard solution. Proceed with 10 μL each of the test solution and the standard solution, and perform the test according to the operating conditions as in the Assay (1), and determine the peak areas of piperacillin, A_T and A_S, in the test solution and the standard solution.

$$\text{Potency (μg) of piperacillin } (C_{23}H_{27}N_5O_7S) = \text{Potency (μg) of piperacillin RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in hermetic containers.

Sulfamethizole
설파메티졸



$C_9H_{10}N_4O_2S_2$: 270.33

4-Amino-*N*-(5-methyl-1,3,4-thiadiazol-2-yl) benzenesulfonamide [*144-82-1*]

Sulfamethizole, when dried, contains NLT 99.0% and NMT 101.0% of sulfamethizole ($C_9H_{10}N_4O_2S_2$).

Description Sulfamethizole occurs as white to pale yellowish white crystals or a crystalline powder, and is odorless.
It is slightly soluble in acetic acid(100) or ethanol(95) and practically insoluble in water or ether.
It dissolves in dilute hydrochloric acid or sodium hydroxide TS.
It is gradually colored by light.

Identification Determine the infrared spectra of Sulfamethizole and sulfamethizole RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 208 and 211 ℃.

Purity (1) ***Clarity and color of solution*—**Dissolve 0.5 g of Sulfamethizole in 3 mL of sodium hydroxide TS and 20 mL of water; the solution is colorless and clear.

(2) ***Acid*—**Dissolve 1.0 g of Sulfamethizole in 50 mL of water, warm at 70 ℃ for 5 minutes, allow to stand for 1 hour in iced water, and filter. To 25 mL of the filtrate, add 2 drops of methyl red TS and 0.60 mL of 0.1 mol/L sodium hydroxide; the solution exhibits a yellow color.

(3) ***Heavy metals*—**Proceed with 1.0 g of Sulfamethizole as directed under Method 2 and perform the test.

Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic***—Prepare the test solution with 1.0 g of Sulfamethizole according to Method 3 and perform the test (NMT 2 ppm).

(5) ***Related substances***—Dissolve 0.10 g of Sulfamethizole in 10 mL of acetone and use this solution as the test solution. Pipet 1 mL of this solution and add acetone to make exactly 50 mL. Pipet 5 mL of this solution, add acetone to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate and acetic acid(100) (20 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the principal spot from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

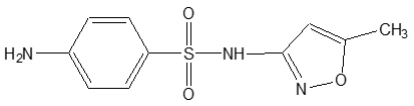
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Sulfamethizole, previously dried, dissolve in 5 mL of hydrochloric acid and 50 mL of water to dissolve, add 10 mL of potassium bromide solution (3 in 10), and cool at NMT 15 ℃. Then, titrate with 0.1 mol/L sodium nitrite VS as directed in the potentiometric titration or amperometric titration under the Titrimetry.

Each mL of 0.1 mol/L sodium nitrite VS
= 27.033 mg of $C_9H_{10}N_4O_2S_2$

Packaging and storage Preserve in light-resistant, well-closed containers.

Sulfamethoxazole
설파메톡사졸



Sulfisomezole $C_{10}H_{11}N_3O_3S$: 253.28
4-Amino-*N*-(5-methyl-1,2-oxazol-3-yl)benzene-sulfonamide [*723-46-6*]

Sulfamethoxazole, when dried, contains NLT 99.0% and NMT 101.0% of sulfamethoxazole ($C_{10}H_{11}N_3O_3S$).

Description Sulfamethoxazole occurs as white crystals or a crystalline powder. It is odorless and has a slightly bitter taste.
It is very soluble in *N*,*N*-dimethylformamide, sparingly soluble in ethanol(95), slightly soluble in ether, and very slightly soluble in water.
It is soluble in sodium hydroxide TS.
It is gradually colored by light.

Identification Determine the infrared spectra of Sulfamethoxazole and sulfamethoxazole RS, when dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 169 and 172 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Sulfamethoxazole in 5 mL of sodium hydroxide TS and 20 mL of water; the solution is clear and colorless.

(2) ***Acidity***—Add 50 mL of water in 1.0 g of Sulfamethoxazole, heat at 70 ℃ for 5 minutes, let it stand in iced water for 1 hour, and filter. Add 2 drops of methyl red TS and 0.60 mL of 0.1 mol/L sodium hydroxide to 25 mL of the filtrate; the resulting solution exhibits a yellow color.

(3) ***Heavy metals***—Proceed with 1.0 g of Sulfamethoxazole according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic***—Proceed with 1.0 g of Sulfamethoxazole according to Method 3 and perform the test (NMT 2 ppm).

(5) ***Selenium***—Weigh about 0.2 g of Sulfamethoxazole and combust as directed under the Oxygen Flask Combustion, using 25 mL of diluted nitric acid (1 in 30) as an absorbent. Use a combustion flask with a volume of 1000 mL, combust, wash the stopper and the inner wall of the flask with 10 mL of water, and use about 20 mL of water to move the solution in the combustion flask into a 150-mL beaker. Heat lightly until it boils, boil for 10 minutes, allow it to cool down at room temperature, and use this solution as the test solution. Separately, pipet 6.0 mL of standard selenium stock solution, add 25 mL of diluted nitric acid (1 in 30) and 25 mL of water, and use this solution as the standard solution. Add diluted ammonia water(28) (1 in 2) to each of the test and standard solutions, adjust the pH to 0.2, add water to dilute to 60 mL, and use 10 mL of water to move the solution to a separatory funnel. Then, wash the separatory funnel with 10 mL of water. Add 0.2 g of hydroxylamine hydrochloride, dissolve by stirring, add 5.0 mL of 2,3-diaminonaphthalene TS, and stopper. Mix by stirring and allow to stand at room temperature for 100 minutes. To the resulting mixture, add 5.0 mL of cyclohexane, shake hard for two minutes, and allow to stand. If the layer is separated, remove the water layer, centrifuge cyclohexane extracts, remove water, and take the cyclohexane layer. With these solutions, proceed in the same manner with a solution prepared by adding 25 mL of water to 25 mL of diluted nitric acid (1 in 30), and perform the test as directed under the Ultraviolet-visible Spectroscopy, using the resulting solution as the control solution. Determine

the absorbance at the absorbance maximum wavelength around 380 nm; the absorbance of the solution obtained from the test solution is not greater than that from the standard solution (NMT 30 ppm).

(6) ***Related substances***—Weigh 0.20 g of Sulfamethoxazole, dissolve in 10 mL of a mixture of ammonia water(28) and methanol (1 in 50), and use this solution as the test solution. Pipet 1 mL of this solution and use a mixture of ammonia water(28) and methanol (1 in 50) to make exactly 10 mL. Pipet 1 mL of this solution, use a mixture of ammonia water(28) and methanol (1 in 50) to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, acetonitrile, and diluted ammonia water (7 in 100) (10:8:1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the principal spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 °C, 4 hours).

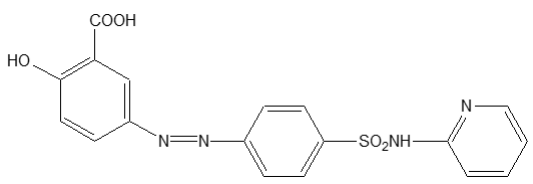
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Sulfamethoxazole, previously dried, dissolve in 30 mL of *N*,*N*-dimethylformamide, add 10 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS until the solution exhibits a pale blue color (indicator: 0.5 mL of thymolphthalein TS). Perform a blank test with a solution prepared by adding 26 mL of water to 30 mL of *N*,*N*-dimethylformamide in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 25.328 mg of $C_{10}H_{11}N_3O_3S$

Packaging and storage Preserve in light-resistant, well-closed containers.

Sulfasalazine
설파살라진



Salazosulfapyridine $C_{18}H_{14}N_4O_5S$: 398.39
6-Oxo-3-[[4-(pyridin-2-ylsulfamoyl)phenyl] hydrazinylidene]cyclohexa-1,4-diene-1-carboxylic acid [*599-79-1*]

Sulfasalazine, when dried, contains NLT 96.0% and NMT 101.0% of sulfasalazine ($C_{18}H_{14}N_4O_5S$).

Description Sulfasalazine occurs as a yellow to yellowish brown file powder. It is odorless and tasteless.
It is sparingly soluble in pyridine, slightly soluble in ethanol(95), and practically insoluble in water, chloroform or ether.
It dissolves in sodium hydroxide TS.

Melting point—Between 240 and 249 ℃ (with decomposition).

Identification (1) Dissolve 0.1 g of Sulfasalazine in 20 mL of dilute sodium hydroxide TS. The solution exhibits a reddish brown color. To this, slowly add 0.5 g of sodium hydrosulfite with shaking to mix. The reddish brown color of the solution slowly disappears. Use this solution for the test in (2) through (4) below.

(2) To 1 mL of the solution obtained under (1), add 40 mL of water, neutralize with 0.1 mol/L hydrochloric acid TS, and add water to make 50 mL. To 5 mL of this solution, add 2 to 3 drops of dilute iron(III) chloride TS; the solution exhibits a red color. To this, drop dilute hydrochloric acid; the solution initially exhibits a violet color which disappears later.

(3) The solution obtained under (1) responds to the Qualitative Analysis for primary aromatic amine.

(4) To 1 mL of the solution obtained under (1), add 1 mL of pyridine and 2 drops of copper(II) sulfate TS, and shake to mix. To this, add 3 mL of water and 5 mL of chloroform, shake to mix, and allow to stand; the chloroform layer exhibits a green color.

(5) Determine the absorption spectra of respective solutions of Sulfasalazine and sulfasalazine RS in dilute sodium hydroxide TS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Purity (1) ***Chloride***—Dissolve 2.0 g of Sulfasalazine in 12 mL of sodium hydroxide TS and 36 mL of water, add 2 mL of nitric acid, shake to mix, and filter. To 25 mL of the filtrate, add 6 mL of dilute nitric acid, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid (NMT 0.014%).

(2) ***Sulfate***—Dissolve 2.0 g of Sulfasalazine in 12 mL of sodium hydroxide TS and 36 mL of water, add 2 mL of hydrochloric acid, shake to mix, and filter. To 25 mL of the filtrate, add 1 mL of dilute hydrochloric acid, and then water to make 50 mL. Perform the test, using this solution as the test solution. Prepare the control solution with 1.0 mL of 0.005 mol/L sulfuric acid (NMT 0.048%).

(3) ***Heavy metals***—Proceed with 1.0 g of Sulfasalazine as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Arsenic***—Put 1.0 g of Sulfasalazine into a decomposition flask, add 20 mL of nitric acid, and heat at a low temperature until it becomes fluidized. After cooling,

add 5 mL of sulfuric acid and heat until white fumes appear. If necessary, after cooling, add 5 mL of nitric acid and heat again. Repeat this procedure until the solution becomes a colorless to pale yellow. After cooling, add 15 mL of saturated ammonium oxalate solution and heat again until white fumes appear. After cooling, add water to make 25 mL. Use 5 mL of this solution as the test solution and perform the test; it is not more intense than the following standard solution (NMT 10 ppm).

Standard solution—Proceed in the same manner without using Sulfasalazine. Put 5 mL of the solution in a generator bottle, add exactly 2 mL of arsenic standard solution, and proceed in the same manner as in the preparation of the test solution.

(5) ***Related substances***—Dissolve 0.20 g of Sulfasalazine in 20 mL of pyridine and use this solution as the test solution. Pipet 1 mL of this solution, add pyridine to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of methanol and water (9 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

(6) ***Salicylic acid***—To 0.10 g of Sulfasalazine, add 15 mL of ether, and shake hard to mix. To this, add 5 mL of dilute hydrochloric acid, and shake hard for 3 minutes to mix. Separate the ether layer, and filter it. To the water layer, add 15 mL of ether, and shake hard for 3 minutes to mix. Separate the ether layer, and filter it. Combine the filtrate with the previously obtained filtrate. Wash the residue on the filter paper with a small amount of ether, combine the filtrate and washings, and evaporate ether with the aid of a current of air at the room temperature. To the residue, add dilute ammonium iron(III) sulfate TS, shake to mix, and if necessary, filter. Wash the residue on the filter paper with a small amount of dilute ammonium iron(III) sulfate TS, and combine the filtrate and washings. To this, add dilute ammonium iron(III) sulfate TS to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of salicylic acid RS, previously dried for 3 hours in a desiccator (silica gel), dissolve in dilute ammonium iron(III) sulfate TS to make exactly 400 mL, and use this solution as the standard solution. With the test solution and the standard solution, perform the test as directed under the Ultraviolet-visible Spectroscopy and determine the absorbances of the test solution and the standard solution, A_T and A_S, at the wavelength 535 nm, using dilute ammonium iron(III) sulfate TS as the control solution; the amount of salicylic acid is NMT 0.5%.

Amount (mg) of salicylic acid ($C_7H_6O_3$)
= Amount (mg) of salicylic acid RS × $\frac{A_T}{A_S}$ × 0.05

Loss on drying NMT 1.0% (1 g, 105 ℃, 2 hours).

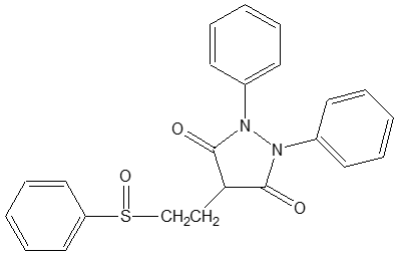
Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 20 mg of Sulfasalazine, previously dried, and perform the test with it as directed under the sulfur determination under the Oxygen Flask Combustion, using 10 mL of diluted hydrogen peroxide(30) solution (1 in 40) as the absorbent.

Each mL of 0.005 mol/L barium perchlorate VS
= 1.9920 mg of $C_{18}H_{14}N_4O_5S$

Packaging and storage Preserve in light-resistant, tight containers.

Sulfinpyrazone
설핀피라존



$C_{23}H_{20}N_2O_3S$: 404.48
4-[2-(Benzenesulfinyl)ethyl]-1,2-diphenylpyrazolidine-3,5-dione [*57-96-5*]

Sulfinpyrazone, when dried, contains NLT 98.5% and NMT 101.0% of sulfinpyrazone ($C_{23}H_{20}N_2O_3S$).

Description Sulfinpyrazone occurs as a white to pale yellowish white powder, is odorless, and has a bitter taste.
It is freely soluble in acetic acid(100) or acetone, soluble in ethanol(95), slightly soluble in ether, and practically insoluble in water.
It dissolves in sodium hydroxide TS.

Melting point—About 138 ℃ (with decomposition)

Identification (1) Dissolve 2 mg of Sulfinpyrazone in 1 mL of acetic acid(100), add 1 mL of palladium(II) chloride TS and 2 mL of chloroform, and shake to mix; the chloroform layer exhibits a yellow color.

(2) Determine the absorption spectra of solutions of Sulfinpyrazone and sulfinpyrazone RS in 0.01 mol/L sodium hydroxide TS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Sulfinpyrazone

and sulfinpyrazone RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Clarity and color of solution*—**Dissolve 0.5 g of Sulfinpyrazone in 10 mL of acetone; the solution is colorless and clear. Also, dissolve 0.5 g of Sulfinpyrazone in 10 mL of sodium hydroxide TS; the solution is colorless and clear.

(2) ***Heavy metals*—**Proceed with 2.0 g of Sulfinpyrazone as directed under Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic*—**Proceed with 1.0 g of Sulfinpyrazone as directed under Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.10 g of Sulfinpyrazone in 5 mL of acetone and use this solution as the test solution. Pipet 1 mL of this solution, add acetone to make exactly 100 mL, and use this solution as the standard solution (1). Separately, pipet 1 mL of the test solution, add acetone to make exactly 200 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Quickly drop 5 μL each of the test solution, the standard solution (1) and the standard solution (2) on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography under the nitrogen gas flow. Develop the plate with a mixture of chloroform and acetic acid(100) (4 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the most intense spot other than the principal spot obtained from the test solution is not more intense than the spot from the standard solution (1). Also, the spots other than the principal spot and above spot obtained from the test solution are not more intense than the spots from the standard solution (2).

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

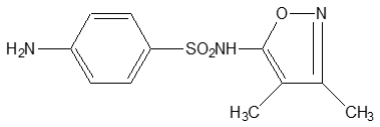
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Sulfinpyrazone, previously dried, dissolve in 40 mL of acetone, add 40 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 40.448 mg of $C_{23}H_{20}N_2O_3S$

Packaging and storage Preserve in well-closed containers.

Sulfisoxazole
설피속사졸



Sulfafurazole $C_{11}H_{13}N_3O_3S$: 267.30
4-Amino-*N*-(3,4-dimethylisoxazol-5-yl) benzenesulfonamide [*127-69-5*]

Sulfisoxazole, when dried, contains NLT 99.0% and NMT 101.0% of sulfisoxazole ($C_{11}H_{13}N_3O_3S$).

Description Sulfisoxazole occurs as white crystals or a crystalline powder. It is odorless and has a slightly bitter taste.
It is freely soluble in pyridine or *n*-butylamine, soluble in methanol, sparingly soluble in ethanol(95), slightly soluble in acetic acid(100), and very slightly soluble in water or ether.
It dissolves in dilute hydrochloric acid, sodium hydroxide TS or ammonia TS.
It is gradually colored by light.

Identification (1) Dissolve 0.01 g of Sulfisoxazole in 1 mL of dilute hydrochloric acid and 4 mL of water. The solution responds to the Qualitative Analysis for primary aromatic amine.

(2) Dissolve 0.02 g of the Sulfisoxazole in 5 mL of water and 1 mL of n-butylamine, add 2 to 3 drops of copper sulfate TS, and shake well to mix. To this solution, add 5 mL of chloroform, shake to mix, and allow to stand; the chloroform layer exhibits a bluish green color.

(3) Dissolve 0.01 g of Sulfisoxazole in 1 mL of pyridine, add 2 drops of copper sulfate TS, and shake well to mix. To this, add 3 mL of water and 5 mL of chloroform, shake to mix, and allow to stand; the chloroform layer exhibits a pale yellowish brown color.

(4) To 0.5 g of Sulfisoxazole, add 2 mL of acetic acid, and heat with a reflux condenser attached to dissolve. To this solution, add 1 mL of acetic anhydride, and boil for 10 minutes. Add 10 mL of water to cool, add about 7 mL of sodium hydroxide solution (3 in 10) to alkalize this solution, and if necessary, filter. To this solution, directly add acetic acid dropwise to acidify. Combine the formed precipitates, recrystallize with methanol, and dry at 105 ℃ for 1 hour; the melting point is between 208 and 210 ℃.

Melting point Between 192 and 196 ℃ (with decomposition).

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Sulfisoxazole in 5 mL of sodium hydroxide TS and 20 mL of water; the solution is colorless and clear.

(2) ***Acid*—**Dissolve 1.0 g of Sulfisoxazole in 50 mL of water, warm at 70 ℃ for 5 minutes, allow to stand for 1 hour in iced water, and filter. To 25 mL of the filtrate,

add 2 drops of methyl red TS and 0.20 mL of 0.1 mol/L sodium hydroxide; the solution exhibits a yellow color.

(3) ***Heavy metals***—Proceed with 1.0 g of Sulfisoxazole as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Selenium***—Burn 0.2 g of Sulfisoxazole as directed under the Oxygen Flask Combustion, using 25 mL of diluted nitric acid (1 in 30) as the absorbent. Use a 1 L volumetric flask as the combustion flask. After burning, wash the stopper and the inner wall of the flask with 10 mL of water, and use about 20 mL of water to move the solution in the combustion flask into a 150-mL beaker. Heat lightly until it boils, boil for 10 minutes, allow it to cool down to the room temperature, and use this solution as the test solution. Separately, pipet 6.0 mL of standard selenium stock solution, add 25 mL of diluted nitric acid (1 in 30) and 25 mL of water, and use this solution as the standard solution. To each of the test solution and the standard solution, add diluted ammonia water(28) (1 in 2) to adjust the pH to 2.0, and add water to dilute to 60 mL. Use 10 mL of water to move each to a respective separatory funnel, and wash the separatory funnel with 10 mL of water. To each, add 0.2 g of hydroxylamine hydrochloride, and stir to dissolve. Then, immediately add 5.0 mL of 2,3-diaminonaphthalene TS, put a stopper, stir to mix, and allow to stand at the room temperature for 100 minutes. To each, add 5.0 mL of cyclohexane, shake hard for 2 minutes, and allow to stand. If layers are separated, remove the water layer, centrifuge the cyclohexane extract to remove water from it, and take the cyclohexane layer. With these solutions, perform the test as directed under the Ultraviolet-visible Spectroscopy, using a control solution that is prepared by proceeding in the same manner using a solution of 25 mL of water in 25 mL of diluted nitric acid (1 in 30). Determine the absorbance at the absorption maximum wavelength about 380 nm; the absorbance of the test solution is not greater than the absorbance of the standard solution (NMT 30 ppm).

(5) ***Related substances***—Dissolve 10 mg of Sulfisoxazole in 1 mL of ethyl acetate and use this solution as the test solution. Separately, dissolve 1 mg of sulfisoxazole RS in 5 mL of ethyl acetate and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography, develop the plate with a mixture of acetone, cyclohexane and acetic acid(100) (5 : 4 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm and 365 nm); the spots other than the principal spot obtained from the test solution are not larger or not more intense than the spots from the standard solution (NMT 2.0%).

Loss on drying NMT 0.5% (2 g, 105 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 1 g of Sulfisoxazole, previously dried, add 50 mL of methanol, and warm to dissolve. After cooling, titrate with 0.2 mol/L sodium hydroxide VS (indicator: 3 drops of phenolphthalein TS). Separately, perform a blank test in the same manner using a solution prepared by adding 18 mL of water to 50 mL of methanol and make any necessary correction.

Each mL of 0.2 mol/L sodium hydroxide VS
= 53.46 mg of $C_{11}H_{13}N_3O_3S$

Packaging and storage Preserve in light-resistant, well-closed containers.

Sulfisoxazole Tablets
설피속사졸 정

Sulfisoxazole Tablets contain NMT 95.0% and NLT 105.0% of the labeled amount of sulfisoxazole ($C_{11}H_{13}N_3O_3S$: 267.30).

Method of preparation Prepare as directed under Tablets, with Sulfisoxazole.

Identification Powder Sulfisoxazole Tablets, weigh an amount equivalent to about 1.0 g of sulfisoxazole, and add 50 mL of ethanol(95). Boil on a steam bath for 3 minutes to extract, and immediately filter into a beaker. Allow to stand until needle-like crystals are produced. After cooling, collect the crystals, recrystallize with a small amount of ethanol(95), and dry at 105 ℃. Determine the infrared spectra of the crystals and sulfisoxazole RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Dissolution Perform the test with 1 tablet of Sulfisoxazole Tablets at 100 revolutions per minute according to Method 1, using 900 mL of diluted hydrochloric acid (1 in 12.5) as the dissolution medium. Take NLT 20 mL of the dissolved solution 30 minutes after starting the test and filter through a membrane filter. Discard the first 10 mL of the filtrate, pipet 2 mL of the subsequent filtrate, add water to make exactly make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of sulfisoxazole RS and dissolve in diluted hydrochloric acid (1 in 12.5) to make exactly 100 mL. Pipet 2 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 267 nm as directed under the Ultraviolet-visible Spectroscopy.

It meets the requirements if the dissolution rate of Sulfoi-

soxazole Tablets in 30 minutes is NLT 70%.

Dissolution rate (%) with respect to the labeled amount of sulfisoxazole ($C_{11}H_{13}N_3O_3S$)

$$= W_S \times \frac{A_T}{A_S} \times \frac{1}{C} \times 900$$

*W*s: Amount (mg) of sulfisoxazole RS

C: Labeled amount (mg) of sulfisoxazole ($C_{11}H_{13}N_3O_3S$) in 1 tablet

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Sulfisoxazole Tablets and powder. Weigh accurately an amount, equivalent to about 20 mg of sulfisoxazole ($C_{11}H_{13}N_3O_3S$), shake for 15 minutes in methanol, extract to make exactly 50 mL, and filter. Discard the first 10 mL of the filtrate, pipet 5 mL of the subsequent filtrate and 8 mL of the internal standard solution, add methanol to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of sulfisoxazole RS, previously dried at 105 ℃ for 4 hours, and dissolve in methanol to make exactly 50 mL. Take exactly 5 mL of this solution and 8 mL of the internal standard solution, add methanol to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, of sulfisoxazole to the peak area of the internal standard.

Amount (mg) of sulfisoxazole ($C_{11}H_{13}N_3O_3S$)

$$= \text{Amount (mg) of sulfisoxazole RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Dissolve about 20 mg of anhydrous caffeine RS in methanol to make 50 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of water, methanol and acetic acid(95) (70 : 30 : 1).

Flow rate: Adjust the flow rate so that the retention time of sulfisoxazole is about 8 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the internal standard and sulfisoxazole are eluted in this order with the resolution being NLT 2.0.

Packaging and storage Preserve in light-resistant, well-closed containers.

Sulfur
황

S: 32.07

[*7704-34-9*]

Sulfur, when dried, contains NLT 99.5% and NMT 101.0% of sulfur (S).

Description Sulfur occurs as a pale yellow to yellow powder. It is odorless and tasteless.
It is freely soluble in water and practically insoluble in water, ethanol(95), or ether.

Identification (1) Ignite Sulfur; it exhibits a blue flame and has an irritating odor of sulfur dioxide.

(2) To 5 mg of Sulfur, add 5 mL of sodium hydroxide TS, and dissolve on a steam bath by heating. After cooling, add 1 drop of sodium pentacyanonitrosylferrate(III) TS; the resulting solution exhibits a bluish purple color.

(3) To 1 mg of Sulfur, add 2 mL of pyridine and 0.2 mL of sodium bicarbonate TS, and boil; the resulting solution exhibits a blue color.

Purity (1) ***Clarity and color of solution***—To 1.0 g of Sulfur, add a mixture of 20 mL of sodium hydroxide solution (1 in 6) and 2 mL of ethanol(95), dissolve by boiling; the resulting solution is clear. Also, dissolve 2.0 g of Sulfur in 10 mL of carbon disulfide; most of it dissolves, or it is slightly turbid.

(2) ***Acid or alkali***—To 2.0 g of Sulfur, add 50 mL of freshly boiled and cooled water, shake to mix, and add 2 drops of phenolphthalein TS; the resulting solution does not exhibit a red color. To this solution, add 1.0 mL of 0.1 mol/L sodium hydroxide TS; the resulting solution exhibits a red color.

(3) ***Arsenic***—Prepare the test solution with 0.20 g of Sulfur, according to Method 3, and perform the test (NMT 10 ppm).

Loss on drying NMT 1.0% (1 g, NMT 0.67 kPa, silica gel, 4 hours).

Residue on ignition NMT 0.2% (1 g).

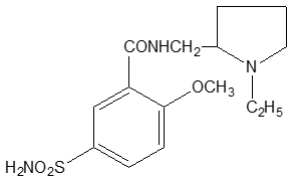
Assay Weigh accurately 0.4 g of Sulfur, previously dried, add 20 mL of potassium hydroxide-ethanol TS and 10 mL of water, dissolve by boiling, and add water to make exactly 100 mL. Pipet 25 mL of this solution, transfer into a 400-mL beaker, add 50 mL of hydrogen peroxide TS, and heat on a steam bath for 1 hour. Next, add dilute hydrochloric acid to make it acidic, add 200 mL of water, heat to boiling, and add barium chloride TS dropwise until a precipitate does not form; again, heat on a steam bath for 1 hour. Filter and collect the precipitate, and wash with water until the washings does not become turbid when silver nitrate TS is added, dry, and strongly heat to a constant mass. Weigh the amount and use it as barium sulfate ($BaSO_4$:

233.39). Perform a blank test in the same manner and make any necessary correction.

Amount (mg) of sulfur (S)
= Amount (mg) barium sulfate (BaSO4) × 0.13739

Packaging and storage Preserve in well-closed containers.

Sulpiride
설피리드



$C_{15}H_{23}N_3O_4S$: 341.43
N-[(1-ethylpyrrolidin-2-yl)methyl]-2-methoxy-5-sulfamoylbenzamide [*15676-16-1*]

Sulpiride, when dried, contains NLT 98.5% and NMT 101.0% of sulpiride ($C_{15}H_{23}N_3O_4S$).

Description Sulpiride occurs as a white crystalline powder and is odorless.
It is freely soluble in acetic acid(100) or dilute acetic acid, sparingly soluble in methanol, slightly soluble in ethanol(95) or acetone, and practically insoluble in water, chloroform or ether.
It dissolves in dilute hydrochloric acid or 0.05 mol/L sulfuric acid TS.

Melting point—Between 175 and 182 ℃ (with decomposition).

Identification (1) Dissolve 0.1 g each of Sulpiride and sulpiride RS in 0.05 mol/L sulfuric acid TS to make 100 mL each. To 5 mL each of the respective solutions, add water to make 100 mL. Determine the absorption spectra of the respective resulting solutions as directed under the Ultraviolet-visible Spectroscopy, using water as the control solution; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Sulpiride and sulpiride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Clarity and color of solution***—Dissolve 2.0 g of Sulpiride in 7 mL of dilute acetic acid and add water to make 20 mL; the solution is clear. Also, determine the absorbance of this solution at the wavelength 450 nm, as directed under the Ultraviolet-visible Spectroscopy, using water as the control solution; the absorbance is NMT 0.020.

(2) ***Heavy metals***—Proceed with 2.0 g of Sulpiride as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 50 mg of Sulpiride in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of the test solution and add methanol to make exactly 100 mL. Pipet 5 mL of this solution, add methanol to make exactly 10 mL, and use it as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, water and acetic acid(100) (4 : 2 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution. Also, allow the plate to stand for 30 minutes in iodine vapor; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Sulpiride, previously dried, dissolve in 80 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of methylosaniline chloride TS). However, the endpoint of the titration is when the violet color of this solution turns to the blue color and then finally to the bluish green color. Perform a blank test in the same manner and make any necessary correction.

Each mL of perchloric acid VS
= 34.143 mg of $C_{15}H_{23}N_3O_4S$

Packaging and storage Preserve in well-closed containers.

Sulpiride Capsules
설피리드 캡슐

Sulpiride Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of sulpiride ($C_{15}H_{23}N_3O_4S$: 341.43).

Method of preparation Prepared as directed under Capsules, with Sulpiride.

Identification Weigh an amount of Sulpiride Capsules, equivalent to 0.5 g of sulpiride according to the labeled amount, add methanol to make 50 mL, filter, and use the filtrate as the test solution. Separately, weigh about 0.5 g

of sulpiride RS, add methanol to make 50 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with methanol as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light; the R_f values of the spots obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 capsule of Sulpiride Capsules at 50 revolutions per minute according to Method 2, using 900 mL of 0.05 mol/L sodium acetate buffer solution, pH 4.0, as the dissolution medium. Take the dissolved solution 45 minutes after starting the dissolution test and filter it. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add the dissolution medium to make exactly *V'* mL of a solution containing about 50 μg of sulpiride per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately 25 mg of sulpiride RS, and dissolve in the dissolution medium to make 100 mL. Take exactly 10 mL of this solution, add the dissolution medium to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of sulpiride in each solution. Meets the requirements if the dissolution rate of Sulpiride Capsules in 45 minutes is NLT 70%.

$$\text{Dissolution rate (\%) of the labeled amount of sulpiride } (C_{15}H_{23}N_3O_4) = W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times \frac{900}{5}$$

*W*s: Amount (mg) of sulpiride RS

C: Labeled amount (mg) of sulpiride ($C_{15}H_{23}N_3O_4S$) in 1 capsule

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Dissolve 6.8 g of potassium dihydrogen phosphate in 1000 mL of water. Separately, dissolve 1 g of sodium 1-octanesulfonate in 1000 mL of water, and combine these two solutions to make 2000 mL. To this solution, add phosphoric acid to adjust the pH to 3.3. To 800 mL of this solution, add 100 mL of methanol and 100 mL of acetonitrile.

Flow rate: 1.5 mL/min

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the contents of NLT 20 capsules of Sulpiride Capsules. Weigh accurately an amount of the contents, equivalent to about 100 mg of sulpiride ($C_{15}H_{23}N_3O_4S$), and add the mobile phase to make 100 mL. After filtering this solution, take 10 mL of the filtrate, add the mobile phase to make exactly 200 mL, and use this solution as the test solution. Separately, weigh accurately 100 mg of sulpiride RS, and add the mobile phase to make 100 mL. Pipet 10 mL of this solution, add the mobile phase to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of sulpiride in each solution.

$$\text{Amount (mg) of sulpiride } (C_{15}H_{23}N_3O_4S) = \text{Amount (mg) of sulpiride RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of sodium octanesulfonate-phosphoric acid solution, methanol and acetonitrile (80 : 10 : 10).

Flow rate: 1.5 mL/min

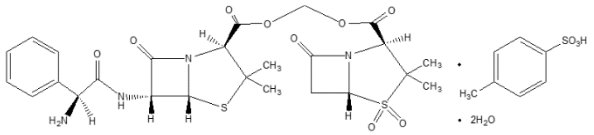
System suitability

System repeatability: Repeat the test 6 times with 10 mL of the standard solution according to the above conditions; the relative standard deviation of the peak areas of sulpiride is NMT 2.0%.

Sodium octanesulfonate-phosphoric acid solution—Add 6.8 g of potassium dihydrogen phosphate to water to make 1000 mL, and mix with a solution of 1 g of sodium 1-octanesulfonate dissolved in 1000 mL of water to make 2000 mL. To this solution, add phosphoric acid to adjust the pH to 3.3.

Packaging and storage Preserve in tight containers.

Sultamicillin Tosilate Hydrate
설타미실린토실산염수화물



$C_{25}H_{30}N_4O_9S_2 \cdot C_7H_8O_3S \cdot 2H_2O$: 802.89
(3*S*)-2,2-dimethyl-1,1-dioxo-1λ^6-penam-3-carbonyloxymethyl (3*S*)-2,2-dimethyl-6b-[(2*R*)-2-amimo-2-phenylactamido]penam-3-carboxylate [*83105-70-8*, anhydride]

Sultamicillin Tosilate Hydrate contains NLT 698 μg and NMT 800 μg (potency) per mg of sultamicillin ($C_{25}H_{30}N_4O_9S_2$: 594.66), calculated on the anhydrous basis and corrected by the amount of solvent.

Method of preparation If there is any possibility of alkyl toluenesulfonate esters (methyl, ethyl, isopropyl, etc.) to be inserted as the potential impurities according to the manufacturing process of Sultamicillin Tosilate Hydrate, take caution with starting material, manufacturing process, and intermediate material control to minimize the residue of impurities in consideration of risk assessment results. If needed, the manufacturing process can be justified by the test data proving that there is no quality risk in final drug substances.

Description Sultamicillin Tosilate Hydrate occurs as a white to yellow crystalline powder.
It is freely soluble in acetonitrile, methanol or ethanol(99.5), and very slightly soluble in water.

Identification Determine the infrared spectra of Sultamicillin Tosilate Hydrate and sultamicillin tosilate hydrate RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +173° and +187° (0.5 g, calculated on the anhydrous basis, a mixture of water and acetonitrile (3:2), 25 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Sultamicillin Tosilate Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Sultamicillin Tosilate Hydrate according to Method 3 and perform the test (NMT 2 ppm).

(3) ***Ampicillin***—Perform this procedure quickly. Weigh accurately about 20 mg of Sultamicillin Tosilate Hydrate, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately an amount equivalent to about 20 mg (potency) of sultamicillin tosilate hydrate RS and dissolve in the mobile phase to make exactly 100 mL. Pipet 6 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of ampicillin in each solution by the automatic integration method; the peak area of the test solution is not greater than that of the standard solution.

Operating conditions

For the detector, column, and column temperature, perform the test as directed under the operating conditions under the Assay.

Mobile phase: Dissolve by adding 3.12 g of sodium dihydrogen phosphate dihydrate to about 750 mL of water, adjust the pH to 3.0 by using diluted phosphoric acid (1 in 10), and add water to make 1000 mL. Add this solution to 80 mL of acetonitrile for liquid chromatography to make 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of ampicillin is about 14 minutes.

System suitability

System performance: Dissolve 12 mg of ampicillin RS, 4 mg of sulbactam RS, and 4 mg of *p*-toluenesulfonic acid monohydrate in 1000 mL of the mobile phase. Proceed with 25 μL of this solution according to the above conditions; sulbactam, *p*-toluenesulfonic acid, and ampicillin are eluted in this order with each resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 25 μL each of the standard solutions according to the above conditions; the relative standard deviation of peak areas of ampicillin is NMT 2.0%.

(4) ***Sulbactam***—Perform this procedure quickly. Weigh accurately about 20 mg of Sultamicillin Tosilate Hydrate, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately an amount equivalent to about 20 mg (potency) of sulbactam RS and dissolve in the mobile phase to make exactly 100 mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of sulbactam in each solution according to the automatic integration method; the peak area of the test solution is not greater than that of the standard solution.

Operating conditions

Perform the test as directed under the operating conditions under the Purity (3).

System suitability

Perform the test as directed under the system suitability under the Purity (3).

(5) ***Penicillic acid***—Weigh accurately about 25 mg of Sultamicillin Tosilate Hydrate, transfer to a 100-mL flask with a stopper, dissolve in 1 mL of acetonitrile, and

add 25 mL of 0.02 mol/L phosphate buffer (pH 3.0). Add exactly 5 mL of 0.005 mol/L iodine to this solution, cover the flask with the stopper tightly, let it stand for 5 minutes, and titrate with 0.005 mol/L sodium thiosulfate VS (indicator: 1.0 mL of starch TS). Perform a blank test in the same manner, and make any necessary correction; the amount of penicillic acid ($C_{25}H_{34}N_4O_{11}S_2$: 630.69) is NMT 3.0%.

Each mL of 0.005 mol/L sodium thiosulfate VS
= 0.2585 mg of $C_{25}H_{34}N_4O_{11}S_2$

(6) ***Residual solvent***—Weigh accurately about 0.1 g of Sultamicillin Tosilate Hydrate, dissolve in 2 mL of methanol, add water to make exactly 20 mL, and use this solution as the test solution. Separately, weigh accurately about 1 g of ethyl acetate and mix it evenly with water to make exactly 200 mL. Pipet 2 mL of this solution, add 10 mL of methanol, add water again to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of ethyl acetate. Calculate the amount of ethyl acetate according to the following equation; it is NMT 2.0%.

$$\text{Content (\%) of ethyl acetate} = \frac{Potency\ (mg)\ of\ ethyl\ acetate}{W_T} \times \frac{A_T}{A_S} \times \frac{1}{5}$$

W_T: Amount (mg) of Sultamicillin Tosilate Hydrate taken

Operating conditions

Detector: A hydrogen flame ionization detector.

Column: Column: A column of about 3 mm in internal diameter and about 3 m in length, packed with porous styrene–divinylbenzene copolymer for gas chromatography of 150 μm to 180 μm in particle diameter (average pore size: 8.5 nm; specific surface area: 300 to 400 m^2/g).

Column temperature: A constant temperature of about 155 °C.

Carrier gas: Nitrogen

Flow rate: Adjust the flow rate so that the retention time of ethyl acetate is about 6 minutes.

System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; the number of theoretical plates of the ethyl acetate peak is NLT 500, and the symmetry factor is NMT 1.5.

System repeatability: Repeat the test 6 times with 5 μL each of standard solutions according to the above conditions; the relative standard deviation of the peak area of ethyl acetate is NMT 5%.

Water Between 4.0% and 6.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.2% (1 g).

Assay Perform this procedure quickly. Weigh accurately about 50 mg (potency) of Sultamicillin Tosilate Hydrate and sultamicillin tosilate hydrate RS, and dissolve each in the mobile phase to make exactly 50 mL. With 5 mL each of these solutions, add exactly 5 mL of the internal standard solution to each, put the mobile phase to make 25 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions and calculate the peak area ratios, Q_T and Q_S, of sultamicillin to the internal standard, respectively.

Potency (mg) of sultamicillin ($C_{25}H_{30}N_4O_9S_2$)
= Potency (mg) of sultamicillin tosilate hydrate RS× $\frac{Q_T}{Q_S}$

Internal standard solution—A solution of isopropyl 4-aminobenzoate in the mobile phase (1 in 2500).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silical gel for liquid chromatography (10 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: Dissolve 3.12 g of sodium dihydrogen phosphate dihydrate in about 750 mL of water, adjust the pH to 3.0 with diluted phosphoric acid (1 in 10), and add water to make 1000 mL. Add this solution to 400 mL of acetonitrile for liquid chromatography to make 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of sultamicillin is about 4 minutes.

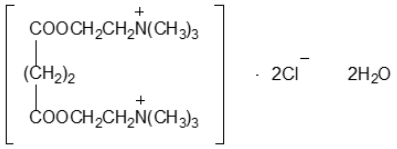
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; *p*-toluenesulfonic acid, sultamicillin, and the internal standard are eluted in this order with each resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of sultamicillin is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Suxamethonium Chloride Hydrate
숙사메토늄염화물수화물



Suxamethonium Chloride

$C_{14}H_{30}Cl_2N_2O_4 \cdot 2H_2O$: 397.34

N,*N*,*N*,*N'*,*N'*,*N'*-Hexamethyl-3,8-dioxa-4,7-dioxodecane-1,10-diaminium dichloride dihydrate [*6101-15-1*]

Suxamethonium Chloride Hydrate contains NLT 98.0% and NMT 101.0% of suxamethonium chloride ($C_{14}H_{30}Cl_2N_2O_4$: 361.31), calculated on the anhydrous basis.

Description Suxamethonium Chloride Hydrate occurs as a white crystalline powder.
It is freely soluble water, methanol and acetic acid(100), slightly soluble in ethanol(95), very slightly soluble in acetic anhydride, and practically insoluble in ether.

Identification (1) Determine the infrared spectra of Suxamethonium Chloride Hydrate and suxamethonium chloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Dilazep Hydrochloride Hydrate (1 in 20) responds to the Qualitative Analysis for chloride.

Melting point Between 159 and 164 °C (hydrate form).

pH Dissolve 1.0 g of Suxamethonium Chloride Hydrate in 10 mL of water; the pH of this solution is between 4.0 and 5.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Suxamethonium Chloride Hydrate in 10 mL of water; the solution is clear and colorless.

(2) ***Related substances***—Dissolve 0.25 g of Suxamethonium Chloride Hydrate in 5 mL of water, and use this solution as the test solution. Pipet 1 mL of the test solution, add water to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 1 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of cellulose for thin-layer chromatography. Develop the plate with a mixture of ammonium acetate (1 in 100), acetone, n-butanol and formic acid (20 : 20 : 20 : 1) to a distance of about 10 cm, and dry the plate at 105 °C for 15 minutes. Spray evenly hexachloroplatinic(IV) acid-potassium iodide TS on the plate, and allow to stand for 15 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Water Between 8.0% and 10.0% (0.4 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Suxamethonium Chloride Hydrate, dissolve in 80 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 18.065 mg of $C_{14}H_{30}Cl_2N_2O_4$

Packaging and storage Preserve in tight containers.

Suxamethonium Chloride Injection
숙사메토늄염화물 주사액

Suxamethonium Chloride Injection is an aqueous solution for injection. Suxamethonium Chloride Injection contains NLT 93.0% and NMT 107.0% of the labeled amount of suxamethonium chloride ($C_{14}H_{30}Cl_2N_2O_4$: 361.31).

The concentration of Suxamethonium Chloride Injection is indicated as the amount of suxamethonium chloride ($C_{14}H_{30}Cl_2N_2O_4$).

Method of preparation Prepare as directed under Injections, with Suxamethonium Chloride Hydrate.

Description Suxamethonium Chloride Injection occurs as a colorless and clear liquid.

Identification Weigh an amount of Suxamethonium Chloride Injection, equivalent to 50 mg of Suxamethonium Chloride Hydrate according to the labeled amount, dissolve in water to make 10 mL, and use this solution as the test solution. Separately, dissolve 50 mg of suxamethonium chloride hydrate RS in 10 mL of water and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 1 μL each of the test solution and the standard solution on a plate of cellulose for thin-layer chromatography. Develop the plate with a mixture of ammonium acetate (1 in 100), acetone, n-butanol and formic acid (20 : 20 : 20 : 1) as the developing solvent to a distance of about 10 cm, and dry the plate at 105 °C for 15 minutes. Spray evenly hexachloroplatinic (IV) acid-potassium iodide TS on the plate; the spots from the test solution and the standard solution are bluish purple and have the same R_f values.

pH Between 3.0 and 5.0.

Purity ***Related substances***—Perform the test as directed under the Assay; the amount of 0.1 mol/L sodium hydroxide VS required for the initial neutralization is NMT 0.7 mL per 0.2 g of suxamethonium chloride

($C_{14}H_{30}Cl_2N_2O_4$).

Sterility Meets the requirements.

Bacterial endotoxins Less than 2.0 EU per mg of suxamethonium chloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Suxamethonium Chloride Injection, equivalent to about 0.2 g of suxamethonium chloride ($C_{14}H_{30}Cl_2N_2O_4$), transfer to a separatory funnel, add 30 mL of freshly boiled and cooled water, and wash 5 times with each 20 mL of ether. Combine the ether washings and extract the combined ether layer with two 10 mL volumes of freshly boiled and cooled water. Combine these extracts and wash twice with each 10 mL of ether. Combine the resulting aqueous layer with the aqueous solution obtained above, add 2 drops of bromothymol blue TS, and neutralize with 0.1 mol/L sodium hydroxide. Add exactly 25 mL of 0.1 mol/L sodium hydroxide and boil under a reflux condenser for 40 minutes. After cooling, titrate the excess sodium hydroxide with 0.1 mol/L hydrochloric acid VS. Add 50 mL of freshly boiled and cooled water to a flask, add 2 drops of bromothymol blue TS, and neutralize with 0.1 mol/L sodium hydroxide. Perform a blank test in the same manner.

Each mL of 0.1 mol/L sodium hydroxide VS
= 18.065 mg of $C_{14}H_{30}Cl_2N_2O_4$

Packaging and storage Preserve in well-closed containers. Avoid freezing and keep at a temperature not exceeding 5 ℃.

Expiration date 12 months from the date of manufacture.

Suxamethonium Chloride for Injection
주사용 숙사메토늄염화물

Suxamethonium Chloride for Injection

Suxamethonium Chloride for Injection contains NLT 93.0% and NMT 107.0% of labeled amount of suxamethonium chloride ($C_{14}H_{30}Cl_2N_2O_4$: 361.31).

The concentration of Suxamethonium Chloride for Injection is expressed as the amount of suxamethonium chloride ($C_{14}H_{30}Cl_2N_2O_4$).

Method of preparation Prepare as directed under Injections, with Suxamethonium Chloride Hydrate.

Description Suxamethonium Chloride for Injection occurs as a white, crystalline powder or a mass.

Identification Weigh an amount of Suxamethonium Chloride for Injection, equivalent to 50 mg of suxamethonium chloride hydrate, according to the labeled amount, dissolve in water to make 10 mL, and use this solution as the test solution. Separately, dissolve 50 mg of suxamethonium chloride hydrate RS in 10 mL of water, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 1 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of cellulose for thin-layer chromatography, develop the plate with a mixture of ammonium acetate (1 in 100), acetone, 1-butanol and formic acid (20 : 20 : 20 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate at 105 ℃ for 15 minutes. Spray evenly hexachloroplatinic(IV) acid-potassium iodide TS on the plate; the colors of the spots from the test solution and the standard solution exhibit a bluish purple color, and their R_f values are the same.

pH Dissolve 0.1 g of Suxamethonium Chloride for Injection in 10 mL of water; the pH of this solution is 4.0 to 5.0.

Purity ***Related substances***—Weigh an amount of Suxamethonium Chloride for Injection, equivalent to 0.25 g of Suxamethonium Chloride Hydrate, according to the labeled amount, and perform the test as directed under the Purity (2) of Suxamethonium Chloride Hydrate.

Sterility Meets the requirements.

Bacterial endotoxins Less than 1.5 EU per mg of suxamethonium chloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

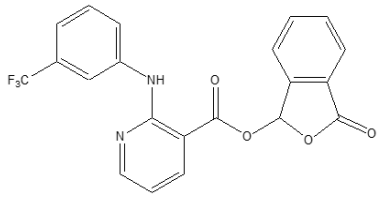
Uniformity of dosage units Meets the requirements.

Assay Take NLT 10 samples of Suxamethonium Chloride for Injection, weigh accurately about 0.5 g of the mass, and perform the test as directed under the Assay of Suxamethonium Chloride Hydrate.

Each mL of 0.1 mol/L perchloric acid VS
= 18.065 mg of $C_{14}H_{30}Cl_2N_2O_4$

Packaging and storage Preserve in hermetic containers.

Talniflumate
탈니플루메이트



$C_{21}H_{13}F_3N_2O_4$: 414.33

(3-Oxo-1*H*-2-benzofuran-1-yl)2-[3-(trifluoromethyl)anilino]pyridine-3-carboxylate, [*66898-62-2*]

Talniflumate contains NLT 98.0% and NMT 102.0% of talniflumate ($C_{21}H_{13}F_3N_2O_4$), calculated on the anhydrous basis.

Description Talniflumate occurs as a white to pale yellow crystalline powder. It is odorless and tasteless.

Identification (1) Determine the infrared spectra of Talniflumate and talniflumate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve about 20 mg of Talniflumate in 5 mL of ethyl acetate, and add methanol to make 100 mL. Take 10.0 mL of this solution, and add methanol to make 100 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelength of about 285 nm.

(3) To 10 mg of Talniflumate, add 1 to 2 drops of 4.5% sodium hydroxide solution, mix with acetone, and add 1 drop of 10% copper sulfate solution; a yellowish green precipitate is formed.

(4) Dissolve 0.1 g of Talniflumate in methanol to make 100 mL, and use this solution as the test solution. Weigh 0.1 g of talniflumate RS, add methanol to make 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of heptane and ethanol (100 : 1.5) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 365 nm); the R_f value and the color of the spots obtained from the test solution and the standard solution are identical.

Melting point Between 165 and 167 ℃.

Purity Weigh accurately about 0.2 g of Talniflumate, add acetonitrile to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 20 mg of 2-(3-trifluoromethyl)anilino nicotinic acid RS, dissolve in methanol to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions; the amount of 2-(3-trifluoromethyl)anilino nicotinic acid is NMT 1%.

$$\text{Content (\%) of related substances} = 100 \times \frac{C_S}{C_T} \times \frac{A_i}{A_S}$$

C_S: Concentration (mg/mL) of 2-(3-trifluoromethyl)anilino nicotinic acid in the standard solution

C_T: Concentration (mg/mL) of Talniflumate in the test solution

A_i: Peak area of related substances obtained from the test solution

A_s: Peak area of 2-(3-trifluoromethyl)anilino nicotinic acid obtained from the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile, 0.1% phosphoric acid, and methanol (76 : 19 : 5).

Flow rate: 1 mL/min

Water NMT 1.0% (0.2 g, volumetric titration, direct titration).

Assay Weigh accurately about 0.5 g of Talniflumate, dissolve in 50 mL of acetic acid(100) by gently heating, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 41.43 mg of $C_{21}H_{13}F_3N_2O_4$

Packaging and storage Preserve in well-closed containers.

Talniflumate Tablets
탈니플루메이트 정

Talniflumate Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of talniflumate ($C_{21}H_{13}F_3N_2O_4$: 414.33).

Method of preparation Prepare as directed under Tablets, with Talniflumate.

Identification The retention times of the major peaks obtained from the test solution and the standard solution

under the Assay are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Talniflumate Tablets and powder them. Weigh accurately an amount of the powder, equivalent to about 35 mg of talniflumate ($C_{21}H_{13}F_3N_2O_4$), and add acetonitrile to make 100 mL. Take 5 mL of this solution, add acetonitrile to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 35 mg of talniflumate RS, proceed in the same manner as in the preparation of the test solution, and use the resulting solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas for talniflumate, A_T and A_S, in the test solution and the standard solution, respectively.

$$\text{Amount (mg) talniflumate } (C_{21}H_{13}F_3N_2O_4) = \text{Amount (mg) of talniflumate RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 287 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and 0.1% phosphoric acid (80 : 20).

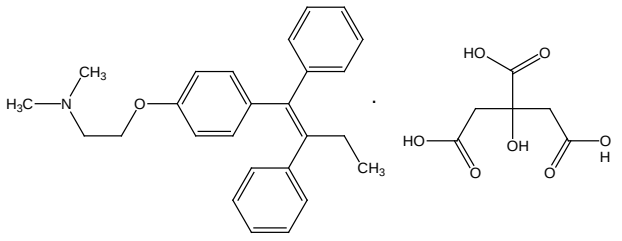
Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Tamoxifen Citrate
타목시펜시트르산염



$C_{26}H_{29}NO \cdot C_6H_8O_7$: 563.64

2-[4-[(*Z*)-1,2-Diphenylbut-1-enyl]phenoxy]-*N*,*N*-dimethylethanamine;2-hydroxypropane-1,2,3-tricarboxylic acid [*54965-24-1*]

Tamoxifen Citrate, when dried, contains NLT 99.0% and NMT 101.0% of tamoxifen citrate ($C_{26}H_{29}NO \cdot C_6H_8O_7$).

Description Tamoxifen Citrate occurs as a white fine crystalline powder.

It is freely soluble in acetic acid(100), sparingly soluble in methanol, and very slightly soluble in water or ethanol(95).

Melting point—About 142 ℃ (with decomposition).

Identification (1) Determine the absorption spectra of solutions of Tamoxifen Citrate and tamoxifen citrate RS in methanol (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Tamoxifen Citrate and tamoxifen citrate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Tamoxifen Citrate (1 in 100) responds to the Qualitative Analysis for citrate.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Tamoxifen Citrate as directed under Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Iron***—Proceed with 1.0 g of Tamoxifen Citrate as directed under Method 3 and use this solution as the test solution. Separately, pipet 5.0 mL of iron standard solution, proceed in the same manner as the test solution, and use this solution as the control solution. Proceed with the test solution and the control solution according to Method A; the test solution is not more intense than the control solution (NMT 50 ppm).

(3) ***E-isomer***—Weigh accurately about 30 mg of Tamoxifen Citrate, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 30 mg of tamoxifen citrate RS, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area, A_T and A_S, of citrate ($C_{26}H_{29}NO \cdot C_6H_8O_7$) of the E-isomer of each solution (NMT 0.3%)

$$\text{Amount (mg) of E-isomer } (C_{26}H_{29}NO \cdot C_6H_8O_7) = 0.05 \times C \times \frac{A_T}{A_S}$$

C: The concentration (μg/mL) of the E-isomer of citrate ($C_{26}H_{29}NO \cdot C_6H_8O_7$) as indicated on the standard solution for tamoxifen citrate RS

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with phenyl silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Dissolve 2 mL of acetic acid(100) and 1.08 g of sodium 1-octanesulfonate in 320 mL of water, and add methanol to make 1000 mL.

Flow rate: 0.7 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the relative retention time of the E-isomer peak to the Z-isomer peak is NMT 0.93.

System repeatability: Repeat the test 5 times with 20 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of tamoxifen is NMT 3.0%.

(4) ***Related substances***—Perform the test quickly using a light-resistant container. Weigh accurately about 15 mg of Tamoxifen Citrate, dissolve in the mobile phase to make 10 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make 100 mL, and use this solution as the standard solution. Pipet 10 μL each of the test solution and the standard solution and perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the peak area from each of the solutions according to the automatic integration method; the peak area other than the tamoxifen peak from the test solution is not greater than 3/10 the peak area of tamoxifen from the standard solution. Also, the total area of the peaks other than tamoxifen from the test solution is not greater than 4/ 5 of the peak area of tamoxifen from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: Dissolve 4.8 g of *N,N*-dimethyl-n-octylamine in 1000 mL of water, and dissolve 0.9 g of sodium dihydrogen phosphate dihydrate in 1000 mL of water. Mix these solutions, add phosphoric acid to adjust the pH to 3.0, take 600 mL of this solution, and add 400 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of tamoxifen is about 21 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution, and add the mobile phase to make 10 mL. Confirm that the peak area of tamoxifen obtained from 10 μL of this solution is equivalent to 8% to 12% of the peak area of tamoxifen from the standard solution.

System performance: Proceed with 10 μL of the standard solution under the above conditions; the number of theoretical plates and symmetry factor of the peak of tamoxifen are NLT 5000 and NMT 1.5, respectively.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of tamoxifen is NMT 1.5%.

Time span of measurement: About 2.5 times the retention time of tamoxifen after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

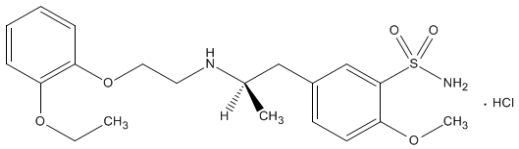
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 1.0 g of Tamoxifen Citrate, previously dried, dissolve in 150 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 56.36 mg of $C_{26}H_{29}NO \cdot C_6H_8O_7$

Packaging and storage Preserve in light-resistant, well-closed containers.

Tamsulosin Hydrochloride
탐스로신염산염



$C_{20}H_{28}N_2O_5S \cdot HCl$: 444.97

5-[(2*R*)-2-[2-(2-Ethoxyphenoxy)ethylamino]propyl]-2-methoxybenzenesulfonamidehydrochloride [*106463-17-6*]

Tamsulosin Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of tamsulosin hydrochloride ($C_{20}H_{28}N_2O_5S \cdot HCl$).

Description Tamsulosin Hydrochloride occurs as white crystals. It is freely soluble in formic acid, sparingly soluble in water, slightly soluble in acetic acid(100), and very slightly soluble in ethanol(99.5).

Melting point—About 230 ℃ (with decomposition).

Identification (1) Determine the absorption spectra of solutions of Tamsulosin Hydrochloride and tamsulosin hydrochloride RS (3 in 160000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Tamsulosin

Hydrochloride and tamsulosin hydrochloride RS as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Cool 5 mL of an aqueous solution of Tamsulosin Hydrochloride (3 in 400) with ice, add 3 mL of dilute nitric acid, shake well, and allow to stand for 30 minutes. Filter the solution, and the filtrate responds to the Qualitative Analysis for chloride.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Tamsulosin Hydrochloride according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—(i) Dissolve 50 mg of Tamsulosin Hydrochloride in 10 mL of mobile phase, and use this solution as the test solution. Pipet 2 mL of the test solution and add the mobile phase to make exactly 50 mL. Pipet 2.5 mL of this resulting solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area obtained from the test solution and the standard solution by the automatic integration method; the total area of peaks other than the peak of tamsulosin from the test solution is not greater than that of tamsulosin from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: Dissolve 4.4 mL of perchloric acid and 1.5 g of sodium hydroxide in 950 mL of water, use sodium hydroxide TS to adjust the pH to 2.0, and add water to make 1000 mL. To 700 mL of this solution, add 300 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of tamsulosin is about 6 minutes.

System suitability

Test for required detectability: Take exactly 1 mL of the standard solution, and add the mobile phase to make exactly 50 mL. Confirm that the peak area of tamsulosin obtained from 10 μL of this solution is equivalent to 1.4% to 2.6% of the peak area of tamsulosin obtained from the standard solution.

System performance: Dissolve 5 mg of tamsulosin hydrochloride and 10 mg of propyl p-hydroxybenzoate in 20 mL of mobile phase. To 2 mL of this solution, add the mobile phase to make 20 mL, and proceed with 10 μL of this solution according to the above conditions; tamsulosin and propyl p-hydroxybenzoate are eluted in this order with the resolution between these peaks being NLT 12.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of tamsulosin is NMT 4.0%.

Time span of measurement: The range until the termination of the tamsulosin peak (except for the solvent peak)

(ii) Perform the test with 10 μL each of the test solution and the standard solution obtained from the Related substances (A) as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas of each solution as directed in the automatic integration method; the total area of peaks other than the tamsulosin peak from the test solution is not greater than the area of the tamsulosin peak from the standard solution.

Operating conditions

Detector, column, and column temperature: Perform the test according to the operating conditions of the Related substances (i).

Mobile phase: Dissolve 4.4 mL of perchloric acid and 1.5 g of sodium hydroxide in 950 mL of water, use sodium hydroxide TS to adjust the pH to 2.0, and add water to make 1000 mL. To this solution, add 1000 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of tamsulosin is about 2.5 minutes.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution and add the mobile phase of related substance (i) to make exactly 50 mL. Confirm that the peak area of tamsulosin obtained from 10 μL of this solution is equivalent to 1.4% to 2.6% of the peak area of tamsulosin obtained from the standard solution.

System performance: Perform the test according to the system performance of related substances (A).

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of tamsulosin is NMT 4.0%.

Time span of measurement: About 5 times the retention time of tamsulosin beginning after the tamsulosin peak.

Isomer Weigh exactly 50 mg of Tamsulosin Hydrochloride, add 25 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution and add methanol to make 100 mL. Take 1 mL of this solution, add the mobile phase to make 10 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the amount of tamsulosin hydrochloride enantiomer; the amount is NMT 0.3%.

$$\text{Content (\%) of tamsulosin hydrochloride enantiomer} = (C_S/C_T) \times (A_i/A_S) \times 100$$

C_S: Concentration of the standard solution (mg/mL)

C_T: Concentration of the test solution (mg/mL)

A_i: Peak area of tamsulosin hydrochloride enantiomer obtained from the test solution

A_S: Peak area of tamsulosin hydrochloride enantiomer obtained from the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with silica gel for liquid chromatography (5 μm in particle diameter, amylose tris(3,5-dimethylphenylcarbamate)).

Column temperature: A constant temperature of about 35℃.

Mobile phase: A mixture of hexane, anhydrous alcohol, methanol, and diethylamine (650 : 200 : 150 : 1).

Flow rate: 0.5 mL/min

System suitability

System performance: Dissolve racemic tamsulosin hydrochloride RS in methanol to make the concentration 40 μg/mL, and use this solution as the system suitability solution. Proceed with the system suitability solution according to the above conditions; the resolution between tamsulosin hydrochloride and tamsulosin hydrochloride enantiomer is NLT 2.0.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.7 g of Tamsulosin Hydrochloride, previously dried, dissolve in 5 mL of formic acid, add 75 mL of a mixture of acetic acid(100) and acetic anhydride (3 : 2), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 44.50 mg of $C_{20}H_{28}N_2O_5S \cdot HCl$

Packaging and storage Preserve in well-closed containers.

Tannic Acid
탄닌산

Tannin [*1401-55-4*]

Tannic Acid is a tannin obtained mainly from Galla Rhois or Galla Halepensis.

Description Tannic Acid occurs as a yellowish white to pale brown amorphous powder, shiny small plate, or spongy particle. It is odorless or has a slightly characteristic odor and a very bitter taste.

It is very soluble in water or ethanol(95) and practically insoluble in ether.

Identification (1) To 5 mL of an aqueous solution of Tannic Acid (1 in 400), add 2 drops of iron(III) chloride TS; the resulting solution exhibits a bluish black color and a bluish black precipitate is formed when allowed to stand.

(2) To each of 5 mL of an aqueous solution of Tannic Acid (1 in 20), add 1 drop of albumin TS, 1 drop of gelatin TS, or 1 mL of starch TS, respectively; each solution forms a precipitate.

Purity (1) ***Rubber, dextrin, or sugar***—Dissolve 3.0 g of Tannic Acid in 15 mL of hot water; the solution is only slightly turbid. Filter this solution after cooling. To 5 mL of the filtrate add 5 mL of ethanol(95); the solution is not turbid. Again, add 3 mL of ether; the solution is not turbid.

(2) ***Resinous substances***—To 5 mL of the filtrate of (1), add 10 mL of water; the solution is not turbid.

(3) ***Heavy metals***—Proceed with 0.5 g of Tannic Acid according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 40 ppm).

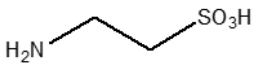
(4) ***Arsenic***—Proceed with 0.67 g of Tannic Acid according to Method 2 and perform the test (NMT 3 ppm).

Loss on drying NMT 12.0% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 1.0% (0.5 g).

Packaging and storage Preserve in light-resistant, tight containers.

Taurine
타우린



$C_2H_7NO_3S$: 125.15

2-Aminoethanesulfonic acid, [*107-35-7*]

Taurine, when dried, contains NLT 98.5% and NMT 101.0% of taurine ($C_2H_7NO_3S$).

Description Taurine occurs as a white crystalline powder with colorless or white crystals. It is odorless.
An aqueous solution of Taurine (1 in 20) is weakly acidic.

Identification (1) To 5 mL of the aqueous solution of Taurine (1 in 20), add 5 drops of dilute hydrochloric acid and 5 drops of sodium nitrite TS; the gas generated is colorless.

(2) To 0.5 g of Taurine, add 7.5 mL of sodium hydroxide TS, heat gently, evaporate to dryness, and

decompose by ignition at 500 ℃ for 2 hours. To the residue, add 5 mL of water, and shake to mix. After filtering, add 1 mL of sodium nitroprusside TS; the resulting solution is reddish purple and clear.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Taurine in 20 mL of water; the solution is colorless and clear.

(2) ***Chloride***—Perform the test with 1.0 g of Taurine. Prepare the control solution with 0.3 mL of 0.01 mol/L hydrochloric acid VS (NMT 0.011%).

(3) ***Sulfate***—Perform the test with 1.5 g of Taurine. Prepare the control solution with 0.45 mL of 0.005 mol/L sulfuric acid VS (NMT 0.014%).

(4) ***Ammonium***—Transfer 0.1 g of Taurine into the flask, dissolve in 70 mL of water, add 1 g of magnesium oxide, and attach the distillation apparatus. Add 2 mL of 0.01 mol/L hydrochloric acid VS into a Nessler tube, and use this as a collector. Immerse the end of the condenser in the solution in the collector, and distill until the distillate becomes 40 mL. To the distillate, add 5 mL of sodium hydroxide TS and water to make 50 mL, and add 0.5 mL of Nessler's TS; the color of the solution is not more intense than the following control solution.

Control solution—Transfer 2.0 mL of ammonium standard solution into the Nessler tube, add 5 mL of sodium hydroxide TS and water to make 50 mL, and add 0.5 mL of Nessler's TS.

(5) ***Heavy metals***—Proceed with 2.0 g of Taurine according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(6) ***Iron***—Weigh accurately about 2.0 g of Taurine, proceed according to Method 1, and use this solution as the test solution. Separately, pipet 2.0 mL of iron standard solution, proceed in the same manner as the test solution, and use this solution as the control solution. Proceed with the test solution and the control solution as directed under Method A; the test solution is not more intense than the control solution (NMT 10 ppm).

(7) ***Arsenic***—Dissolve 1.0 g of Taurine in 5 mL of water and 1 mL of nitric acid, add 5 mL of water and 1 mL of sulfuric acid, and perform the test with this solution (NMT 2 ppm).

(8) ***Related substances***—Dissolve 1.0 g of Taurine in 50 mL of water, and use this solution as the test solution. Pipet 1 mL of this solution and add water to make exactly 50 mL. Pipet 1 mL of this solution, add water to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography, develop the plate with a mixture of water, anhydrous ethanol, 1-butanol, and acetic acid(100) (150 : 150 : 100 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly ninhydrin-butanol TS on the plate, and heat at 105 ℃ for 5 minutes; the number of spots other than the principal spot obtained from the test solution is NMT 1 and those spots are not more intense than the spots from the standard solution.

(9) ***Readily carbonizable substances***—Weigh 0.1 g of Taurine, and dissolve in 1mL of sulfuric acid for readily carbonizable substances; the resulting solution is colorless.

Loss on drying NMT 0.2% (1.0 g, 105 ℃, 2 hours).

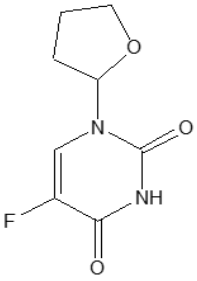
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Taurine, previously dried, dissolve in 50 mL of water, add 5 mL of formalin, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of phenolphthalein TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 12.515 mg of $C_2H_7NO_3S$

Packaging and storage Preserve in well-closed containers.

Tegafur
테가푸르



and enantiomer

$C_8H_9FN_2O_3$: 200.17

(*RS*)-5-Fluoro-1-(tetrahydrofuran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione [*17902-23-7*]

Tegafur, when dried, contains NLT 98.0% and NMT 101.0% of tegafur ($C_8H_9FN_2O_3$).

Description Tegafur occurs as a white crystalline powder.
It is soluble in methanol or acetone and sparingly soluble in water or ethanol(95).
It is soluble in dilute sodium hydroxide TS.
A solution of Tegafur in methanol (1 in 50) exhibits no optical rotation.

Identification (1) Determine the absorption spectra of Tegafur and a solution of tegafur RS in 0.01 mol/L sodium hydroxide TS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit

similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Tegafur and tegafur RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Proceed with 10 mg of Tegafur as directed under the Oxygen Flask Combustion, using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as the absorbent; the obtained test solution responds to the Qualitative Analysis (2) for fluoride.

Melting point Between 166 and 171 ℃.

pH Dissolve 0.5 g of Tegafur in 50 mL of water; the pH of this solution is between 4.2 and 5.2.

Purity (1) ***Clarity and color of solution***—Dissolve 0.2 g of Tegafur in 10 mL of dilute sodium hydroxide TS; the resulting solution is colorless and clear.

(2) ***Chloride***—Dissolve 0.8 g of Tegafur in 40 mL of water by warming. After cooling, filter if necessary, and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid (NMT 0.011%).

(3) ***Heavy Metals***—Dissolve 1.0 g of Tegafur in 40 mL of water by warming. After cooling, filter if necessary, and add 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Transfer 1.0 g of Tegafur into a crucible, and add 10 mL of a solution of magnesium nitrate in ethanol(95) (1 in 10). After burning the ethanol by firing, ignite at 750 ℃ to 850 ℃ to incinerate. If there is a residual carbide, wet it with a small amount of nitric acid and ignite again to incinerate. After cooling, dissolve the residue in 10 mL of dilute hydrochloric acid by warming on a steam bath, use this solution as the test solution, and perform the test (NMT 2 ppm).

(5) ***Related substances***—Dissolve 0.1 g of Tegafur in 10 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform and ethanol(95) (5 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spot obtained from the standard solutions.

Losson drying NMT 0.5% (1 g, 105 °C, 4 hours).

Residue on ignition NMT 0.1% (1 g, platinum crucible).

Assay Weigh accurately about 0.15 g of Tegafur, previously dried, transfer into the iodine bottle, dissolve in 75 mL of water, and add exactly 25 mL of 1/60 mol/L potassium bromate. Next, add quickly 1.0 g of potassium bromide and 12 mL of hydrochloric acid, immediately close the stopper, mix by occasional shaking, and allow to stand for 30 minutes. Add 1.6 g of potassium iodide, mix by gently shaking, allow to stand for exactly 5 minutes, and titrate free iodine with 0.1 mol/L sodium thiosulfate VS (indicator: 2 mL of starch TS). Perform a blank test in the same manner.

Each mL of 1/60 mol/L potassium bromate VS
= 10.008 mg of $C_8H_9FN_2O_3$

Packaging and storage Preserve in tight containers.

Tegafur and Uracil Capsules
테가푸르·우라실 캡슐

Tegafur and Uracil Capsules contain NLT 90.0% and NMT 110.0% of the labeled amounts of tegafur ($C_8H_9FN_2O_3$: 200.17) and uracil ($C_4H_4N_2O_2$: 112.09).

Method of preparation Prepare as directed under Capsules, with Tegafur and Uracil.

Identification Weigh an amount of Tegafur and Uracil Capsules equivalent to 50 mg of tegafur (an amount equivalent to 0.1 g of uracil) according to the labeled amount, add 20 mL of methanol (4 in 5), shake to dissolve, and filter. Use the filtrate as the test solution. Separately, weigh about 25 mg of tegafur RS and 50 mg of uracil RS each, add 10 mL of methanol to each, and use these solutions as the standard solutions. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with the mixture of butanol and acetic acid(100) (5 : 1) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm), and the R_f values of the spots from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the contents in NLT 20 capsules of Tegafur and Uracil Capsules. Weigh accurately an amount equivalent to about 0.1 g of tegafur ($C_8H_9FN_2O_3$) [about 0.2 g as uracil ($C_4H_4N_2O_2$)] add water, and sonicate and dissolve to make 200 mL. Pass through a filter and use the filtrate as the test solution. Separately, weigh

accurately about 0.1 g of tegafur RS and about 0.2 g of uracil RS, add water to make 200 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of tegafur and uracil, $_{T1}$, A_{T2}, A_{S1} and A_{S2}, in each solution.

$$\text{Amount (mg) of tegafur } (C_8H_9FN_2O_3) = \text{Amount (mg) of tegafur RS} \times \frac{A_{T1}}{A_{S1}}$$

$$\text{Amount (mg) of uracil } (C_4H_4N_2O_2) = \text{Amount (mg) of uracil RS} \times \frac{A_{T2}}{A_{S2}}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

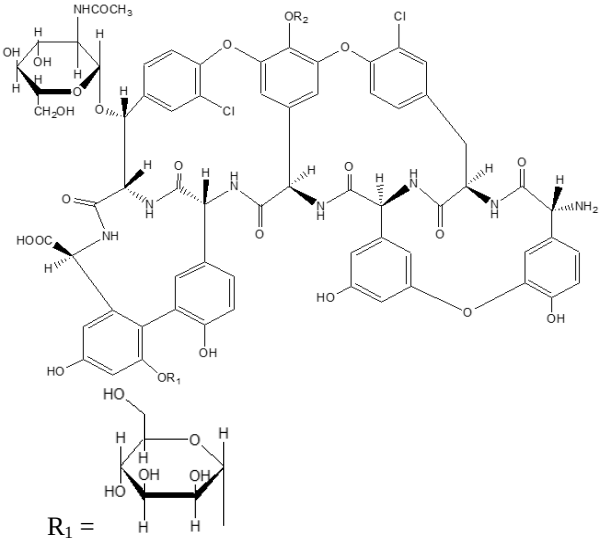
Column: A stainless steel column about 4.0 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 to 10 μm in particle diameter).

Mobile phase: 20% methanol

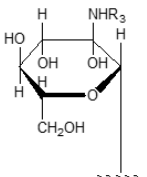
Flow rate: 1.0 mL/min

Packaging and storage Preserve in well-closed containers.

Teicoplanin
테이코플라닌



R_1 =



Teicoplanin A_2 group: R_2 = T $A_{2\text{-}1}$

$R_3 = COCH_2CH_2CH=CHCH_2CH_2CH_2CH_2CH_3$ Teicoplanin $A_{2\text{-}2}$

$R_3 = COCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH(CH_3)_2$ Teicoplanin $A_{2\text{-}3}$

$R_3 = COCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$ Teicoplanin $A_{2\text{-}4}$

$R_3 = COCH_2CH_2CH_2CH_2CH_2CH_2CH(CH_3)CH_2CH_3$ Teicoplanin $A_{2\text{-}5}$

$R_3 = COCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH(CH_3)_2$ Teicoplanin A_3

R_2 = H

Teicoplanin $A_{2\text{-}1}$ $C_{88}H_{95}Cl_2N_9O_{33}$: 1877.64
(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50a*R*)-34-(2-Acetylamino-2-deoxy-β-D-glucopyranosyloxy)-15-amino-22,31-dichloro-56-[2(Z)-dec-4-enoylamino-2-deoxy-β-D-glucopyranosyloxy]-2,3,16,17,18,19,35,37,36,38,48,49,50,50a-tetradecahydro-6,11,40,44-tetrahydroxy-42-(α-D-mannopyranosyloxy)-2,16,36,50,51,59,-hexaoxo-1*H*,15*H*,34*H*-20,23:30.33-dietheno-3,18:35,48-bis(iminomethano)-4,8:10,14:25,28:43,47-tetrametheno-28*H*-[1,14,6,22]dioxadi-azacyclooctacosino[4,5-m][10,2,16]benzoxadiaza-cyclotetracosine-38-carboxylic acid [*91032-34-7*]

Teicoplanin $A_{2\text{-}2}$ $C_{88}H_{97}Cl_2N_9O_{33}$: 1879.66
(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50a*R*)-34-(2-Acetylamino-2-deoxy-β-D-glucopyranosyloxy)-15-amino-22,31-dichloro-56-[2-deoxy-2(8-metylnonanoyl-amino)-β-D-glucopyranosyloxy]-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-6,11,40,44-tetrahydroxy-42-(α-D-mannopyranosyloxy)-2,16,36,50,51,59,-hexaoxo-1*H*,15*H*,34*H*-20,23:30.33-dietheno-3,18:35,48-*bis*(iminomethano)-4,8:10,14:25,28:43,47-tetrametheno-28*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5-*m*][10,2,16]benzoxa-diazacyclotetracosine-38-carboxylic acid [*91032-26-7*]

Teicoplanin $A_{2\text{-}3}$ $C_{88}H_{97}Cl_2N_9O_{33}$: 1879.66
(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50a*R*)-34-(2-Acetylamino-2-deoxy-β-D-glucopyranosyloxy)-15-amino-22,31-dichloro-56-[2-decanoylamino-2-deoxy-β-D-glucopyranosyloxy]-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-6,11,40,44-tetrahydroxy-42-(α-D-mannopyranosyloxy)-2,16,36,50,51,59,-hexaoxo-1*H*,15*H*,34*H*-20,23:30.33-dietheno-3,18:35,48-*bis*(imino-methano)-4,8:10,14:25,28:43,47-tetrametheno-28*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosine-38-carboxylic acid [*91032-36-9*]

Teicoplanin $A_{2\text{-}4}$ $C_{89}H_{99}Cl_2N_9O_{33}$: 1893.68
(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50a*R*)-34-(2-Acetylamino-2-deoxy-β-D-glucopyranosyloxy)-15-amino-22,31-dichloro-56-[2-deoxy-2-(8-methyldecanoylamino-β-D-glucopyranosyloxy]-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-6,11,40,44-tetrahydroxy-42-(α-D-mannopyranosyloxy)-2,16,36,50,51,59,-hexaoxo-1*H*,15*H*,34*H*-20,23:30.33-dietheno-3,18:35,48-*bis*(iminomethano)-4,8:10,14:25,28:43,47-tetrametheno-28*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5-

m][10,2,16]benzoxa-diazacyclotetracosine-38-carboxylic acid [*91032-37-0*]
Teicoplanin A_{2-5} $C_{89}H_{99}Cl_2N_9O_{33}$: 1893.68
(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50a*R*)-34-(2-Acetylamino-2-deoxy-β-D-glucopyranosyloxy)-15-amino-22,31-dichloro-56-[2-deoxy-2-(9-methyldecanoylamino-β-D-glucopyranosyloxy]-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-6,11,40,44-tetrahydroxy-42-(α-D-mannopyranosyloxy)-2,16,36,50,51,59,-hexaoxo-1*H*,15*H*,34*H*-20,23:30.33-dietheno-3,18:35,48-*bis*(iminomethano)-4,8:10,14:25,28:43,47-tetramethano-28*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5-*m*][10,2,16]benzoxadi-azacyclotetracosine-38-carboxylic acid [*91032-38-1*]
Teicoplanin A_{3-1} $C_{72}H_{68}Cl_2N_8O_{28}$: 1564.25
(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50a*R*)-34-(2-Acetylamino-2-deoxy-β-D-glucopyranosyloxy)-15-amino-22,31-dichloro-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-6,11,40,44-tetrahydroxy-42-(α-D-mannopyranosyloxy)-2,16,36,50,51,59,-hexaoxo-1*H*,15*H*,34*H*-20,23:30.33-dietheno-3,18:35,48-*bis*(iminomethano)-4,8:10,14:25,28:43,47-tetramethano-28*H*-[1,14,6,22]dioxadiazacyclo-octacosino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosine-38-carboxylic acid [*93616-27-4*]
[*61036-62-2*, Teicoplanin]

Teicoplanin is a mixture of glycopeptide substances having antibacterial activity produced by culturing *Actinoplanes teichomyceticus*. Teicoplanin contains NLT 900 μg (potency) of teicoplanin ($C_{72\sim89}H_{68\sim99}Cl_2N_{8\sim9}O_{28\sim33}$) per mg, calculated on the anhydrous, sodium chloride-free and solvent-free basis.

Description Teicoplanin occurs as a white to pale yellowish white powder.
It is freely soluble in water, sparingly soluble in *N*,*N*-dimethylformamide and practically insoluble in acetonitrile, methanol, ethanol(95), acetone, acetic acid(100) or ether.

Identification (1) To 1 mL of an aqueous solution of Teicoplanin (1 in 100), add 2 mL of ninhydrin TS, and warm for 5 minutes; the solution exhibits a bluish purple color.

(2) To 1 mL of an aqueous solution of Teicoplanin (3 in 100), add slowly 2 mL of anthrone TS, and shake gently to mix; the solution exhibits a dark brown color.

(3) Determine the infrared spectra of Teicoplanin and teicoplanin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

pH Dissolve 0.5 g of Tecoplanin in 10 mL of water; the pH of this solution is between 6.3 and 7.7.

Content Ratio Dissolve about 20 mg of Teicoplanin in water to make 10 mL, and use this solution as the test solution. Perform the test with 20 μL of the test solution as directed under the Liquid Chromatography according to the following operating conditions. Calculate the sum of the peak areas of the teicoplanin A_2 group, S_a, the sum of the peak areas of the teicoplanin A_3 group, S_b, and the sum of the peak areas of other contents, S_c according to the automatic integration method. Determine the amount of each content by the following formula; the teicoplanin A_2 group is NLT 80.0%, the teicoplanin A_3 group is NMT 15.0%, and the other contents are NMT 5.0%. The order of elution of each teicoplanin content and the relative retention times with respect to teicoplanin A_{2-2} are as follows.

Name of content	Elution order	Relative retention time
Teicoplanin A_3 group		≤0.42
Teicoplanin A_{3-1}	1	0.29
Teicoplanin A_2 group		0.42<, ≤1.25
Teicoplanin A_{2-1}	2	0.91
Teicoplanin A_{2-2}	3	1.00
Teicoplanin A_{2-3}	4	1.04
Teicoplanin A_{2-4}	5	1.17
Teicoplanin A_{2-5}	6	1.20
Other contents		1.25<

$$\text{Content (\%) of the Teicoplanin } A_2 \text{ group} = \frac{S_a}{S_a + 0.83S_b + S_c} \times 100$$

$$\text{Content (\%) of the teicoplanin } A_3 \text{ group} = \frac{0.83S_b}{S_a + 0.83S_b + S_c} \times 100$$

$$\text{Content (\%) of other contents} = \frac{S_c}{S_a + 0.83S_b + S_c} \times 100$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: Dissolve 7.80 g of sodium dihydrogen phosphate dihydrate in 1650 mL of water, add 300 mL of acetonitrile, adjust the pH to 6.0 with sodium hydroxide TS, and add water to make 2000 mL.

Mobile phase B: Dissolve 7.80 g of sodium dihydrogen phosphate dihydrate in 550 mL of water, add 1400 mL of acetonitrile, adjust the pH to 6.0 with sodium hydroxide TS, and add water to make 2000 mL.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 32	100 → 70	0 → 30
32 - 40	70 → 50	30 → 50
40 - 42	50 → 100	50 → 0

Flow rate: 1.8 mL/min

Time span of measurement: About 1.7 times the retention time of Teicoplanin $A_{2\text{-}2}$ after solvent peak.

System suitability

Test for required detectability: Ensure that the peak height of Teicoplanin $A_{2\text{–}2}$ obtained from the test solution is about 90% of the full scale.

System performance: Proceed with 20 μL of the test solution and perform the test under the above operating conditions; the symmetry factor of the Teicoplanin $A_{3\text{–}1}$ peak is NMT 2.2.

System repeatability: Proceed with each 20 μL of the test solution and perform the test 3 times under the above operating conditions; the relative standard deviation of the peak area of Teicoplanin $A_{2\text{–}2}$ is NMT 2.0%.

Purity (1) ***Sodium chloride***—Weigh accurately about 0.5 g of Teicoplanin, dissolve in 50 mL of water, titrate with 0.1 mol/L silver nitrate VS (indicator: 1 mL of potassium chromate TS), and calculate the amount of sodium chloride; the content of sodium chloride is NMT 5.0%.

Each mL of 0.1 mol/L silver nitrate VS
= 5.844 mg of NaCl

(2) ***Heavy metals***—Proceed with 1.0 g of Teicoplanin according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Water NMT 15.0% (0.2 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, it is exempt from the requirements when there is a terminal sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins Less than 0.75 EU/mg (potency) of teicoplanin when used in the manufacturing of sterile preparations.

Assay ***Cylinder plate method***—(1) Test organism: Use *Bacillus subtilis* ATCC 6633 as the test bacterium.

(2) Medium: Agar media for seed and base layer Use the culture medium in (A) (2) (a) ① ⓐ under the Microbial Assays for Antibiotics.

(3) Standard solution: Weigh accurately about 50 mg (potency) of teicoplanin RS, dissolve in phosphate buffer solution (pH 6.0) to make exactly 50 mL, and use this solution as the standard stock solution. Keep the standard stock solution at below 5 °C and use it within 14 days. Pipet an appropriate amount of the standard stock solution, dilute with phosphate buffer solution (pH 6.0) so that each mL contains 160 μg (potency) and 40 μg (potency) of teicoplanin RS, respectively, and use these solutions as the high-concentration standard solution and the low-concentration standard solution.

(4) Test solutions: Weigh accurately about 50 mg (potency) of Teicoplanin and dissolve in phosphate buffer solution (pH 6.0) to make exactly 50 mL. Pipet an appropriate amount of this solution, dilute with phosphate buffer solution (pH 6.0) so that each mL contains 160 μg (potency) and 40 μg (potency) of teicoplanin, respectively, and use these solutions as the high-concentration test solution and the low-concentration test solution. Perform the test with these solutions as directed in (A) (8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in light-resistant, tight containers (at below 5 °C).

Teicoplanin for Injection
주사용 테이코플라닌

Teicoplanin for Injection is an injection dissolved before use. Teicoplanin for Injection contains NLT 90.0% and NMT 120.0% of the labeled amount of teicoplanin.

Method of preparation Prepare as directed under Injections, with Teicoplanin.

Description Teicoplanin for Injection occurs as a white or pale yellow powder.

Identification Weigh about 25 mg (potency) each of Teicoplanin for Injection and teicoplanin RS, dissolve in 1% methanol solution to make exactly 25 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions; the retention times of the major peaks obtained from the test solution and the standard solution are the same.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (8 to 10 μm in particle diameter).

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: Dissolve 1.95 g of sodium dihy-

drogen phosphate in a mixture of acetonitrile and water (1 : 9), and add 1 mol/L sodium hydroxide TS to adjust the pH to exactly 6.0 and make 500 mL.

Mobile phase B: Dissolve 1.95 g of sodium dihydrogen phosphate in a mixture of acetonitrile and water (7 : 3), and add 1 mol/L sodium hydroxide TS to adjust the pH to exactly 6.0 and make 500 mL.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0	100	0
48	60	40
51	0	100

Flow rate: 2 mL/min

pH Dissolve Teicoplanin for Injection in water to make 0.1 g/mL; the pH of the solution is between 7.2 and 7.8.

Water NMT 2.5% (0.5 g, volumetric titration, direct titration)

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.32 EU per mg (potency) of teicoplanin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

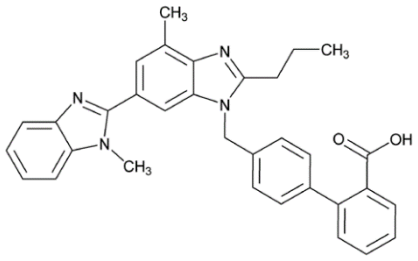
Assay ***Cylinder plate method***—(1) Medium: Agar media for seed and base layer Use the medium in (A) (2) (a) ① ⓐ under the Microbial Assays for Antibiotics.

(2) Test organism: Use *Bacillus subtilis* ATCC 6633 as the test organism.

(3) Weigh accurately about 20 mg (potency) of Teicoplanin for Injection according to the labeled potency, and dissolve in phosphate buffer solution, pH 7.4 to obtain a solution with a suitable concentration. Pipet an appropriate amount of this solution, dilute with phosphate buffer solution, pH 7.4 to obtain solutions having known concentrations of 20.0 μg and 5.0 μg (potency) per mL, and use these solutions as the high-concentration test solution and the low-concentration test solution, respectively. Separately, weigh accurately about 20 mg (potency) of teicoplanin RS, dissolve in phosphate buffer solution, pH 7.4 to prepare the standard stock solution with a suitable concentration. Pipet an appropriate of the standard stock solution, dilute with phosphate buffer solution, pH 7.4 to obtain solutions with known concentrations of 20.0 μg and 5.0 μg (potency) per mL, respectively, and use these solutions as the high-concentration standard solution and the low-concentration standard solution, respectively. With these solutions, perform the test as directed in (A) (8) under the Microbial Assays for Antibiotics.

Packaging and storage Preserve in hermetic containers.

Telmisartan
텔미사르탄



$C_{33}H_{30}N_4O_2$: 514.62

2-(4-{[4-Methyl-6-(1-methyl-1*H*-1,3-benzodiazol-2-yl)-2-propyl-1*H*-1,3-benzodiazol-1-yl]methyl}phenyl)benzoic acid [*144701-48-4*]

Riboflavin, when dried, contains NLT 98.0% and NMT 101.0% of riboflavin ($C_{33}H_{30}N_4O_2$).

Description Telmisartan occurs as a white to pale yellow crystalline powder.
It is sparingly soluble in dichloromethane, slightly soluble in methanol, and practically insoluble in water.
It dissolves in 1 mol/L sodium hydroxide.

Identification (1) Determine the infrared spectra of Telmisartan and telmisartan RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If the two spectra are different, dissolve Telmisartan and telmisartan RS in ethanol(95) and heat it if necessary. Cool this solution with iced water and filter the precipitate. Dry the precipitate obtained through this process at 105 °C and then measure again.

(2) The retention time of the major peak obtained from the test solution corresponds to that from the standard solution in the related substances.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Telmisartan according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Dissolve about100 mg of Telmisartan, weighed accurately, in 20 mL of methanol and 100 μL of sodium hydroxide TS, 1 mol/L, and sonicate it, and then add methanol to make 40 mL, and use this solution as the test solution. After preparation, protect the test solution from light and use it immediately. Separately, dissolve 100 mg of telmisartan RS, weighed accurately, in 20 mL of methanol and 100 μL of 1 mol/L sodium hydroxide, and then sonicate it, and add methanol

to make 40 mL. Pipet 1 mL of Telmisartan, add methanol to make 100 mL, and use this solution as the standard solution. Perform the test with each 2 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of each solution by the automatic integration and calculate the amount of related substances in the test solution; the relative retention time with respect to telmisartan is NMT 0.1% for telmisartan-related substance I {1,7′-dimethyl-2′-propyl-1H,3′H-2,5′-bibenzo[d]imidazole} of about 0.3, Telmisartan amide of about 0.7, telmisartan-related substance II {4′-[(1,7′-dimethyl-2propyll-1′H,1H-2,5′-bibenzo[d] imidazol-1'-yl)methyl]biphenyl-2-carboxylic acid} of about 0.9, and telmisartan diecid of about 1.1 and the relative retention time with respect to telmisartan t-butyl ester of about 1.7 and telmisartan-unknown related substances of about 1.8 is NMT 0.2%. Other each related substances are NMT 0.1%, and the sum of total related substances is NMT 1.0%. However, related substances containing NMT 0.05% are excluded.

$$\text{Content (\%) of each related substance} = \frac{A_T}{A_S} \times \frac{C_S}{C_T} \times 100$$

A_i: Peak area of each related substance in the test solution

A_S: Peak area of each related substance in the test solution

C_S: Concentration of telmisartan RS in the standard solution

C_U: Concentration of telmisartan in the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and about 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Control the step or gradient elution by mixing the mobile phases A and B as directed following.

Mobile phase A: Dissolve 2.0 g of potassium dihydrogen phosphate and 3.8 g of sodium 1-pentanesulfonate in 1000 mL of water and add phosphoric acid to adjust the pH to 3.0.

Mobile phase B: A mixture of acetonitrile and methanol (4 : 1).

Column temperature: A constant temperature of about 40 °C.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 2	70	30
2 - 27	70 → 20	30 → 80
27 - 32	20	80
32 - 32.1	70	30
32.1 - 37	70	30

Flow rate: 1 mL/min

System suitability

System performance: Dissolve 100 mg of telmisartan RS and 100 mg of telmisartan-related substance II RS, weighed accurately, in 20 mL of methanol and 100 μL of 1 mol/L sodium hydroxide, sonicate it, then add methanol to make 40 mL, and use this solution as the system suitability solution. Proceed with 2 μL of the system suitability solution according to the above operating conditions; the resolution between the peaks of telmisartan and telmisartan-related substance II is NLT 3.0, and the symmetry factor of telmisartan-related substance II is between 0.9 and 1.5.

System repeatability: Repeat the test 6 times with 2 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area for Telmisartan is NMT 5.0%.

Loss on drying NMT 1.5% (1 g, 105 ℃).

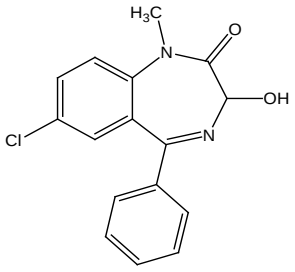
Residue on ignition NMT 0.1% (1 g).

Assay Dissolve about 190 mg of Telmisartan, weighed accurately, in 5 mL of anhydrous formic acid, add 75 mL of acetic anhydride and titrate it with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 25.73 mg of $C_{33}H_{30}N_4O_2$

Packaging and storage Preserve in light-resistant, tight containers.

Temazepam
테마제팜



$C_{16}H_{13}O_2N_2Cl$: 300.74

7-Chloro-3-hydroxy-1-methyl-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-2-one [*846-50-4*]

Temazepam contains NLT 98.0% and NMT 102.0% of temazepam ($C_{16}H_{13}O_2N_2Cl$), calculated on the dried basis.

Description Temazepam occurs as a white crystalline powder.

It is sparingly soluble in ethanol(95) and very slightly

soluble in water.

Melting point—157 ℃ to 163 ℃.

Identification (1) Determine the absorption spectra of solutions of Temazepam and temazepam RS in methanol (1 in 80000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Temazepam and temazepam RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) The retention time of the major peak obtained from the test solution under the Assay is the same as that of the major peak from the standard solution.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Temazepam according to Method 2 and perform the test. Prepare the control solution with 2 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Weigh exactly 0.1 g of Temazepam, dissolve in chloroform to make exactly 10 mL, and use this solution as the test solution. Weigh exactly 0.1 g of temazepam RS, and dissolve in chloroform to make exactly 10 mL. To 1.0 mL of this solution, add chloroform to make 100 mL and 200 mL, respectively, and use these solutions as the standard solution (1) and the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution, standard solution (1), and standard solution (2) on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of cyclohexane, chloroform, methanol, and ammonia water(28) (50 : 40 : 12 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the principal spots obtained from the standard solution (1) (1.0%), and the total intensity of the spots other than the principal spot obtained from the test solution is not greater than 4 times the spots obtained from the standard solution (2) (2.0%).

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 40 mg each of Temazepam and temazepam RS, dissolve in the diluent to make exactly 200 mL, and use these solutions as the test solution and the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of temazepam in each solution.

Content (%) of the temazepam ($C_{16}H_{13}O_2N_2Cl$)

$$= \frac{A_T}{A_S} \times \frac{C_S}{C_T} \times 100$$

C_S: Concentration [mg/mL] of the standard solution
C_T: Concentration [mg/mL] of the test solution

Diluent—A mixture of methanol and water (90 : 10).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless-steel column about 4 mm in internal diameter and about 25 cm in length, packed with dimethylsilyl silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of phosphate buffer solution and acetonitrile (53 : 47).

Flow rate: 2.0 mL/min

System suitability

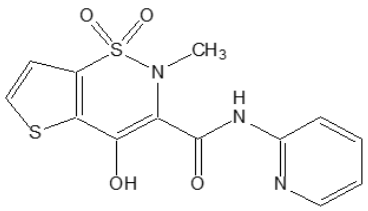
System performance: Proceed with 10 μL of the standard solution according to the above conditions; the number of theoretical plates and the symmetry factor are NLT 800 and NMT 2, respectively.

System repeatability: Repeat the test 5 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of temazepam is NMT 2.0%.

Phosphate buffer solution—Dissolve 2.7 g of potassium dihydrogen phosphate in water to make 1000 mL, and adjust the pH to 3.0 with phosphoric acid.

Packaging and storage Preserve in light-resistant, well-closed containers.

Tenoxicam
테녹시캄



$C_{13}H_{11}N_3O_4S_2$: 337.37

(3*Z*)-3-{Hydroxy[(pyridin-2-yl)amino]methylidene}-2-methyl-2*H*,3*H*,4*H*-1$l^{6},5,2-thieno[2,3-e][1$l^{6},2]thiazine-1,1,4-trione [*59804-37-4*]

Tenoxicam contains NLT 99.0% and NMT 101.0% of tenoxicam ($C_{13}H_{11}N_3O_4S_2$), calculated on the anhydrous basis.

Description Tenoxicam occurs as a yellow crystalline powder.

It is sparingly soluble in dichloromethane, very slightly soluble in ethanol(95), and practically insoluble in water.

It is soluble in acid or alkali solution.
It exhibits polymorphism.

Identification Determine the infrared spectra of Tenoxicam and tenoxicam RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If there is any difference between the two spectra, dissolve Tenoxicam and tenoxicam RS in a small amount of dichloromethane, respectively, evaporate on a steam bath to dryness, and repeat the test with the residues.

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Tenoxicam in 20 mL of dichloromethane; the solution is clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Tenoxicam according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Weigh exactly 0.40 g of Tenoxicam, dissolve in a mixture of methanol and ammonia water(28) (96 : 4) to make exactly 5 mL, and use this solution as the test solution. Take 1.0 mL of this solution, and add a mixture of methanol and ammonia water(28) (96 : 4) to make exactly 20 mL. Then again, take 1.0 mL of this solution, add a mixture of methanol and ammonia water(28) (96 : 4) to make exactly 20 mL, and use this solution as the standard solution (1). Separately, weigh exactly 20 mg of tenoxicam RS and 20 mg of salicylic acid RS, dissolve in a mixture of methanol and ammonia water(28) (96 : 4) to make 5 mL, and use this solution as the standard solution (2). Weigh exactly 20 mg of pyridin-2-amine, and dissolve in a mixture of methanol and ammonia water(28) (96 : 4) to make exactly 5 mL. To 2.0 mL of this solution, add a mixture of methanol and ammonia water(28) (96 : 4) to make exactly 50 mL, and use this solution as the standard solution (3). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of dichloromethane, acetone, methanol, and formic acid (70 : 20 : 5 : 5) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spot corresponding to pyridin-2-amine obtained from the test solution is not more intense than the spot obtained from standard solution (3), and the spots other than the principal spot obtained from the test solution pyridin-2-amine are not more intense than the spot obtained from standard solution (1).

Water NMT 0.5% (1 g, volumetric titration, direct titration).

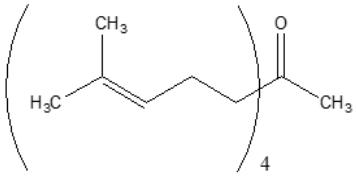
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.25 g of Tenoxicam, dissolve in 5 mL of formic acid, add 70 mL of acetic acid(100), and mix. Titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 33.738 mg of $C_{13}H_{11}N_3O_4S_2$

Packaging and storage Preserve in light-resistant, well-closed containers.

Teprenone
테프레논



$C_{23}H_{38}O$: 330.54
(5*E*,9*E*,13*E*)-6,10,14,18-Tetramethylnonadeca-5,9,13,17-tetraen-2-one, [*6809-52-5*]

Teprenone is composed of mono-cis isomer and trans isomer, and the ratio is about 2 : 3. Teprenone contains NLT 97.0% and NMT 101.0% of teprenone ($C_{23}H_{38}O$), calculated on the anhydrous basis.

Teprenone occurs as a colorless to light yellow clear oily liquid. It has a slightly peculiar odor and no taste.

Teprenone is sparingly soluble in methanol, ethanol, acetone, chloroform, or hexane, and practically insoluble in water.

Teprenone is affected by air.

Identification (1) Add 1 mL of phosphomolybdic acid and acetic acid(100) solution (1 in 100) to 2 mL of dehydrated ethanol solution (1 in 100) of Teprenone, and heat it on a steam bath for 5 minutes, then add 5 to 6 drops of sulfuric acid, and heat it; the solution exhibits blue to bluish green.

(2) Add 2 mL of 2, 4-dinitrophenylhydrazine solution to 2 mL of Teprenone in anhydrous ethanol (1 in 100) and shake to mix; a yellow to orange-yellow precipitate is formed.

(3) Weigh 10 mg of Teprenone, dissolve in 2 mL of hexane, and use this solution as the test solution. Perform the test with 2 μL to 4 μL of the test solution as directed under the Gas Chromatography according to the following conditions. Calculate the two adjacent major peak areas S_{C1} and S_T; the ratio of S_{C1} and S_T is about 2:3. However, the area of the one with a small retention time (mono-cis isomer) of two adjacent major peaks is S_{C1}, and the area of the other one with a large retention time (all-trans isomer) is S_T.

Operating conditions

Detector: A flame ionization detector

Column: A glass column about 3 to 4 mm in internal diameter and about 1.5 to 2 m in length, packed with 149 μm to 177 μm diatomaceous earth for gas chromatography coated with 5% polyethylene glycol-2-nitrotelephthalate, or packed with equivalent or greater.

Column temperature: A constant temperature of about 210 °C.

Carrier gas: Nitrogen or helium

Flow rate: Adjust flow rate so that the retention time of trans sieve is 15 to 20 minutes.

Refractive index n_D^{20}: Between 1.485 and 1.491.
Specific gravity d_{20}^{20}: Between 0.882 and 0.890.

Purity (1) ***Clarity and color of solution***—Dissolve about 1 g of Teprenone in 10 mL of dehydrated ethanol; the solution is colorless to light yellow in color and clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Teprenone according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Teprenone according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Others Cis-isomer***—Perform the test according to the Identification (3), and determine the peak areas Sc_2 and Sc_3 corresponding to the di-cis isomer and tri-cis isomer; the sum of the peak areas of Sc_2 and Sc_3 with respect to the total peak area is NMT 1%.

(5) ***Other related substance***—Perform the test as directed under the Gas Chromatography according to the Identification (3); the peak area ratio of other related substances (excluding solvent peaks, S_T, S_{C1}, S_{C2} and S_{C3}) with respect to the total peak area is NMT 1%.

Water NMT 0.5% (0.3 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.1 g each of Teprenone and teprenone RS, add 10.0 mL of the internal standard solution, add ethyl acetate to make 100.0 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 2 μL to 4 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions. Circulate the ratio Q_T and Q_S of the peak areas of the mono cis isomer and all-cis isomer forms with respect to the peak areas of the internal standards of the test solution and the standard solution.

$$\text{Amount (mg) of teprenone } (C_{23}H_{38}O) = \text{Amount (mg) of teprenone RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Weigh about 0.5 g of di-en-butyl phthalate and dissolve in ethyl acetate to make 100 mL.

Operating conditions

Detector: A flame ionization detector

Column: A glass column about 3 mm to 4 mm in internal diameter and about 1.5 m to 2 m in length, packed with 149 μm to 177 μm diatomaceous earth for gas chromatography coated with 5% of polyethylene glycol-2-nitrotelephthalate, or packed with equivalent or greater.

Column temperature: A constant temperature of about 210 °C.

Carrier gas: Nitrogen or helium

Flow rate: 40 mL/min

Packaging and storage Preserve in tight containers.

Teprenone Capsules
테프레논 캡슐

Teprenone Capsules contain NLT 93.0% and NMT 107.0% of the labeled amount of teprenone ($C_{23}H_{38}O$: 330.54).

Method of preparation Prepare as directed under Capsules, with Teprenone.

Identification (1) Weigh an amount of Teprenone Capsules, equivalent to 0.1 g of teprenone according to the labeled amount, add 10 mL of ethanol(99.5), shake to dissolve, and centrifuge. Pipet 2 mL of the clear supernatant, add 1 mL of a solution of molybdic acid in acetic acid(100) (1 in 100), and heat on a steam bath for 5 minutes. Add 5 to 6 drops of sulfuric acid and continue heating; the solution exhibits a color of blue to bluish green.

(2) Weigh a portion of the contents of Teprenone Capsules, equivalent to 0.1 g of teprenone according to the labeled amount, add 10 mL of ethanol(99.5), shake to dissolve, and centrifuge. Pipet 2 mL of the clear supernatant, add 2 mL of 2,4-dinitrophenylhydrazine TS, and shake to mix; a yellow to orange precipitate is produced.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the contents of NLT 20 capsules of Teprenone Capsules. Weigh accurately an amount equivalent to about 50 mg of teprenone ($C_{23}H_{38}O$) and dissolve in methanol to make exactly 100 mL. Pipet 2 mL of this solution, transfer to a 10-mL volumetric flask, add 1 mL of the internal standard solution and hexane to make exactly 10 mL. Use this solution as the test solution. Separately, weigh accurately about 50 mg of teprenone RS and prepare a solution in the same manner as the test solution, and use this solution as the standard solution. Perform the test with each 2 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, for the

sum of the peak areas of mono-cis and all-trans isomers to those of the internal standard.

$$\text{Amount (mg) of teprenone } (C_{23}H_{38}O) = \text{Amount (mg) of teprenone RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of phthalic acid-di-n-butyl in hexane (1 in 10000).

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A column about 0.32 mm in internal diameter and 30.0 m in length, coated with 5% phenyl - 95% methyl polysiloxane to 0.25 μm.

Column temperature: Maintain the initial temperature to 200 °C, raise the temperature to 240 °C at the rate of 10 °C per minute and further to 245 °C at the rate of 2 °C per minute, and maintain this temperature for 3,5 minutes.

Sample injection port temperature: 250 °C

Detector temperature: 250 °C

Carrier gas: Nitrogen

Flow rate: 2 mL/min

Total flow: About 60 mL.

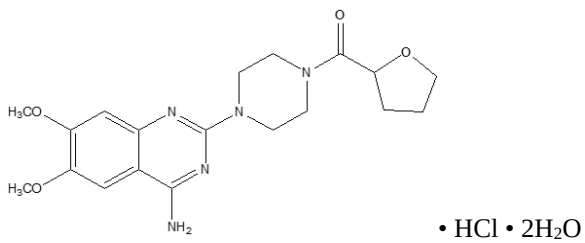
System suitability

System performance: Proceed with 2 μL of the standard solution according to the above conditions; the internal standard and mono-cis and all-trans isomers of teprenone are eluted in this order with the resolution between the peaks of mono-cis and all-trans isomers of teprenone being NLT 3.

System repeatability: Repeat the test 6 times with 2 μL each of the standard solution according to the above conditions; the relative standard deviation of the ratios for the sum of the peak areas of teprenone (mono-cis and all-trans isomers) to the peak area of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Terazosin Hydrochloride Hydrate
테라조신염산염수화물



• HCl • $2H_2O$

$C_{19}H_{25}N_5O_4 \cdot HCl \cdot 2H_2O$: 459.92

6,7-Dimethoxy-2-{4-[(oxolan-2-yl)carbonyl]piperazin-1-yl}quinazolin-4-amine dihydrate hydrochloride [*70024-40-7*]

Terazosin Hydrochloride Hydrate, when dried, contains NLT 98.0% and NMT 102.0% of terazosin hydrochloride ($C_{19}H_{25}N_5O_4 \cdot HCl$).

Description Terazosin Hydrochloride Hydrate occurs as a white to pale yellow crystalline powder.

It is sparingly soluble in water, slightly soluble in methanol, very slightly soluble in ethanol(95), and practically insoluble in acetone.

Identification (1) Determine the infrared spectra of Terazosin Hydrochloride Hydrate and terazosin hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

(3) Dissolve 0.1 g of Terazosin Hydrochloride Hydrate in 10 mL of a mixture of methanol and water (9 : 1); the solution responds to the Qualitative Analysis for chloride.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Terazosin Hydrochloride Hydrate as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—(i) Tetrahydro-2-furan carboxylic acid: Weigh accurately about 0.1 g of Terazosin Hydrochloride Hydrate, transfer into a 50-mL centrifuge tube, add 5.0 mL of acetone and 5.0 mL of internal standard solution, and shake for 30 minutes. After centrifuging for approximately 10 minutes, filter the solution using a nylon membrane filter with a pore size of NMT 0.45 μm (previously washed with acetone). Discard the first 1 mL of the filtrate, and use the subsequent filtrate as the test solution. Separately, weigh accurately tetrahydro-2-furan carboxylic acid RS, and dissolve in acetone to make exactly 1.0 mg/mL. Dissolve this solution in acetone to make exactly 100 μg/mL, and use this solution as the standard stock solution. Transfer 5.0 mL of standard stock solution and 5.0 mL of internal standard solution into a 50-mL centrifuge tube, mix, and filter the solution using a nylon membrane filter with a pore size of NMT 0.45 μm (previously washed with acetone). Discard the first 1 mL of the filtrate and use the subsequent filtrate as the standard solution. Separately, pipet 2.0 mL of acetic acid(100), and add acetone to make exactly 100 mL. Mix 5.0 mL of this solution and 5.0 mL of acetone, and filter the solution using a nylon membrane filter with a pore size of NMT 0.45 μm (previously washed with acetone). Discard the first 1 mL of the filtrate and use the subsequent filtrate as the blank test solution. Perform the test with 0.2 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of tetrahydro-2-furan carboxylic acid to that of the internal standard, respectively (NMT 0.1%). However, perform the test with about 0.2 μL of the blank test solution as directed under

the Gas Chromatography according to the following conditions; confirm the absence of any additional peaks.

$$\text{Content (\%) of tetrahydro-2-furan carboxylic acid} = \frac{C}{W} \times \frac{Q_T}{Q_S}$$

C: Concentration (μg/mL) of tetrahydro-2-furan carboxylic acid in the standard solution

W: Amount (mg) of terazosin hydrochloride in the test solution

Internal standard solution—Weigh accurately about 0.1 g of capric acid, transfer into a 100-mL volumetric flask, dissolve in acetone, fill up to the gauge line, and mix. Mix 10.0 mL of this solution and 2.0 mL of acetic acid(100) in a 100-mL volumetric flask, add acetone to dilute, fill up to the gauge line, and mix.

Operating conditions

Detector: A flame ionization detector

Column: A fused silica column about 0.53 mm in internal diameter and about 10 m in length, of which the inner surface is coated with polyethylene glycol compound TPA for gas chromatography (1.2 μm in thickness).

Column temperature: A constant temperature of about 170 °C.

Inlet temperature: A constant temperature of about 230 °C.

Detector temperature: A constant temperature of about 240 °C.

Carrier gas: Helium

Flow rate: 9 mL/min

System suitability

System performance: Proceed with the standard solution under the above conditions; the relative retention time of tetrahydro-2-furan carboxylic acid and capric acid is 1.0 and 1.2, respectively, and the resolution between the resolution between these peaks is NLT 2.3.

System repeatability: When repeating the test 6 times with the standard solution under the above conditions, the relative standard deviation of the ratio of peak area of the tetrahydro-2-furan carboxylic acid is NMT 6.5%.

(ii) 1-[(Tetrahydro-2-furanyl)piperazine]: Weigh accurately about 125 mg of Terazosin Hydrochloride Hydrate, dissolve in a mixture of acetonitrile and water (1 : 1) to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately 1-[(tetrahydro-2-furanyl)piperazine] RS, and dissolve in acetonitrile to make exactly 1.0 mg/mL. Dissolve this solution in acetonitrile to make exactly 5 μg/mL, and use this solution as the standard solution. Use acetonitrile as the blank test solution. Separately, dissolve about 2.0 g of 3,5-dinitrobenzoyl chloride in 250 mL of acetonitrile, and use this solution as the derivatization solution. Add 5 mL each of the blank test solution, the standard solution, and the test solution to the separate 100-mL volumetric flask, mix with 5.0 mL of phosphate buffer solution, add 10.0 mL of the derivatization solution, and allow to stand at room temperature for 20 minutes. Add a mixture of acetonitrile and water (1 : 1) to dilute, fill up to the gauge line, and mix. Perform the test with 50 μL each of the blank test solution, the standard solution, and the test solution, which are derivatized, as directed under the Liquid Chromatography according to the following conditions, and determine the area of each peak obtained from each solution by the automatic integration method. The content of 1-[(tetrahydro-2-furanyl)piperazine] is NMT 0.1% by using the following formula:

$$\text{Content (\%) of 1-[(tetrahydro-2-furanyl)piperazine]} = \frac{C}{W} \times \frac{A_T}{A_S} \times 2500$$

C: Concentration (mg/mL) of 1-[(tetrahydro-2-furanyl)piperazine] in the standard solution

W: Amount (mg) of terazosin hydrochloride in the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 25 cm in length, packed with octylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Control the step or gradient elution by mixing the mobile phases A and B as followings.

Mobile phase A: Water

Mobile phase B: Acetonitrile

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 35	82	18
35 - 40	82 → 10	18 → 90
40 - 75	10	90
75 - 80	10 → 82	90 → 18
80 - 100	82	18

Flow rate: 1.5 mL/min. However, between 40 and 80 minutes, change the flow rate to 2.0 mL/min.

System suitability

System performance: The retention time for 1-[(tetrahydro-2-furanyl)piperazine] appears after 22 minutes, and the number of theoretical plate is NLT 3500.

System repeatability: Repeat the test 6 times with 50 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of 1-[(tetrahydro-2-furanyl)piperazine] is NMT 3.0%.

Phosphate buffer solution—Weigh accurately about 96.3 g of dibasic potassium phosphate and 3.85 g of potassium dihydrogen phosphate, transfer into a 500-mL volumetric flask, and add water to dilute to the gauge

line. Use the diluted phosphoric acid solution (10 in 100) or sodium hydroxide solution (10 in 100), and adjust the pH to 8.0 ± 0.1. Transfer 25.0 mL of this solution into a 100-mL volumetric flask, and add water to dilute to the gauge line. Use the diluted phosphoric acid solution (10 in 100) or sodium hydroxide solution (10 in 100), and adjust the pH to 8.0 ± 0.1.

(iii) *Other related substances*—Weigh accurately about 200 mg of Terazosin Hydrochloride Hydrate, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. Pipet 1 mL of this solution, and add the mobile phase to make exactly 100 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 10 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution according to the automatic integration method, and calculate the amount of each related substance; terazosin related substance I with relative retention time of 0.4 to the terazosin hydrochloride obtained from the test solution is NMT 0.3%, terazosin related substance III with relative retention time of 1.8 is NMT 0.4%, any individual related substances eluting before the terazosin peak is NMT 0.3%, terazosin hydrochloride related substance II with a relative retention time of 1.2, as well as any other individual related substances, is NMT 0.1%, and the total related substances is NMT 0.6%. However, exclude any peaks smaller than 0.05%.

$$\text{Content (\%) of related substances} = \frac{A_T}{A_S} \times rf \times \frac{1}{10}$$

A_T: Peak area of each related substance obtained from the test solution

A_S: Peak area of terazosin hydrochloride obtained from the standard solution

rf: The correction factor for each related substance for terazosin hydrochloride peak

Terazosin related substance I: 1.03
Terazosin related substance II: 1.41
Terazosin related substance III: 0.69
Other related substances: 1.00

Operating conditions

For the detector, mobile phase, flow rate, etc., perform the test as directed under the operating conditions under the Assay.

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Time span of measurement: For 40 minutes after injecting the samples.

System suitability

Test for required detectability: Pipet 5 mL of the standard solution, and add the mobile phase to make exactly 10 mL. Proceed with 20 μL of this solution according to the above conditions; confirm that the signal-to-noise ratio of the terazosin hydrochloride peak is NLT 10.

System performance: Proceed with 20 μL of the standard solution according to the above operating conditions; the number of theoretical plates and the symmetry factor of the peak of terazosin hydrochloride are NLT 10000 and 0.8 - 2.0, respectively.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of terazosin is NMT 2.0%.

Loss on drying NMT 9.0% (1 g, in vacuum, 105 ℃, 3 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.1 g of Terazosin Hydrochloride Hydrate, add the mobile phase to make exactly 200 mL, and use this solution as the test stock solution. Pipet 10.0 mL of the test stock solution, and add the mobile phase to make exactly 50 mL. Pipet 10.0 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately terazosin hydrochloride RS, dissolve in the mobile phase to make 0.5 mg/mL, and use this solution as the standard stock solution. Pipet 10.0 mL of the standard stock solution and add the mobile phase to make exactly 50 mL. Pipet 10.0 mL of this solution, add the mobile phase to it make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test standard solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of terazosin hydrochloride, A_T and A_S, from each of the solutions.

$$\text{Amount (mg) of terazosin hydrochloride } (C_{19}H_{25}N_5O_4 \cdot HCl) = C \times \frac{A_T}{A_S} \times 10000$$

C: Concentration (mg/mL) of terazosin hydrochloride RS in the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of pH 3.2 citric acid buffer solution and acetonitrile (1685 : 315).

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 20 μL of the

standard solution according to the above conditions; the number of theoretical plates and the symmetry factor are NLT 12000 and 0.9 to 1.3, respectively.

System repeatability: Repeat the test 6 times according to the above conditions with 20 μL of the standard solution each time; the relative standard deviation of the peak area is NMT 0.9%.

pH 3.2 citric acid buffer solution—Dissolve 12.0 g of sodium citrate dihydrate and 28.5 g of citric acid (100) in 1950 mL of water. Adjust pH to 3.2 ± 0.1 with citric acid (100) or sodium citrate, and add water to make 2000 mL.

Packaging and storage Preserve in tight containers at a temperature between 20 and 25 °C.

Terazosin Hydrochloride Tablets
테라조신염산염 정

Terazosin Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of labeled amount of terazosin ($C_{19}H_{25}N_5O_4$: 387.43).

Method of preparation Prepare as directed under Tablets, with Terazosin Hydrochloride.

Identification (1) Weigh a portion of powdered Terazosin Hydrochloride Tablets, equivalent to 10 mg of terazosin hydrochloride according to the labeled amount, place in a 100-mL volumetric flask, dilute with 0.1 mol/L hydrochloric acid filled up to 50% of the volumetric flask's volume, sonicate for 10 minutes, allow to stand to cool to room temperature, and fill with 0.1 mol/L hydrochloric acid up to the gauge line. Take 5 mL of this solution, dilute with 0.1 mol/L hydrochloric acid to make 100 mL, shake to mix, and filter 20 mL of this solution through a membrane filter with 0.45 μm of pore diameter, discarding the first 5 mL of the filtrate. Use this subsequent filtrate as the test solution. Separately, dissolve terazosin hydrochloride RS in 0.1 mol/L hydrochloric acid to make a concentration of 0.005 mg/mL, sonicate for 10 minutes to dissolve completely, and filter through a nylon filter with 0.45 μm of pore diameter, discarding the first 5 mL of the filtrate. Use this subsequent filtrate as the standard solution. Determine the absorption spectra of the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit absorption maxima and minima at the same wavelengths.

(2) Perform the test as directed under the Assay; the retention times of the major peaks obtained from the test solution and the standard solution are the same.

Purity ***Related substances***—Weigh accurately the mass of NLT 20 tablets of Terazosin Hydrochloride Tablets and powder. Weigh accurately an amount of the powder, equivalent to about 15 mg of terazosin hydrochloride, put in in a 50-mL volumetric flask, dilute with 25 mL of the mobile phase, sonicate for NLT 10 minutes, and shake to mix for NLT 20 minutes. To this solution, add the mobile phase to make 50 mL. Filter this solution through a nylon or Teflon filter with 0.45 μm of pore diameter, discard the first 5 mL of the filtrate, and use the remaining filtrate as the test solution. Separately, dissolve terazosin hydrochloride RS in the mobile phase to make a concentration of 0.003 mg/mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions to determine the peak area of each solution by the automatic integration method, and calculate the amount of related substances in the test solution; terazosin hydrochloride related substances I {N-(4-amino-6,7-dimethoxy-2-quinazolinyl)piperazine} having the relative retention time to terazosin hydrochloride of about 0.52, terazosin hydrochloride related substances II {2-chloro-4-amino-6,7-dimethoxy-2-quinazoline} having that of about 1.37 and terazosin hydrochloride related substances III {*N*,*N*-bis-(4-amino-6,7-dimethoxy-2-quinazolinyl)piperazine} having that of about 3.85 are NMT 0.4% respectively, other individual related substances are NMT 0.2%, and the sum of total related substances is NMT 1.2%. However, the correction factors for the peak areas of terazosin related substances I and terazosin related substances II are 1.1 and 1.2, respectively.

$$\text{Amounts (\%) of related substances} = \frac{A_T}{A_S} \times \frac{C_S}{C_T} \times \frac{1}{F} \times \frac{387.43}{423.89} \times 100$$

C_S: Concentration (mg/mL) of terazosin hydrochloride in the standard solution

C_T: Concentration (mg/mL) of terazosin in the test solution

A_T: Peak areas of the individual related substances in the test solution

A_S: Peak area of terazosin hydrochloride in the standard solution

F: Correction factor

387.43: Molecular weight of terazosin

423.89: Molecular weight of terazosin hydrochloride

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 246 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of buffer solution and acetonitrile (19 : 6).

Flow rate: 1 mL/min

System suitability

System performance: Dissolve terazosin hydrochloride RS in the mobile phase to make 0.15 μg/mL, and

use this solution as the system suitability solution. Perform the test with 10 μL each of the standard solution and the system suitability solution according to the operating conditions above; the capacity factor (retention factor) of the terazosin peak from the standard solution is NLT 1.0, its symmetry factor is NMT 2.0, and the signal-to-noise ratio of the terazosin peak from the system suitability solution is NLT 10.

System repeatability: Repeat the test 6 times with 10 μL of the standard solution according to the above conditions; the relative standard deviation of the peak areas of terazosin is NMT 2.0%.

Time span of measurement: About 4.5 times the retention time of terazosin after the solvent peak.

Buffer solution—Dissolve 4.1 g of potassium dihydrogen phosphate and 1.1 g of sodium 1-heptanesulfonate monohydrate in 950 mL of water, adjust with phosphoric acid to pH 3.0 ± 0.10, dilute with water to make 1000 mL, filter the solution through a nylon filter with 0.45 μm of pore diameter, and use this solution as the buffer solution.

Dissolution Perform the test with 1 tablet of Terazosin Hydrochloride Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take 20 mL of the dissolved solution 30 minutes after starting the test and filter through a membrane filter with a pore size of 0.45 μm. Discard the first 10 mL of the filtrate, add water to the subsequent filtrate so that each mL contains about 5 μg of terazosin ($C_{19}H_{25}N_5O_4$), and use this solution as the test solution. Separately, dissolve terazosin hydrochloride RS in water to make a concentration of terazosin hydrochloride 0.1 mg/mL. Take 5.0 mL of this solution, add water to make 100.0 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance at the absorbance maximum wavelength of around 245 nm. The dissolution rate of Terazosin Hydrochloride Tablets in 30 minutes is NLT 75%.

$$\text{Dissolution rate (\%) of terazosin } (C_{19}H_{25}N_5O_4) = \frac{A_T}{A_S} \times \frac{C_S}{L} \times \frac{387.43}{423.89} \times V \times 100$$

A_T: Absorbance of the test solution

A_S: Absorbance of the standard solution

C_S: Concentration (mg/mL) of terazosin hydrochloride in the standard solution

L: Labeled amount (mg/tablet) of terazosin in 1 tablet

387.43: Molecular weight of terazosin

423.89: Molecular weight of terazosin hydrochloride

V: Volume of the dissolution medium, 900mL

Uniformity of dosage units Perform the test with 1 tablet of Terazosin Hydrochloride Tablets as directed under the Assay; it meets the requirements of the Procedure for content uniformity.

Assay Weigh accurately the mass of NLT 20 tablets of Terazosin Hydrochloride Tablets and powder them. Weigh accurately an amount of the powder, equivalent to about 10 mg of terazosin hydrochloride ($C_{19}H_{25}N_5O_4 \cdot HCl$), place in a 200-mL volumetric flask, add 100 mL of the diluent, sonicate for NLT 10 minutes, and shake for NLT 10 minutes. Repeat this process until the sample is uniformly dispersed. Allow the solution to stand at room temperature until cooled, and add the diluent to make 200 mL. Filter through a membrane filter with 0.45 μm of pore diameter, discarding the first 5 mL of the filtrate, and use the remaining filtrate as the test solution. Separately, dissolve terazosin hydrochloride RS in the diluent to have a concentration of 0.55 mg/mL for terazosin hydrochloride, sonicate for 5 minutes to dissolve completely, and use this solution as the standard stock solution. Add the diluent to the standard stock solution and make the concentration of terazosin hydrochloride 0.055 mg/mL. Filter through a membrane filter with 0.45 μm of pore diameter, discarding the first 5 mL of the filtrate, and use the remaining filtrate as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the area of the peak of terazosin hydrochloride in the test solution, A_T, and in the standard solution, A_S.

$$\text{Content (\%) of terazosin } (C_{19}H_{25}N_5O_4) = \frac{A_T}{A_S} \times \frac{C_S}{C_T} \times \frac{387.43}{423.89} \times 100$$

C_S: Concentration (mg/mL) of terazosin hydrochloride in the standard solution

C_T: Concentration (mg/mL) of terazosin in the test solution

387.43: Molecular weight of terazosin

423.89: Molecular weight of terazosin hydrochloride

Diluent—Add 0.85 mL of hydrochloric acid to 1000 mL methanol to make 0.01 mol/L hydrochloric acid-methanol solution. Use a mixture of the 0.01 mol/L hydrochloric acid-methanol solution and water (2 : 3) as the diluent.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm)

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter)

Mobile phase: Add acetic acid(100) to a mixture of acetonitrile and water (7 : 3) to make a concentration of 10.00 mL/L, degas, filter through a nylon filter with 0.45 μm of pore diameter, add 0.20 mL of diethylamine to the

filtrate and mix.

Flow rate: 1 mL/min

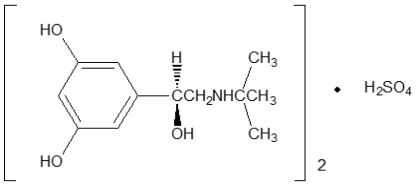
System suitability

System performance: Place 50 mg of naproxen RS in a 100-mL volumetric flask, add 25 mL of acetonitrile, sonicate to dissolve, add water to make 100 mL, and use this solution as the naproxen standard solution. Add the diluent to the naproxen standard solution and the standard stock solution for assay to prepare a mixture containing 0.05 mg/mL of naproxen and 0.055 mg/mL of terazosin, filter through a membrane filter with 0.45 μm of pore diameter, discard the first 5 mL of the filtrate, and use the remaining filtrate as the system suitability solution. Perform the test with 25 μL of the system suitability solution according to the above conditions; the resolution between the naproxen and terazosin peaks is NLT 2.0, and the symmetry factor of the terazosin peak is NMT 1.8.

System repeatability: Repeat the test 6 times with 25 μL of the standard solution according to the above conditions; the relative standard deviation of the peak areas of terazosin is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Terbutaline Sulfate
테르부탈린황산염



and enantiomer

$(C_{12}H_{19}NO_3)_2 \cdot H_2SO_4$: 548.65

5-[2-(*tert*-Butylamino)-1-hydroxyethyl]benzene-1,3-diol; sulfuric acid [*23031-32-5*]

Terbutaline Sulfate contains NLT 98.5% and NMT 101.0% of terbutaline sulfate [$(C_{12}H_{19}NO_3)_2 \cdot H_2SO_4$], calculated on the anhydrous basis.

Description Terbutaline Sulfate occurs as white to brownish white crystals or a crystalline powder. It is odorless or has a slight odor of acetic acid.

It is freely soluble in water and practically insoluble in acetonitrile, acetic acid(100), ethanol(95), ether, or chloroform.

It is gradually colored by light or air.

Melting point—About 255 °C (with decomposition).

Identification (1) Dissolve 1 mg of Terbutaline Sulfate in 1 mL of water, and add 5 mL of pH 9.5 tris buffer solution, 0.5 mL of 4-aminoantipyrine solution (1 in 50), and 2 drops of potassium hexacyanoferrate(III) solution (2 in 25); the resulting solution exhibits a purple color.

(2) Determine the absorption spectra of solutions of Terbutaline Sulfate and terbutaline sulfate RS in 0.01 mol/L hydrochloric acid TS (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths. A maximum sometimes splits into two.

(3) An aqueous solution of Terbutaline Sulfate (1 in 50) responds to the Qualitative Analysis for sulfate.

pH Dissolve 0.10 g of Terbutaline Sulfate in 10 mL of water; the pH of this solution is between 4.0 and 4.8.

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Terbutaline Sulfate in 10 mL of water; the resulting solution is colorless to pale yellow and clear.

(2) ***Chloride***—Perform the test with 2.0 g of Terbutaline Sulfate. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid (NMT 0.004%).

(3) ***Heavy metals***—Proceed with 2.0 g of Terbutaline Sulfate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(4) ***Arsenic***—Prepare the test solution with 1.0 g of Terbutaline Sulfate according to Method 3 and perform the test (NMT 2 ppm).

(5) ***Related substances***—Weigh accurately 50 mg of Terbutaline Sulfate, add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately 30 mg of terbutaline sulfate RS, dissolve in the mobile phase to make 100 mL, pipet 1.0 mL of this solution, and add the mobile phase to make 100 mL of a solution containing 3 μg of terbutaline sulfate per mL. Use this solution as the standard solution. Perform the test with 20 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of each solution as directed in the automatic integration method; the amount of total related substances is NMT 1.0%.

$$\text{Content (\%) of related substances} = 5000 \times \frac{C}{W} \times \frac{A_T}{A_S}$$

C: Concentration (mg/mL) of terbutaline sulfate in the standard solution

W: Sampling amount (mg)

A_T: Peak area of each related substance obtained from the test solution

A_S: Peak area of terbutaline obtained from the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 276 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 3.15 g of ammonium formate in 900 mL of water, adjust the pH to 3.0 with

formic acid, add 5.49 g of sodium 1-hexanesulfonate, and add water to make 1000 mL. To 770 mL of this solution, add 230 mL of methanol.

Flow rate: 1 mL/min

System suitability

System performance: Weigh accurately 25 mg of terbutaline sulfate RS and 10 mg of related substance I {3,5-dihydroxy-ω-t-butylaminoacetophenone sulfate}, dissolve in mobile phase to make 25 mL of solutions, each containing 1.0 mg and 0.4 mg per mL, and use these solutions as the system suitability solution. Proceed with 20 μL of these solutions according to the above conditions; the relative retention time for terbutaline related substance I to terbutaline is 0.9 with the resolution being NLT 2.0. The number of theoretical plates and the symmetry factor of the peak of terbutaline are NLT 1500 and NMT 2.0, respectively.

System repeatability: Repeat the test 5 times with 20 μL each of the system suitability solution according to the above conditions; the relative standard deviation of the peak areas of terbutaline is NMT 2.0%.

(6) ***3,5-Dihydroxy-ω-t-butylaminoacetophenone sulfate***—Dissolve 0.50 g of Terbutaline Sulfate in 0.01 mol/L hydrochloric acid TS to make exactly 25 mL, and perform the test with this solution as directed under Ultraviolet-visible Spectroscopy; the absorbance at the wavelength of 330 nm is NMT 0.47.

(7) ***Related substances***—Dissolve about 0.50 g of Terbutaline Sulfate in phosphoric acid solution (59 in 1000) to make exactly 10 mL, and use this solution as the test solution. Separately, dissolve 1.50 g of acetic acid(100) in phosphoric acid (59 in 1000) to make exactly 100 mL. Pipet 2 mL of this solution, add phosphoric acid (59 in 1000) to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 2 μL each of the test solution and standard solution as directed under the Gas Chromatography according to the following conditions. Determine the peak area of acetic acid, A_T and A_S, of each solution; A_T is not greater than A_S.

Operating conditions

Detector: A flame ionization detector

Column: A column, about 3 mm in internal diameter and about 1 m in length, packed with polyethylene glycol 6000 coated in 180 μm to 250 μm terephthalic acid for gas chromatography at a rate of 10%.

Column temperature: A constant temperature of about 120 °C.

Carrier gas: Nitrogen

Flow rate: Adjust the flow rate so that the retention time of acetic acid is about 5 minutes.

System suitability

System performance: Dissolve 50 mg each of acetic acid(100) and propionic acid in 100 mL of phosphoric acid solution (59 in 1000). Proceed with 2 μL of this solution according to the above conditions; acetic acid and propionic acid are eluted in this order with the resolution being NLT 2.0.

System repeatability: Repeat the test 6 times with 2 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak area of acetic acid is NMT 3.0%.

Water NMT 0.5% (1 g, volumetric titration, direct titration).

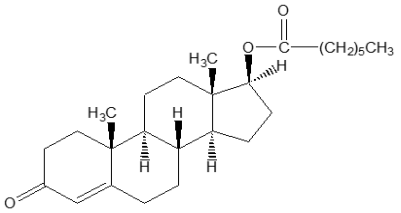
Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.5 g of Terbutaline Sulfate, add 50 mL of a mixture of acetic acid(100) and acetonitrile (1 : 1), and dissolve by warming while stirring. After cooling, titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry; however, use a saturated methanol solution of potassium chloride as the internal solution).

Each mL of 1 mol/L perchloric acid VS
= 54.87 mg of $(C_{12}H_{19}NO_3)_2 \cdot H_2SO_4$

Packaging and storage Preserve in light-resistant, tight containers.

Testosterone Enanthate
테스토스테론에난테이트



$C_{26}H_{40}O_3$: 400.59

[(8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-10,13-Dimethyl-3-oxo-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-17-yl]heptanoate [*315-37-7*]

Testosterone Enanthate, when dried, contains NLT 95.0% and NMT 105.0% of testosterone enanthate ($C_{26}H_{40}O_3$).

Description Testosterone Enanthate occurs as a white to pale yellow crystal, crystalline powder, or pale yellowish brown viscous liquid. It is odorless or has a slightly characteristic odor.

It is very soluble in ethanol(95), 1,4-dioxane, or ether and practically insoluble in water.

Melting point—About 36 °C.

Identification To 25 mg of Testosterone Enanthate, add 2 mL of potassium hydroxide in methanol solution (1 in 100), and heat on a steam bath under a reflux condenser for 1 hour. After cooling, add 10 mL of water, filter the precipitate by suction, wash the residue until the washings become neutral, and dry the residue in a desiccator (in vacuum, phosphorus pentoxide) for 4 hours; the melt-

ing point is between 151 and 157 ℃.

Optical rotation $[\alpha]_D^{20}$: Between +81° and +86° (0.1 g after drying, ethanol(99.5), 10 mL, 100 mm).

Purity (1) ***Acid***—Dissolve 0.5 g of Testosterone Enanthate in 10 mL of a neutralized solution of bromothymol blue TS in ethanol, and add 2 drops of bromothymol blue TS and 0.50 mL of 0.01 mol/L sodium hydroxide VS; the resulting solution exhibits a pale blue color.

(2) ***Free heptanoic acid***—Weigh accurately 0.5 g of Testosterone Enanthate, dissolve in 10 mL of neutralized ethanol, previously prepared by adding 2 to 3 drops of bromothymol blue TS in ethanol until the color of the solution turns pale blue, and titrate with 0.01 mol/L sodium hydroxide VS; the consumed amount is NMT 0.6 mL (NMT 0.16% of heptanoic acid).

(3) ***Related substances***—Weigh accurately 0.1 g of Testosterone Enanthate, dissolve in methanol to make exactly 10 mL of a solution containing about 10 mg per mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of testosterone enanthate RS, dissolve in methanol to make solutions each containing about 0.01 mg, 0.05 mg, 0.1 mg, and 0.2 mg per mL, and use these solutions as the standard solution (1), the standard solution (2), the standard solution (3), and the standard solution (4), respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution, the standard solution (1), the standard solution (2), the standard solution (3), and the standard solution (4) on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography, develop the plate with a mixture of cyclohexane and ethyl acetate (2 : 1) as the developing solvent to a distance of about three-fourths of the length of the plate, and air-dry the plate. Spray a solution of 20g of p-toluenesulfonic acid monohydrate in 100 mL of alcohol on the plate, dry at 110 ℃ for 15 minutes, and examine the plate under ultraviolet light (main wavelength: 366 nm); any spot in the test solution is not larger or more intense than the principal spot of the standard solution (3) (NMT 1.0%). The sum of all the spots other than the principal spot from the test solution is NMT 2.0%.

Loss on drying NMT 0.5% (0.5 g, in vacuum, phosphorus pentoxide, 4 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately about 0.1 g of Testosterone Enanthate, previously dried, and dissolve in ethanol(95) to make exactly 100 mL. Pipet 10 mL of this solution, and add ethanol(95) to make exactly 100 mL. Again, pipet 10 mL of this solution, and add ethanol(95) to make exactly 100 mL. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy, and determine the absorbance of this solution, *A*, at the absorbance maximum wavelength at about 241 nm.

$$\text{Amount (mg) of testosterone enanthate } (C_{26}H_{40}O_3) = \frac{A}{426} \times 100000$$

Packaging and storage Preserve in light-resistant, tight containers at below 30 ℃.

Testosterone Enanthate Injection
테스토스테론에난테이트 주사액

Testosterone Enanthate Injection is an oily solution of injection, which contains NLT 90.0% and NMT 110.0% of the labeled amount of testosterone enanthate ($C_{26}H_{40}O_3$: 400.59).

Method of preparation Prepare as directed under Injections, with Testosterone Enanthate.

Description Testosterone Enanthate occurs as a clear, colorless to pale yellow oily liquid.

Identification Weigh an amount of Testosterone Enanthate Injection, equivalent to 50 mg of testosterone enanthate, according to the labeled amount, add 8 mL of petroleum ether, and extract three times with 10 mL each of diluted acetic acid (7 in 10). Combine the extracts, wash with 10 mL of petroleum ether, add 0.5 mL of diluted sulfuric acid (7 in 10) to 0.1 mL of the extract and heat on a steam bath for 5 minutes. After cooling, add 0.5 mL of iron(III) chloride-acetic acid TS; the color of the solution is blue.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Take exactly a volume of Testosterone Enanthate Injection, equivalent to about 50 mg of testosterone enanthate ($C_{26}H_{40}O_3$), and add chloroform to make exactly 100 mL. Pipet 15 mL of this solution, add 5 mL of the internal standard solution and methanol to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of testosterone enanthate RS, previously dried for 4 hours in a desiccator (in vacuum, phosphorus pentoxide), proceed in the same manner as the test solution, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, of testosterone enanthate to the peak area of the internal

standard.

$$\text{Amount (mg) of testosterone enanthate } (C_{26}H_{40}O_3) = \text{Amount (mg) of testosterone enanthate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of phenanthrene in methanol (1 in 2000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: An ordinary temperature

Mobile phase: A mixture of acetonitrile and water (85 : 15).

Flow Rate: Adjust the flow rate so that the retention time of testosterone enanthate is about 10 minutes.

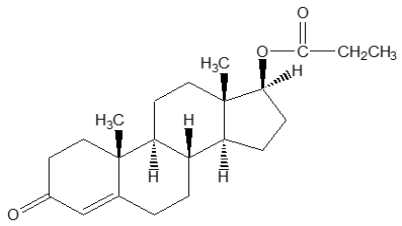
System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the internal standard and testosterone enanthate are eluted in this order with the resolution being NLT 2.5.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratios of testosterone enanthate RS to that of the internal standard is NMT 2.0%.

Packaging and storage Preserve in light-resistant, hermetic containers.

Testosterone Propionate
테스토스테론프로피오네이트



$C_{22}H_{32}O_3$: 344.49

[(8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-10,13-Dimethyl-3-oxo-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-17-yl]propanoate [*57-85-2*]

Testosterone Propionate, when dried, contains NLT 97.0% and NMT 103.0% of testosterone propionate ($C_{22}H_{32}O_3$).

Description Testosterone Propionate occurs as white to pale yellow crystals or a crystalline powder and is odorless. It is freely soluble in methanol or in ethanol(95) and practically insoluble in water.

Identification (1) Determine the absorption spectra of solutions of Testosterone Propionate and testosterone propionate RS in ethanol(95) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Testosterone Propionate and testosterone propionate RS, previously dried, as directed under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +83° and +90° (0.1 g after drying, ethanol(95), 10 mL, 100 mm).

Melting point Between 118 and 123 ℃.

Purity ***Related substances***—Dissolve about 40 mg of Testosterone Propionate in ethanol(95) and use the solution as the test solution. Pipet 1 mL of the test solution, add ethanol(95) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin Layer Chromatography. Spot each 10 μL of the test and standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform and diethylamine (19 : 1) to a distance of about 15 cm and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 366 nm); any spot other than the principal spot obtained from the test solution is not more intense than the spot from the standard solution.

Loss on drying NMT 0.5% (0.5 g, in vacuum, phosphorus pentoxide, 4 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately each about 10 mg of Testosterone Propionate and testosterone propionate RS, previously dried, and dissolve in methanol to make exactly 100 mL, respectively. Pipet 5.0 mL of these solutions, add exactly 5 mL of the internal standard solution and then methanol to make exactly 20 mL, and use these solutions as the test solution and the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions. Determine the ratios of the peak area, Q_T and Q_S of tetosterone propionate to the peak area of the internal standard of each solution.

$$\text{Amount (mg) of testosterone propionate } (C_{22}H_{32}O_3) = \text{Amount (mg) of testosterone propionate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of progesterone in methanol (9 in 100000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 241 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of acetonitrile and water (7: 3).

Flow rate: Adjust the flow rate so that the retention time of Testosterone Propionate is about 10 minutes.

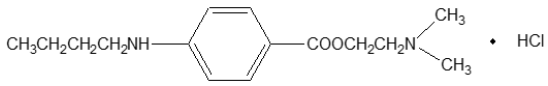
System suitability

System performance: Proceed with 5 μL of the standard solution under the above operating conditions; the internal standard and testosterone propionate are eluted in this order with the resolution being NLT 9.

System repeatability: Repeat the test six times with 5 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area ratio of testosterone propionate to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Tetracaine Hydrochloride
테트라카인염산염



$C_{15}H_{24}N_2O_2 \cdot HCl$: 300.82

2-(Dimethylamino)ethyl 4-(butylamino)benzoate hydrochloride [*136-47-0*]

Tetracaine Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of tetracaine hydrochloride ($C_{15}H_{24}N_2O_2 \cdot HCl$).

Description Tetracaine Hydrochloride occurs as white crystals or a crystalline powder. It is odorless, has a slightly bitter taste, and paralyzes the tongue.

It is very soluble in formic acid, freely soluble in water, soluble in ethanol(95), sparingly soluble in ethanol(99.5), slightly soluble in acetic anhydride, and practically insoluble in ether.

An aqueous solution of Tetracaine Hydrochloride (1 in 10) is neutral.

Melting point—About 148 °C.

Identification (1) Dissolve 0.5 g of Tetracaine Hydrochloride in 50 mL of water, add 5 mL of ammonia TS, shake to mix, allow to stand in a cold place, and filter the extracted crystals. Wash with water until the filtrate becomes neutral, and dry it in a desiccator (silica gel) for 24 hours; the melting point of the crystals so obtained is between 42 and 44 ℃.

(2) Dissolve about 0.1 g of Tetracaine Hydrochloride in 8 mL of water and add 3 mL of ammonium thiocyanate TS; a crystalline precipitate is formed. Filter the precipitate formed. Dry the precipitate at 80 ℃ for 2 hour; the precipitate melts between 130 and 132 ℃.

(3) Determine the absorption spectra of solutions of Tetracaine Hydrochloride and tetracaine hydrochloride RS in ethanol(99.5) (1 in 200000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) A solution of Tetracaine Hydrochloride (1 in 10) responds to the Qualitative Analysis for chloride.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Tetracaine Hydrochloride as directed under Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances—***Weigh 0.5 g of Tetracaine Hydrochloride, dissolve in water to make 10mL, prepare a solution containing 50 mg per mL, and use this solution as the test solution. Separately, weigh 20 mg of 4-(butylamino)benzoic acid, dissolve in methanol to make exactly 100 mL, make a solution containing 0.2 mg per mL, and use this solution as the standard solution. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of chloroform, methanol and isopropylamine (98 : 7 : 2) to a distance of about three-fourths of the length of the plate, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not larger or more intense than the spot from the standard solution. The sum of all the spots other than the principal spot from the test solution is NMT 0.8%.

Loss on drying NMT 1.0% (1 g, 105 ℃, 4 hours).

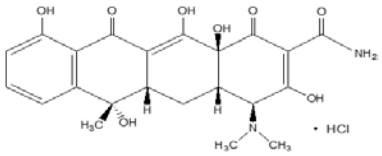
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Tetracaine Hydrochloride, previously dried, dissolve in 2 mL of formic acid, add 80 mL of acetic anhydride, allow to stand on a steam bath at 30 ℃ for 15 minutes, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 30.082 mg of $C_{15}H_{24}N_2O_2 \cdot HCl$

Packaging and storage Preserve in tight containers.

Tetracycline Hydrochloride
테트라사이클린염산염



$C_{22}H_{24}N_2O_8 \cdot HCl$: 480.90
(4*S*,4a*R*,5*S*,5a*R*,6*R*,12aS)-4-(Dimethylamino)-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide hydrate [*64-75-5*]

Tetracycline Hydrochloride is the hydrochloride of a kind of tetracycline substance having antibacterial activity produced by the growth of *Streptomyces aureofaciens.*

Tetracycline Hydrochloride contains NLT 950 μg and NMT 1010 μg (potency) of tetracycline hydrochloride ($C_{22}H_{24}N_2O_8$: 475.58) per mg, calculated on the dried basis.

Description Tetracycline Hydrochloride occurs as a yellow to pale brown crystalline powder.
It is freely soluble in water and sparingly soluble in ethanol(95).

Identification (1) Determine the absorption spectra of Tetracycline Hydrochloride and tetracycline hydrochloride RS (1 in 62500) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Tetracycline Hydrochloride and tetracycline hydrochloride RS as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous of Tetracycline Hydrochloride (1 in 100) responds to the Qualitative Analysis (2) for chloride.

pH Dissolve 1.0 g of Tetracycline Hydrochloride in 100 mL of water; the pH of this solution is between 1.8 and 2.8.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Tetracycline Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Tetracycline Hydrochloride according to Method 4 and perform the test (NMT 2 ppm).

(3) ***Related substances***—Weigh accurately about 25 mg of Tetracycline Hydrochloride, dissolve exactly in 50 mL of 0.01 mol/L hydrochloric acid TS, and use this solution as the test solution. Pipet 3 mL of Tetracycline Hydrochloride, add 0.01 mol/L hydrochloric acid TS to make exactly 100 mL, and use this solution as the standard solution. Take exactly 20 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of each solution by the automatic integration method; each peak area other than Tetracycline from the test solution is not larger than the peak area of Tetracycline from the standard solution. The sum of peak areas other than Tetracycline from the test solution is not greater than 3 times the peak area of Tetracycline from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with spherical styrene-divinylbenzene copolymer for liquid chromatography (0.01 nm in pore diameter).

Column temperature: 60 °C

Mobile phase: Dissolve 3.5 g of dibasic potassium phosphate, 2.0 g of tetrabutylammonium hydrogen sulfate and 0.4 g of disodium dihydrogen ethylenediaminetetraacetate dihydrate in 300 mL of water, and adjust the pH to pH 9.0 with sodium hydroxide TS. To this solution, add 90 g of t-butyl alcohol, and add water to make 1000 mL.

Flow rate: Adjust the flow rate so that the retention time of Tetracycline is about 5 minutes.

System suitability

Test for required detectability: Pipet 3 mL of the standard solution and add 0.1 mol/L hydrochloric acid TS to make exactly 100 mL. Confirm that the peak area of tetracycline obtained from 20 μL of this solution is 1 to 5% of the peak area of tetracycline obtained from the standard solution.

System performance: Weigh about 0.05 g of tetracycline hydrochloride RS and dissolve in 25 mL of the water. Heat 5 mL of this solution on a steam bath for 60 minutes and add water to make 25 mL. Proceed with 20 μL of this solution according to the above conditions; the retention time of 4-epoxytetracycline is about 3 minutes; 4-eptetracycline and tetracycline are eluted in this order with the resolution being NLT 2.5.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solutions; the relative standard deviation of the peak area of tetracycline is NMT 1.0%.

Time span of measurement: About 7 times the retention time of tetracycline after the solvent peak.

Loss on drying NMT 2.0% (1.0 g, in vacuum, 60 °C, 3 hours).

Residue on ignition NMT 0.3% (1.0 g).

Sterility It meets the requirements when used in the manufacturing of a sterile preparation. However, it is excluded when there is a terminal sterilization process in the manufacturing process of sterile preparations.

Bacterial endotoxins Less than 0.5 EU per mg (potency) of tetracycline hydrochloride when used in the manufacturing of sterile preparations.

Histamine It meets the requirements when used in the manufacturing of a sterile preparation. Proceed with an

appropriate amount of Tetracycline Hydrochloride to prepare a solution containing 5.0 mg (potency) per mL in Isotonic Sodium Chloride Injection, and use the solution as the test solution. Use 0.6 mL of the solution for the test.

Assay Weigh accurately about 50 mg (potency) each of Tetracycline Hydrochloride and tetracycline hydrochloride RS, dissolve in the mobile phase A to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of tetracycline hydrochloride in the test solution and the standard solution.

Potency (μg) of tetracycline hydrochloride ($C_{22}H_{24}N_2O_8$)
= Potency (μg) of tetracycline hydrochloride RS× $\frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Adjust a mixture of mobile phase A and mobile phase B (950 : 50) to pH 7.6 to 7.7 with ammonium hydroxide and phosphoric acid.

Mobile phase A: A mixture of 0.1 mol/L ammonium oxalate and dimethylformamide (680 : 270).

Mobile phase: 0.2 mol/L ammonium monohydrogen phosphate

Flow rate: 2.0 mL/min

Packaging and storage Preserve in light-resistant, tight containers.

Tetracycline Hydrochloride Capsules
테트라사이클린염산염 캡슐

Tetracycline Hydrochloride Capsules contain NLT 90.0% and NMT 120.0% of the labeled amount of tetracycline hydrochloride ($C_{22}H_{24}N_2O_8$·HCl : 480.90).

Method of preparation Prepare as directed under Capsules, with Tetracycline Hydrochloride.

Identification (1) Take the contents of Tetracycline Hydrochloride Capsules, weigh an amount equivalent to 2 to 3 mg of tetracycline, and add 2 mL of sulfuric acid; the resulting solution exhibits purple.

(2) The retention times of the major peaks from the test solution and the standard solution obtained under the Assay are the same.

Purity ***4-epianhydrotetracycline hydrochloride***—Weigh accurately the contents of NLT 20 capsules of Tetracycline Hydrochloride Capsules, weigh accurately the amount equivalent to about 50 mg (potency) according to the labeled potency, dissolve in the mobile A to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of 4-epianhydrotetracycline hydrochloride RS, dissolve in the mobile phase A to make exactly 1000 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of 4-epianhydrotetracycline RS, A_T and A_S, in each solution (NMT 3.0%).

Content (%) of 4-epianhydrotetracycline hydrochloride

$$= 10 \times \frac{C_s}{T} \times \frac{A_i}{A_S}$$

C_s: Concentration [μg(potency)/mL] of 4-epianhydrotetracycline hydrochloride in the standard solution

T: Amount [μg(potency)/mL] of 4-epianhydrotetracycline hydrochloride in the test solution

A_i: Peak area of 4-epianhydrotetracycline hydrochloride in the test solution

A_S: Peak area of 4-epianhydrotetracycline hydrochloride in the standard solution

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, perform the test according to the conditions as directed under the Assay.

Loss on drying NMT 4.0% (0.1 g, 0.7 kPa, 60 ℃, 3 hours).

Dissolution Take 1 capsule of Tetracycline Hydrochloride Capsule and perform the test at 75 revolutions per minute according to Method 2, using 900 mL of water as the test solution, with the distance between the bottom edge of the stirring blade and the inside bottom of the flask fixed at 45 ± 5 mm during the test. For 0.5 g of capsules, take the dissolved solution after 60 minutes from the start of the test and filter. Discard the first 10 mL of the filtrate, pipet V mL of the subsequent filtrate, add the dissolution medium to make exactly V' mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of tetracycline hydrochloride RS, dissolve in the dissolution medium to obtain a solution having the same concentration as the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorbance maximum wavelength of about 276 nm as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as a control solution. It meets the requirements when the dissolution rate for 60 minutes is NLT 80% (Q). However, 0.5 g of the capsules meet the requirement when the dissolution rate for 90 minutes is NLT 80% (Q).

Dissolution rate (%) with respect to the labeled amount of tetracycline hydrochloride ($C_{22}H_{24}N_2O_8 \cdot HCl$)

$$= C_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 90000$$

Cs: Concentration [mg (potency)/mL] of the standard solution

C: Labeled amount [mg (potency)] of tetracycline hydrochloride ($C_{22}H_{24}N_2O_8.HCl$) in 1 capsule

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the contents of 20 capsules of Tetracycline Hydrochloride Capsules, weigh the amount equivalent to about 50 mg (potency) according to the labeled potency, dissolve in the mobile phase A to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg (potency) of tetracycline hydrochloride RS, dissolve in the mobile phase A to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of tetracycline hydrochloride, A_T and A_S, in each solution.

Potency (μg) of tetracycline hydrochloride ($C_{22}H_{24}N_2O_8 \cdot HCl$) = Potency (μg) of tetracycline hydrochloride RS× $\frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 250 mm in length, packed with octylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Adjust a mixture of the mobile phase A and the mobile phase B (950 : 50) to pH 7.6 to 7.7 with 3 mol/L ammonium hydroxide solution and phosphoric acid.

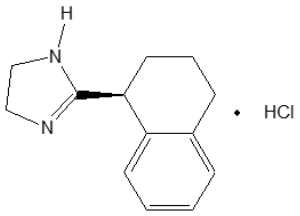
Mobile phase A: A mixture of 0.1 mol/L ammonium oxalate TS and dimethylformamide (680 : 270).

Mobile phase B: 0.2 mol/L ammonium monohydrogen phosphate

Flow rate: 2.0 mL/min

Packaging and storage Preserve in tight containers.

Tetrahydrozoline Hydrochloride
테트라히드로졸린염산염



and enantiomer

$C_{13}H_{16}N_2 \cdot HCl$: 236.74

2-(1,2,3,4-Tetrahydronaphthalen-1-yl)-4,5-dihydro-1*H*-imidazolehydrochloride [*522-48-5*]

Tetrahydrozoline Hydrochloride contains NLT 98.0% and NMT 100.5% of tetrahydrozoline hydrochloride ($C_{13}H_{16}N_2 \cdot HCl$), calculated on the dried basis.

Description Tetrahydrozoline Hydrochloride occurs as a white solid and is odorless.

It is freely soluble in water or ethanol(95), slightly soluble in chloroform, and practically insoluble in ether.

Melting point—About 256 °C (with decomposition).

Identification (1) Determine the absorption spectra of aqueous solutions of Tetrahydrozoline Hydrochloride and tetrahydrozoline hydrochloride RS (1 in 4000) as directed under the Ultraviolet-visible Spectroscopy; both exhibit an absorption maximum and minimum at the same wavelengths. The difference in absorbances of the solutions, calculated on the dried basis, at the absorption maximum wavelength of around 241 nm and 271 nm is NMT 4.0%.

(2) Determine the infrared spectra of Tetrahydrozoline Hydrochloride and tetrahydrozoline hydrochloride RS, previously dried at 105 °C for 2 hours, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit maxima at the same wavenumbers.

(3) A solution of Nortriptyline Hydrochloride (1 in 200) responds to the Qualitative Analysis for chloride.

Purity (1) ***Heavy metals***—Proceed with 0.40 g of Tetrahydrozoline Hydrochloride, dissolve in 23 mL of water, add 2 mL of 1 mol/L acetic acid as directed under Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 50 ppm).

(2) ***Related substances***—Weigh 0.1 g of Tetrahydrozoline Hydrochloride, dissolve in 10 mL of methanol, and use this solution as the test solution. Separately, weigh 10 mg of tetrahydrozolin hydrochloride RS (previously dried at 105℃ for 2 hours), and dissolve in methanol to make 10 mL. Pipet 0.1 mL, 0.5 mL, 1.0 mL and 2.0 mL each of the test solution, add methanol to make 10 mL, and use these solutions as the standard solutions (1), (2), (3) and (4), respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solutions (1), (2), (3) and (4) on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of methanol, acetic acid(100) and water (8 : 1 : 1) as the developing solvent to a distance of about 15 cm, and air-

dry the plate. Spray evenly hexachloroplatinic(IV) acid-potassium iodide TS on the plate, and examine the plate under ultraviolet light (254 nm and 366 nm); the intensities of all spots other than the principal spot obtained from the test solution are NMT 2.0% of the total spots, as compared to those obtained from the standard solution.

Loss on drying NMT 1.0% (1 g, 105 ℃, 2 hours).

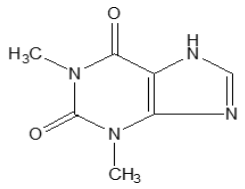
Residue on ignition NMT 0.1% (1 g).

Assay Weigh exactly about 0.2 g of Tetrahydrozoline Hydrochloride, previously dried, dissolve in 100 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 23.674 mg of $C_{14}H_{14}N_2 \cdot HCl$

Packaging and storage Preserve in tight containers.

Theophylline
테오필린



$C_7H_8N_4O_2$: 180.16
1,3-Dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione
[*58-55-9*]

Theophylline, when dried, contains NLT 99.0% and NMT 101.0% of theophylline ($C_7H_8N_4O_2$).

Description Theophylline occurs as white crystals or a crystalline powder.
It is soluble in *N*,*N*-dimethylformamide and slightly soluble in water or ethanol(99.5).
It dissolves in 0.1 mol/L hydrochloric acid TS.

Identification (1) Determine the absorption spectra of Theophylline and theophylline RS in hydrochloric acid TS (1 in 200000) as directed Under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Theophylline and theophylline RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy, respectively; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 271 and 275 ℃.

Purity (1) ***Acid***—To 0.5 g of Theophylline, add 75 mL of water, 2.0 mL of 0.01 mol/L sodium hydroxide TS and 1 drop of methyl red TS; the solution is yellow.

(2) ***Heavy metals***—Proceed with 1.0 g of Theophylline according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Theophylline according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.10 g of Theophylline in 3 mL of *N*,*N*-dimethylformamide, add 10 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each 10 μL of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of acetone-chloroform-methanol-1-butanol-ammonia water(28) (3 : 3 : 2 : 2 : 1) to a distance of about 10 cm and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); any spot other than the principal spot obtained from the test solution is not more intense than the spot from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 °C, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.25 g of Theophylline, previously dried, dissolve in 100 mL of water, add exactly 20 mL of 0.1 mol/L silver nitrate solution, and shake to mix. Titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 18.016 mg of $C_7H_8N_4O_2$

Packaging and storage Preserve in well-closed containers.

Theophylline Tablets
테오필린 정

Theophylline Tablets contain NLT 94.0% and NMT 106.0% of the labeled amount of theophylline ($C_7H_8N_4O_2$: 180.17).

Method of preparation Prepare as directed under Tablets, with Theophylline.

Identification (1) Take Theophylline Tablets, previously powdered, in the amount equivalent to 0.5 g of theophylline according to the labeled amount, soften it with 10

mL and 5 mL of hexane separately, and discard the hexane from each. Soften each residue twice with 10 mL of a mixture of ammonia TS and water (1 : 1) each time, and filter. Combine the filtrates, evaporate to concentration to about 15 mL, neutralize with 6 mol/L acetic acid TS using a litmus paper, if necessary, and cool to about 15 ℃ with shaking. Filter it, wash the residue with cold water, and dry the washed residue at 105 ℃ for 2 hours; the melting point is between 270 and 274 ℃.

(2) Determine the infrared spectra of the dried residue obtained in (1) and theophylline RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) The retention times of the major peaks obtained from the test solution and the standard solution in the Assay are the same.

Dissolution Perform the test with 1 tablet of Theophylline Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take the dissolution medium 45 minutes after starting the test, filter, dilute with the dissolution medium if necessary, and use this solution as the test solution. Separately, weigh accurately a suitable quantity of theophylline RS, previously dried at 105 ℃ for 4 hours, use it to make a solution of a certain concentration, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as the control solution, and determine the absorbance at the absorbance maximum wavelength (λmax) of about 272 nm.

It meets the requirements when the dissolution rate of Theophylline Tablets in 45 minutes is NLT 80%.

Uniformity of dosage units Meets the requirements.

Assay To 10 tablets of Theophylline Tablets, add 50 mL of water and 50 mL of ammonia TS, shake well to mix for complete disintegration. To this, add water to make exactly 500 mL, and filter with suction using a dry filter paper. Discard the first 20 mL of the filtrate. From the remaining filtrate, pipet the amount (V mL) equivalent to about 10 mg of theophylline ($C_7H_8N_4O_2$) according to the labeled amount, add 20.0 mL of the internal standard solution, and add the mobile phase to make exactly 100 mL. Use this solution as the test solution. Separately, weigh accurately a suitable quantity of theophylline RS, previously dried at 105 ℃ for 4 hours, and dissolve in the mobile phase to obtain a solution having known concentration of 1 mg per mL. Pipet 10 mL of this solution, add 20.0 mL of the internal standard solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of theophylline to the internal standard, respectively.

$$\text{Amount (mg) of theophylline } (C_7H_8N_4O_2) = 5000 \times \frac{C}{V} \times \frac{Q_T}{Q_S}$$

C: Concentration (mg/mL) of the standard solution

Internal standard solution—Weigh accurately about 50 mg of theobromine, dissolve in 10.0 mL of ammonia TS, and add the mobile phase to make exactly 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column, about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography.

Mobile phase: To 70 mL of acetonitrile, add the buffer solution to make 1000 mL.

Flow rate: 1 mL/min

System suitability

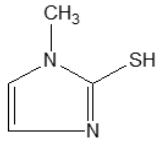
System performance: Proceed with 20 μL of the standard solution according to the above conditions; the resolution is NLT 1.5.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the ratios of the peak area of theophylline to that of the internal standard is NMT 1.5%.

Buffer solution—Dissolve 2.72 g of sodium acetate trihydrate in 200 mL of water, and add 20.0 mL of acetic acid(100) and then water to make 2 L.

Packaging and storage Preserve in well-closed containers.

Thiamazole
티아마졸



Methimazole $C_4H_6N_2S$: 114.17

3-Methyl-1*H*-imidazole-2-thione [*60-56-0*]

Thiamazole, when dried, contains NLT 98.0% and NMT 101.0% of thiamazole ($C_4H_6N_2S$).

Description Thiamazole occurs as white to pale yellowish crystals or a crystalline powder. It has a slight, characteristic odor and a bitter taste.

It is freely soluble in water or ethanol(95) and slightly soluble in ether.

Dissolve 1.0 g of Thiamazole in 50 mL of water; the pH of the solution is between 5.0 and 7.0.

Identification (1) Dissolve 5 mg of Thiamazole in 1 mL of water, add 1 mL of sodium hydroxide TS, shake to mix, and add 3 drops of sodium pentacyanonitrosylferrate(III) TS; the color of the solution gradually changes from yellow through yellowish green to green. To this solution, add 1 mL of acetic acid(31); the color of the solution changes to blue.

(2) To 2 mL of an aqueous solution of Thiamazole (1 in 200), add 1 mL of sodium carbonate TS and 1 mL of diluted Folin TS (1 in 5); the solution exhibits a deep blue color.

Melting point Between 144 and 147 °C.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Thiamazole according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Selenium***—Weigh 0.10 g of Thiamazole and prepare the test solution as directed under the Oxygen Flask Combustion with 25 mL of diluted nitric acid (1 in 30) as the absorbent. Apply a small amount of water to the upper part of apparatus A, open C carefully and transfer the test solution to a beaker. Wash C, B and the inner wall of A with 25 mL of water and combine the washings with the test solution. Boil this solution gently for 10 minutes, cool to room temperature, add water to make exactly 50 mL, and use this solution as the test solution. Separately, pipet 2 mL of selenium standard stock solution, add diluted nitric acid (1 in 60) to make exactly 50 mL and use this solution as the standard solution. Pipet 40 mL each of the test solution and the standard solution into separate beakers and adjust the pH of each solution to 1.8 - 2.2 with ammonia water(28). To each solution, add 0.2 g of hydroxylamine hydrochloride, shake gently to mix and dissolve, then add 5 mL of 2,3-diaminonaphthalene TS, shake and allow to stand for 100 minutes. Transfer each solution to a separatory funnel, wash the beakers with 10 mL of water, combine the washings, add 5.0 mL of cyclohexane, shake well for 2 minutes and extract. Take the cyclohexane layer and centrifuge to remove water. Perform the test with these solutions as directed under the Ultraviolet-visible Spectroscopy, using a solution prepared with 40 mL of diluted nitric acid (1 in 60) in the same manner as the control solution. The absorbance of the solution obtained from the test solution at the absorbance maximum wavelength around 378 nm is not greater than the absorbance of the solution obtained from the standard solution.

(3) ***Arsenic***—Proceed with 1.0 g of Thiamazole according to Method 1 and perform the test (NMT 2 ppm).

Loss on drying NMT 0.5% (1 g, 105 °C, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.25 g of Thiamazole, previously dried, dissolve in 75 mL of water, add 15 mL of 0.1 mol/L sodium hydroxide VS with a burette and add 30 mL of silver nitrate TS while stirring. Add 1 mL of bromothymol blue TS and titrate with 0.1 mol/L sodium hydroxide VS, until the solution exhibits a persistent bluish green color. Sum up the amount of 0.1 mol/L sodium hydroxide VS consumed.

Each mL of 0.1 mol/L sodium hydroxide VS
= 11.417 mg of $C_4H_6N_2S$

Packaging and storage Preserve in light-resistant, well-closed containers.

Thiamazole Tablets
티아마졸 정

Thiamazole Tablets contain NLT 94.0% and NMT 106.0% of the labeled amount of thiamazole ($C_4H_6N_2S$: 114.17).

Method of preparation Prepare as directed under Tablets, with Thiamazole.

Identification (1) Weigh an amount of Thiamazole Tablets, previously powdered, equivalent to 50 mg of thiamazole according to the labeled amount, add 20 mL of hot ethanol, shake for 15 minutes to mix, filter, and evaporate the filtrate to dryness on a steam bath. Dissolve the residue in 10 mL of water, filter, if necessary, and use the filtrate as the test solution. To 1 mL of the test solution, add 1 mL of sodium hydroxide TS, shake to mix, and add 3 drops of sodium nitroprusside TS; the solution slowly turns from yellow to yellowish green to green color. To this solution, add 1 mL of acetic acid(31); the solution turns to blue.

(2) Perform the test with 2 mL of the test solution obtained in (1), as directed under the Identification (2) under Thiamazole.

Dissolution Perform the test with 1 tablet of Thiamazole Tablets at 100 revolutions per minute according to Method 1, using 500 mL of water as the dissolution medium. Take the dissolved solution after 30 minutes from the start of the test and filter. Discard the first 10 mL of the filtrate, pipet V mL of the subsequent filtrate, add the dissolution medium to make exactly V' mL, and use this solution as the test solution. Separately, weigh accurately a suitable amount of thiamazole RS, dissolve in the dissolution medium to obtain a solution having the same concentration as the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using methanol as the control solution, and determine the absorbances, A_T and A_S, at the absorbance maximum wavelength of about 252 nm. It meets the requirements when the dissolution rate in 30 minutes is NLT 80% (Q).

Dissolution rate (%) of the labeled amount of thiamazole

$$(C_4H_6N_2S) = C_S \times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 50000$$

C_S: Concentration (mg/mL) of the standard solution

C: Amount (mg) of the labeled amount of thiamazole ($C_4H_6N_2S$) in 1 tablet

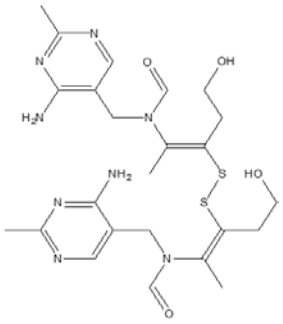
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Thiamazole Tablets, and powder. Weigh accurately an amount, equivalent to about 0.15 g of thiamazole ($C_4H_6N_2S$), add 80 mL of water, and shake for 15 minutes to mix. To this, add water to make exactly 100 mL, centrifuge, and filter. Discard the first 20 mL of the filtrate, pipet 50 mL of the subsequent filtrate, and add 1 mL of bromothymol blue TS. If the solution exhibits a blue color, neutralize it with 0.1 mol/L hydrochloric acid until it exhibits a green color. To this solution, add 4.5 mL of 0.1 mol/L sodium hydroxide solution with a burette, and mix by stirring. While stirring, add 15 mL of 0.1 mol/L silver nitrate solution and titrate with 0.1 mol/L sodium hydroxide VS until the resulting solution exhibits a persistent bluish green color. Combine the consumed amount of 0.1 mol/L sodium hydroxide solutions used throughout this process.

Each mL of 0.1 mol/L sodium hydroxide VS
= 11.417 mg of $C_4H_6N_2S$

Packaging and storage Preserve in light-resistant, well-closed containers.

Thiamine Disulfide
티아민디설피드



$C_{24}H_{34}N_8O_4S_2$: 562.71

N,*N*′-[Dithiobis[2-(2-hydroxyethyl)-1-methyl-2,1-ethenediyl]]bis[*N*-[(4-amino-2-methyl-5-pyrimidinyl)methyl] formamide], [*67-16-3*]

Thiamine Disulfide contains NLT 98.0% and NMT 102.0% of thiamine disulfide ($C_{24}H_{34}N_8O_4S_2$), calculated on the anhydrous basis.

Description Thiamine Disulfide occurs as white crystals or a crystalline powder and is odorless or has a slight, characteristic odor.

It is slightly soluble in ethanol, and practically insoluble in water or ether.

It dissolves in dilute hydrochloric acid or dilute nitric acid.

The pH of a saturated solution of Thiamine Disulfide is almost neutral.

Identification (1) Dissolve 50 mg each of Thiamine Disulfide and thiamine disulfide RS in 50 mL of ethyl acetate and use these solutions as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Then, develop the plate with a mixture of water and methanol (1 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the colors and R_f values of the spots from the test solution and the standard solution are the same.

(2) To 5 mg of Thiamine Disulfide, add 1 mL of lead acetate TS and 1 mL of sodium hydroxide solution (1 in 10) and warm the mixture; the color of the resulting solution changes to blackish brown, and when the solution is left to stand, blackish brown precipitates are formed.

(3) To 2 mL of a solution of Thiamine Disulfide in 0.1 mol/L hydrochloric acid TS (1 in 200), add 2 mL of picric acid TS; yellow precipitates are formed.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Thiamine Disulfide in 20 mL of water; the resulting solution is clear.

(2) ***Chloride***—Dissolve 0.20 g of Thiamine Disulfide in 6 mL of dilute nitric acid, add water to make 50 mL, and use this solution as the test solution to perform the test. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.053%).

(3) ***Sulfate***—Dissolve 1.5 g of Thiamine Disulfide in 6 mL of dilute hydrochloric acid, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid and 6 mL of dilute hydrochloric acid and add water to make 50 mL (NMT 0.011%).

(4) ***Nitrate***—Dissolve 0.5 g of Thiamine Disulfide in 2 mL of dilute hydrochloric acid and water to make 25 mL. To 2 mL of this solution, carefully add 2 mL of sulfuric acid while cooling in iced water, shake to mix, and superimpose iron(II) sulfate TS; no dark brown ring is formed at the interface.

(5) ***Heavy metals***—Proceed with 1.0 g of Thiamine Disulfide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(6) ***Arsenic***—Proceed with 1.0 g of Thiamine Disulfide according to Method 3 and perform the test (NMT 2

ppm).

(7) ***Thiochrome reaction-positive substance***— Weigh accurately about 0.1 g of Thiamine Hydrochloride, dissolve in 10 ml of 0.1 mol/L hydrochloric acid, add water to make exactly 100 mL, and use this solution as the test solution. Transfer exactly 2 mL each of the test solutions to glass-stoppered centrifuge tubes T and T′ and add 3 mL each of acidic potassium chloride TS. Put 3 mL of cyanogen bromide TS for thiamine assay into T, shake to mix, rapidly add 2 mL of sodium hydroxide solution (3 in 10), shake to mix, add exactly 15 mL of isobutanol, stopper the tube, and shake vigorously to mix for 2 minutes. Put 2 mL of sodium hydroxide solution (3 in 10) into T′, shake to mix, rapidly add 3 mL of sodium hydroxide solution (3 in 10), shake to mix, add 3 mL of cyanogen bromide TS for thiamine assay, shake to mix, add exactly 15 mL of isobutanol, stopper the tube, and shake vigorously to mix for 2 minutes. Separately, weigh accurately about 0.1 g of thiamine hydrochloride RS (water is determined previously) and add 10 mL of 0.1 mol/L hydrochloric acid TS and water to make exactly 200 mL. Pipet 2 mL of this solution, add 0.01 mol/L hydrochloric acid TS to make exactly 100 mL, and use this solution as the standard solution. Transfer exactly 2 mL each of the standard solutions to glass-stoppered centrifuge tubes S and S′ and proceed in the same manner as the test solution. Centrifuge each centrifuge tube at a slow rate for 2 minutes, take and transfer each isobutanol layer to another test tube. If necessary, add 1 to 2 g of anhydrous sodium sulfate, mix with gentle shaking, allow to stand and take the clear layer of isobutanol. With these solutions, perform the test as directed under the Fluorescence Spectroscopy. Determine fluorescence intensities F_T & F_T' and F_S & F_S' at maximum excitation wavelength about 370 nm and maximum fluorescence wavelength about 440 nm and convert into percentage (%) for anhydride corresponding to values obtained from the following equation and the values obtained from water; the content (%) of thiochrome reaction-positive substance is NMT 0.5%.

Amount (mg) of thiochrome reaction-positive substance
= Amount (mg) of thiamine disulfide RS, calculated on the anhydrous basis × $(F_T - F_T') / (F_S - F_S') \times 0.78 \times (1 / 500)$

0.78: Conversion factor from thiamine disulfide ($C_{12}H_{17}ClN_4OS \cdot HCl$) to thiamine ($C_{12}H_{17}N_4OS^+$)

Water NMT 10.0% (0.2 g, volumetric titration, direct titration).

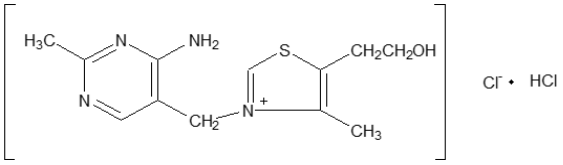
Residue on ignition NMT 0.5% (1 g).

Assay Weigh accurately about 0.4 g each of Thiamine Disulfide, dissolve in 50 mL of acetic acid(100) and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of methylrosaniline chloride TS). the endpoint of the titration is when the color of the solution changes from violet to blue. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 28.135 mg of $C_{24}H_{34}N_8O_4S_2$

Packaging and storage Preserve in light-resistant, tight containers.

Thiamine Hydrochloride
티아민염산염



Vitamin B1 Hydrochloride $C_{12}H_{17}ClN_4OS \cdot HCl$: 337.27
3-[(4-Amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-3-ium chloride hydrochloride [*67-03-8*]

Thiamine Hydrochloride contains NLT 98.5% and NMT 101.0% of thiamine hydrochloride ($C_{12}H_{17}ClN_4OS \cdot HCl$), calculated on the anhydrous basis.

Description Thiamine Hydrochloride occurs as white crystals or a crystalline powder and is odorless or has a slight, characteristic odor.
It is freely soluble in water, sparingly soluble in methanol, slightly soluble in ethanol(95), and practically insoluble in ether.

Melting point—About 245 °C (with decomposition).

Identification (1) To 5 mL of an aqueous solution of Thiamine Hydrochloride (1 in 500), add 2.5 mL of sodium hydroxide TS and 0.5 mL of potassium hexacyanoferrate(III) TS. Then, add 5 mL of 2-methyl-1-propanol, shake the mixture vigorously for 2 minutes, allow to stand and examine it under ultraviolet light (main wavelength: 365 nm); the 2-methyl-1-propanol layer exhibits a bluish purple fluorescence. This fluorescence disappears when the mixture is acidified and reappears when alkalified.

(2) Determine the absorption spectra of aqueous solutions of Timolol Maleate and timolol maleate RS as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Timolol Maleate and timolol maleate RS, previously dried at 105 °C for 2 hours, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers. If there is a difference between the two spectra, dissolve each in water, evaporate water to dryness, dry the residue at 105 °C for 2 hours and repeat the test in the same manner.

(4) An aqueous solution of Thiamine Hydrochloride

(1 in 500) responds to the Qualitative Analysis for chloride.

pH Dissolve 1.0 g of Thiamine Hydrochloride in 100 mL of water; the pH of this solution is between 2.7 and 3.4.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Thiamine Hydrochloride in 10 mL of water; the solution is clear and the color is not more intense than that of the following control solution.

Control solution—To 1.5 mL of $\frac{1}{60}$ mol/L potassium bichromate solution, add water to make 1000 mL.

(2) ***Sulfate***—Perform the test with 1.5 g of Thiamine Hydrochloride. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid (NMT 0.011%).

(3) ***Nitrate***—Dissolve 0.5 g of Thiamine Hydrochloride in 25 mL of water. Add 2 mL of sulfuric acid to 2 mL of this solution, shake to mix, cool and superimpose iron(II) sulfate TS; no dark brown ring is formed at the interface.

(4) ***Heavy metals***—Proceed with 1.0 g of Thiamine Hydrochloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(5) ***Related substances***—Dissolve 0.1 g of Thiamine Hydrochloride in 100 mL of the mobile phase and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to it make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the total area of the peaks other than the major peak is not greater than the area of the major peak from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

For system performance, proceed as directed under the system suitability under the Assay.

Test for required detectability: Pipet 5 mL of the standard solution and add water to make exactly 50 mL. Confirm that the peak area of thiamine obtained from 10 μL of this solution is equivalent to 7% to 13% of that from the standard solution.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of thiamine is NMT 1.0%.

Time span of measurement: About 3 times the retention time of thiamine.

Water NMT 5.0% (30 mg, coulometric titration).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.1 g each of Thiamine Hydrochloride and thiamine hydrochloride RS (water is determined previously) and dissolve in the mobile phase to make exactly 50 mL. Pipet 10 mL each of the solutions, add exactly 5 mL of the internal standard solution, then add the mobile phase to make exactly 50 mL and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and calculate the ratios, Q_T and Q_S, of the peak area of thiamine to that of the internal standard.

Amount (mg) of thiamine hydrochloride ($C_{12}H_{17}ClN_4OS \cdot HCl$) = Amount (mg) of thiamine hydrochloride RS, calculated on the anhydrous basis $\times \frac{Q_T}{Q_S}$

Internal standard solution—A solution of methyl benzoate in methanol (1 in 50).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Dissolve 1.1 g of sodium 1-octanesulfonate in 1000 mL of diluted acetic acid(100) (1 in 100). To 600 mL of this solution, add 400 mL of a mixture of methanol and acetonitrile (3 : 2).

Flow rate: Adjust the flow rate so that the retention time of thiamine is about 12 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; thiamine and the internal standard are eluted in this order with the resolution being NLT 6.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of thiamine is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Thiamine Hydrochloride Injection
티아민염산염 주사액

Vitamin B1 Hydrochloride Injection

Thiamine Hydrochloride Injection is an aqueous

injection and contains NLT 95.0% and NMT 115.0% of the labeled amount of thiamine hydrochloride ($C_{12}H_{17}ClN_4OS \cdot HCl$: 337.27).

Method of preparation Prepare as directed under Injections, with Thiamine Hydrochloride.

Description Thiamine Hydrochloride Injection occurs as a clear, colorless liquid.

pH—Between 2.5 and 4.5.

Identification To an amount of Thiamine Hydrochloride Injection equivalent to 50 mg of Thiamine Hydrochloride according to the labeled amount, add water to make 25 mL. Perform the test with 5 mL of this solution as directed under the Identification (1) of Thiamine Hydrochloride.

Sterility Meets the requirements.

Bacterial endotoxins Less than 6.0 EU per mg of thiamine hydrochloride

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Thiamine Hydrochloride Injection equivalent to about 20 mg of thiamine hydrochloride ($C_{12}H_{17}ClN_4OS \cdot HCl$), diluted with 0.001 mol/L hydrochloric acid TS, if necessary, add 20 mL of methanol, and add 0.001 mol/L hydrochloric acid TS to make exactly 100 mL. Pipet 25 mL of this solution, add 5 mL of the internal standard solution, and 0.001 mol/L hydrochloric acid TS to make 50 mL, and use the resulting solution as the test solution. Separately, weigh accurately about 0.1 g of thiamine hydrochloride RS (previously determined the water) and dissolve 0.001 mol/L hydrochloric acid TS to make exactly 50 mL. Pipet 10 mL of this solution, add 20 mL of methanol, and add 0.001 mol/L hydrochloric acid TS to make exactly 100 mL. Pipet 25 mL of this solution, add exactly 5 mL of the internal standard solution, add 0.001 mol/L hydrochloric acid TS to make exactly 50 mL, and use the resulting solution as the standard solution. Perform the test as directed under the Assay under Thiamine Hydrochloride.

Amount (mg) of thiamine hydrochloride ($C_{12}H_{17}ClN_4OS \cdot HCl$)
= Amount (mg) of thiamine hydrochloride RS (calculated on the anhydrous basis) $\times \frac{Q_T}{Q_S} \times \frac{1}{5}$

Internal standard solution—A solution of methyl benzoate in methanol (1 in 200).

Packaging and storage Preserve in light-resistant, tight containers.

Thiamine Hydrochloride Tablets
티아민염산염 정

Vitamin B1 Hydrochloride Tablets

Thiamine Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of thiamine hydrochloride ($C_{12}H_{17}ClN_4OS \cdot HCl$: 337.27).

Method of preparation Prepare as directed under Tablets, with Thiamine Hydrochloride.

Identification (1) Weigh an amount of Hydrochloride Tablets, previously powdered, equivalent to 10 mg of thiamine hydrochloride according to the labeled amount, add 10 mL of 0.5 mol/L sodium hydroxide TS, and filter. Perform the test with 5 mL of the filtrate as directed under the Identification (2) under Thiamine Hydrochloride.

(2) Weigh an amount of Thiamine Hydrochloride Tablets, previously powdered, equivalent to 10 mg of thiamine hydrochloride according to the labeled amount, add 10 mL of water, and filter. To 2 mL of the filtrate, add iodine TS and silver nitrate TS (1 in 20); a reddish brown precipitate and a black precipitate are formed, respectively.

(3) To the filtrate obtained in (2), add 1 mL of lead acetate TS and 1 mL of 2.5 mol/L sodium hydroxide solution; the resulting solution exhibits a yellow color. Heat it on a steam bath for several minutes; the resulting solution turns to a brown color and a lead sulfide precipitate is separated.

(4) The filtrate obtained in (2) responds to the Qualitative Analysis for chloride.

Dissolution Perform the test with 1 tablet of Thiamine Hydrochloride Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution medium. Take the dissolution medium 45 minutes after starting the test, filter, use it as the test solution, and perform the test as directed under the Assay. If necessary, weigh accurately a suitable amount of thiamine hydrochloride RS, proceed in the same manner as in the preparation of the test solution, use the resulting solution as the standard solution, and perform the test.

It meets the requirements when the dissolution rate of Thiamine Hydrochloride Tablets in 45 minutes is NLT 75%.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Thiamine Hydrochloride Tablets and powder. Weigh accurately an amount, equivalent to about 20 mg of thiamine hydrochloride ($C_{12}H_{17}ClN_4OS \cdot HCl$), add 60 mL of 0.01 mol/L hydrochloric acid TS, heat on a steam bath for

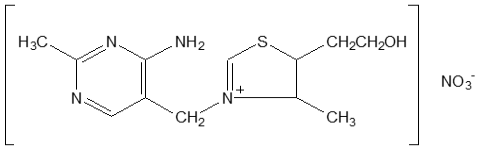
30 minutes, and shake vigorously for 10 minutes to mix. After cooling, add methanol to make exactly 100 mL, and centrifuge. Pipet 25 mL of the clear supernatant, add exactly 5 mL of the internal standard solution, then add water to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of thiamine hydrochloride RS (previously measured the water content in the same manner as in Thiamine Hydrochloride), and dissolve in 0.01 mol/L hydrochloric acid TS to make exactly 50 mL. Pipet 10 mL of this solution, add 50 mL of 0.01 mol/L hydrochloric acid TS, and add methanol to make exactly 100 mL. Pipet 25 mL of this solution, add exactly 5 mL of the internal standard solution, add water to make 50 mL, and use this solution as the standard solution. Perform the test as directed under the Assay under Thiamine Hydrochloride.

Amount (mg) of thiamine hydrochloride ($C_{12}H_{17}ClN_4OS \cdot HCl$)
= Amount (mg) of thiamine hydrochloride RS, calculated on the anhydrous basis $\times \frac{Q_T}{Q_S} \times \frac{1}{5}$

Internal standard solution—A solution of methyl benzoate in methanol (1 in 200).

Packaging and storage Preserve in light-resistant, tight containers.

Thiamine Nitrate
티아민질산염



Vitamin B1 Nitrate $C_{12}H_{17}N_5O_4S$: 327.36
3-[(4-Amino-2-methylpyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-3-ium chloride nitrate [*532-43-4*]

Thiamine Nitrate, when dried, contains NLT 98.0% and NMT 102.0% of thiamine nitrate ($C_{12}H_{17}N_5O_4S$).

Description Thiamine Nitrate occurs as white crystals or a crystalline powder. It is odorless or has a slight, characteristic odor.
It is sparingly soluble in water, very slightly soluble in ethanol(95) and practically insoluble in ether.

Melting point—About 193 °C (with decomposition).

Identification (1) Determine the infrared spectra of Thiamine Nitrate and thiamine nitrate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Thiamine Nitrate (1 in 50) responds to the Qualitative Analysis (1) and (2) for nitrate.

pH Dissolve 1.0 g of Thiamine Nitrate in 100 mL of water; the pH of this solution is between 6.5 and 8.0.

Purity (1) ***Chloride***—Perform the test with 0.20 g of Thiamine Nitrate. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid solution (NMT 0.053%).

(2) ***Sulfate***—Dissolve 1.5 g of Thiamine Nitrate in 30 mL of water and 2 mL of dilute hydrochloric acid, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid and 2 mL of dilute hydrochloric acid and add water to make 50 mL (NMT 0.011%).

(3) ***Heavy metals***—Dissolve about 1.0 g of Thiamine Nitrate in 30 mL of water by warming, cool, and add 12 mL of 6 mol/L acetic acid TS and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Related substances***—Weigh accurately 0.1 g of Thiamine Nitrate, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. With 10 μL of the test solution, perform the test as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of this solution by the automatic integration method; the total area of the peaks other than the major peak from the test solution is NMT 1.0% of the area of all peaks from the test solution.

Operating conditions

For the detector, column temperature, and mobile phase, proceed as directed in the operating conditions under the Assay.

Column: A stainless steel column about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Flow rate: 0.75 mL/min

Time span of measurement: About 3 times the peak retention time of thiamine.

Loss on drying NMT 1.0% (0.5 g, 105 °C, 2 hours).

Residue on ignition NMT 0.2% (1 g).

Assay Weigh accurately about 0.1 g each of Thiamine Nitrate, previously dried, and thiamine hydrochloride RS (previously determined the water) and dissolve each of them in the mobile phase to make exactly 50 mL. Pipet 10 mL each of these solutions, add exactly 5 mL each of the internal standard solution, add the mobile phase to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and calcu-

late the peak area ratios, Q_T and Q_S, of thiamine to that of the internal standard.

Amount (mg) of thiamine nitrate ($C_{12}H_{17}N_5O_4S$)
= Amount of thiamine hydrochloride RS calculated on the anhydrous basis (mg)$\times \frac{Q_T}{Q_S} \times 0.9706$

Internal standard solution—A solution of methyl benzoate in methanol (1 in 50).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: Dissolve 1.1 g of sodium 1-octanesulfonate in 1000 mL of diluted acetic acid(100) (1 in 100). To 600 mL of this solution, add 400 mL of a mixture of methanol and acetonitrile (3 : 2).

Flow rate: Adjust the flow rate so that the retention time of thiamine is about 12 minutes.

System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; thiamine and the internal standard are eluted in this order with the resolution being NLT 6.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above conditions; the relative standard deviation of the ratios of the peak area of thiamine to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

33.3% Thiamine Nitrate Powder
티아민질산염 3배산

33.3% Thiamine Nitrate Powder contains NLT 32.6% of thiamine nitrate ($C_{12}H_{17}N_5O_4S$: 327.36).

Method of preparation Prepare by finely dispersing Thiamine Nitrate in edible fatty acid. 33.3% Thiamine Nitrate Powder is a drug substance.

Description 33.3% Thiamine Nitrate Powder occurs as a white to pale yellow powder.

Identification (1) Take 2 mL each of aqueous solution of 33.3% Thiamine Nitrate Powder (1 in 500) and add 2 to 3 drops of iodine TS; a reddish brown precipitate or turbidity is formed. Add 1mL of picric acid TS; a yellow precipitate or turbidity is formed.

(2) Add 1 mL of lead acetate TS and 1 mL of sodium hydroxide solution (1 in 10) to 5 mL of aqueous solution of 33.3% Thiamine Nitrate Powder (1 in 500) and warm; the solution turns yellow and then brown. Allow to stand; a blackish brown precipitate is formed.

(3) Weigh accurately an amount of 33.3% Thiamine Nitrate Powder, equivalent to 10 mg of thiamine nitrate, dissolve in 5 mL of methanol, filter, and use the filtrate as the test solution. Separately, weigh accurately about 10 mg of thiamine nitrate RS, dissolve in methanol to make 5 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescence indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, acetic acid(100) and acetone (9 : 4 : 1) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f value and the color of the spots obtained from the test solution and the standard solutions are the same.

(4) An aqueous solution of 33.3% Thiamine Nitrate Powder (1 in 50) responds to the Qualitative Analysis (1) and (2) for nitrate.

Water NMT 1.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh 0.1 g of 33.3% Thiamine Nitrate Powder, previously dried, and about 30 mg of thiamine nitrate RS (previously determined the water), and add the mobile phase to make 50 mL, respectively. Take 10.0 mL each of these solutions, add exactly 5.0 mL of the internal standard solution, then add the mobile phase to make 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S of thiamine to that of the internal standard.

Amount (mg) of thiamine nitrate ($C_{12}H_{17}N_5O_4S$)
= Amount (mg) of thiamine nitrate RS, calculated on the anhydrous basis (mg)$\times \frac{Q_T}{Q_S}$

Internal standard solution—A solution of methyl benzoate in methanol (1 in 50).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Dissolve 1.1 g of sodium 1-octanesulfonate in 1000 mL of diluted acetic acid(100) (1

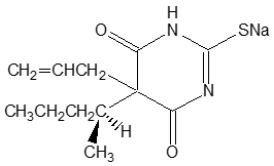
in 100). To 600 mL of this solution, add 400 mL of a mixture of methanol and acetonitrile (3 : 2).

Flow rate: Adjust the flow rate so that the retention time of thiamine is about 12 minutes.

Selection of column: Proceed with 10 μL of the standard solution under the above conditions; thiamine and the internal standard are eluted in this order with the resolution being NLT 5.

Packaging and storage Preserve in light-resistant, tight containers.

Thiamylal Sodium
티아밀랄나트륨



and enantiomer

$C_{12}H_{17}N_2NaO_2S$: 276.33

Sodium 5-allyl-6-oxo-5-(2-pentanyl)-2-thioxo-1,2,5,6-tetrahydro-4-pyrimidinolate [*337-47-3*]

Thiamylal Sodium, when dried, contains NLT 98.0% and NMT 102.0% of thiamylal sodium ($C_{12}H_{17}N_2NaO_2S$).

Description Thiamylal Sodium occurs as pale yellow crystals or a powder.
It is very soluble in water, and freely soluble in ethanol(95).
Dissolve 1.0 g of Thiamylal Sodium in 10 mL of water; the pH of the solution is between 10.0 and 11.0.
It is hygroscopic.
It is gradually decomposed by light.
Its solution in ethanol(95) (1 in 10) shows no optical rotation.

Identification (1) Determine the absorption spectra of solutions of Thiamylal Sodium and thiamylal sodium RS in ethanol (7 in 1000000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Thiamylal Sodium and thiamylal sodium RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Thiamylal Sodium (1 in 10) responds to the Qualitative Analysis for sodium salt.

Purity (1) ***Clarity and color of solution***—To 1.0 g of Thiamylal Sodium in a 11- to 13-mL glass-stoppered test tube, add 10 mL of freshly boiled and cooled water, stopper the test tube, allow to stand and dissolve by gently shaking; the resulting solution is clear and pale yellow.

(2) ***Heavy metals***—Proceed with 1.0 g of Thiamylal Sodium according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Related substances***—Dissolve about 1 g of Thiamylal Sodium in 10 mL of ethanol(95) and use this solution as the test solution. Pipet 1 mL and 3 mL of the test solution, respectively, add ethanol(95) to make exactly 200 mL, and use these solutions as the standard solution (1) and the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solutions (1) and (2) on a plate of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of toluene, methanol and ethyl acetate (40 : 7 : 3) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Allow the plate to stand in iodine vapor overnight; the spots with a R_f value of about 0.1 obtained from the test solution are not more intense than the spots obtained from the standard solution (2). Also, the spots other than the principal spot of the test solution, the spot at origin and the spot mentioned above are not more intense than the spots obtained from the standard solution (1).

Loss on drying NMT 2.0% (1 g, 105 ℃, 1 hour).

Assay Weigh accurately about 0.25 g of Thiamylal Sodium, dissolve in 50 mL of methanol and 5 mL of dilute hydrochloric acid, and add methanol to make exactly 100 mL. Pipet 10 mL of this solution and add methanol to make exactly 100 mL. Pipet 5 mL of this solution, add exactly 10 mL of the internal standard solution and the mobile phase to make exactly 200 mL, and use this solution as the test solution. Separately, weigh accurately about 23 mg of thiamylal RS, previously dried at 105 ℃ for 1 hour, dissolve in 50 mL of methanol and 0.5 mL of dilute hydrochloric acid, and add methanol to make exactly 100 mL. Pipet 5 mL of this solution, add exactly 10 mL of the internal standard solution and the mobile phase to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, of thiamylal to that of the internal standard.

$$\text{Amount (mg) of thiamylal sodium } (C_{12}H_{17}N_2NaO_2S) = \text{Amount (mg) of thiamylal RS} \times \frac{Q_T}{Q_S} \times 10 \times 1.0864$$

Internal standard solution—A solution of phenyl benzoate in methanol (3 in 500).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 289 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanised silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of methanol, 0.05 mol/L acetic acid of pH 4.6, and sodium acetate buffer solution (13 : 7).

Flow rate: Adjust the flow rate so that the retention time of thiamylal is about 6 minutes.

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above conditions; thiamylal and the internal standard are eluted in this order with the resolution being NLT 12.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the ratios of the peak area of thiamylal to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Thiamylal Sodium for Injection
주사용 티아밀랄나트륨

Thiamylal Sodium for Injection is an injection dissolved before use. Thiamylal Sodium for Injection contains NLT 93.0% and NMT 107.0% of the labeled amount of thiamylal sodium ($C_{12}H_{17}N_2NaO_2S$).

Method of preparation Prepare as directed under Injections, with a mixture of Thiamylal Sodium and Dried Sodium Carbonate at the mass ratio of 100 : 7.

Description Thiamylal Sodium for Injection occurs as a pale yellow crystal, powder or a mass.
It is hygroscopic.
It is slowly decomposed by light.

Identification (1) Proceed with 1.0 g of Thiamylal Sodium for Injection, add 20 mL of ethanol(95), shake vigorously to mix, and filter. Dissolve the residue in 1 mL of water and add 1 mL of barium chloride TS; a white precipitate is formed. Also, centrifuge the solution, gently remove the clear supernatant, and add dilute hydrochloric acid dropwise to the precipitate; the precipitate is dissolved while forming bubbles.

(2) Proceed with 50 mg of Thiamylal Sodium for Injection, add 100 mL of ethanol(95), shake vigorously to mix, and filter. To 3 mL of the filtrate, add ethanol(95) to make 200 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 236 nm and 240 nm and between 287 nm and 291 nm.

pH Dissolve 1.0 g of Thiamylal Sodium for Injection in 40 mL of water; the pH of this solution is between 10.5 and 11.5.

Purity ***Related substances***—Proceed with 1.0 g of Thiamylal Sodium for Injection, add 10 mL of ethanol(95), shake vigorously to mix, and filter. Use the resulting solution as the test solution. Perform the test as directed under the Purity (3) under Thiamylal Sodium.

Sterility Meets the requirements.

Bacterial endotoxins Less than 1.0 EU per mg of Thiamylal Sodium for Injection

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

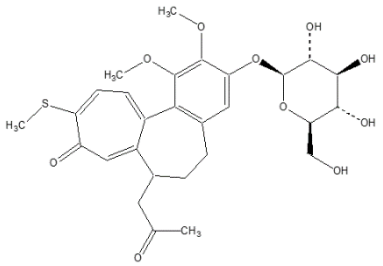
Assay Carefully open 10 units of Thiamylal Sodium for Injection, dissolve the content in water, wash each container with water, and combine the washings with the previously dissolved solution. To this, add water to make exactly *V* mL having a known concentration of about 5 mg of thiamylal sodium ($C_{12}H_{17}N_2NaO_2S$) per mL. Pipet 5 mL of this solution, add 0.5 mL of dilute hydrochloric acid, and add methanol to make exactly 100 mL. Pipet 5 mL of this solution, add exactly 10 mL of the internal standard solution, add the mobile phase to make 200 mL, and use the resulting solution as the test solution. Perform the test as directed under the Assay under Thiamylal Sodium.

Amount (mg) of thiamylal sodium ($C_{12}H_{17}N_2NaO_2S$) in 1 unit of Thiamylal Sodium for Injection
= Amount (mg) of thiamylal sodium RS
$\times \frac{Q_T}{Q_S} \times \frac{V}{50} \times 1.0864$

Internal standard solution—A solution of phenyl benzoate in methanol (3 in 500).

Packaging and storage Preserve in light-resistant, hermetic containers.

Thiocolchicoside
티오콜키코시드



$C_{27}H_{33}NO_{10}S$: 563.62
N-[(7*S*)-3-(β-*D*-Glucopyranosyloxy)-5,6,7,9-tetrahydro-1,2-dimethoxy-10-(methylthio)-9-oxobenzo[a]heptalen-7-yl]-acetamide, [*602-41-5*]

Thiocolchicoside contains NLT 98.5% and NMT 101.0% of thiocolchicoside ($C_{27}H_{33}NO_{10}S$) and NLT 5.5% and NMT 5.9% of sulfur (S), calculated on the dried basis.

Description Thiocolchicoside occurs as a yellow crystalline powder.
It is soluble in water and methanol, and practically insoluble in ethanol and chloroform.

Identification Dissolve 50 mg of Thiocolchicoside and thiocolchicoside RS in 10 mL of methanol, and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of 1-butanol, water and acetic acid (4 : 1 : 1) as the developing solvent and air-dry the plate. Spray evenly with a mixture of chlorosulfuric acid and acetic acid (1 : 1); the R_f values of spots obtained from the test solution and the standard solution are the same.

Optical rotation $[\alpha]_D^{20}$: Between -580° and -610° (after drying, 10 mg, water, 100 mL).

Absorbance $E_{1cm}^{1\%}$ (260 nm): Between 380 and 400 (after drying, 10 mg, water, 1000 mL).
$E_{1cm}^{1\%}$ (372 nm): Between 322 and 338 (after drying, 10 mg, water, 1000 mL).

Purity ***Colchicoside and other impurities***—Dissolve 0.25 g of Thiocolchicoside in anhydrous ethanol to make 10 mL and use this solution as the test solution. Separately, weigh accurately about 0.125 g of colchicoside RS and add methanol to make 20 mL. Take 1,2,4 and 8 mL each of this solution, add methanol to make 100 mL, and use these solutions as the standard solutions a,b,c and d. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of 1-butanol, water and acetic acid (4 : 1 : 1) as the developing solvent and air-dry the plate. Spray evenly with a mixture of chlorosulfuric acid and acetic acid (1 : 1) and examine the plate under ultraviolet light: the spot of the test solution appearing at the same R_f value (R_f value: about 0.35) as that of the standard solution is not greater or more intense than the spots from the standard solution c. The number of spots of impurities other than the principal spot from the test solution and the spot of colchicoside is 2 to 3, and these spots are not greater or more intense than the spots from the standard solution a.

Loss on drying NMT 3.0% (1 g, 105 °C, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay (1) ***Thiocolchicoside***—Weigh accurately about 0.35 g of Thiocolchicoside, dissolve in 5 mL of acetic acid(100), add 50 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 56.36 mg of $C_{27}H_{33}NO_{10}S$

(2) ***Sulfur***—Weigh accurately about 0.1 g of Thiocolchicoside and perform the test as directed under the sulfur assay under the Oxygen Flask Combustion. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.005 mol/L barium perchlorate VS
= 0.1603 mg of S

Packaging and storage Preserve in tight containers.

Thiocolchicoside Capsules
티오콜키코시드 캡슐

Thiocolchicoside Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of thiocolchicoside ($C_{27}H_{33}NO_{10}S$: 563.62).

Method of preparation Prepare as directed under Capsules, with Thiocolchicoside.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Purity ***Colchicoside***—Weigh accurately the mass of the contents of about 10 Thiocolchicoside Capsules. Weigh accurately an amount equivalent to about 4 mg of thiocolchicoside ($C_{27}H_{33}NO_{10}S$) and add water to make exactly 100 mL. Filter this solution through a 0.45 μm membrane filter and use the filtrate as the test solution.

Separately, weigh accurately about 40 mg of colchicoside RS and add water to make 100 mL. To 10.0 mL of this solution, add water to make 100 mL, filter through a 0.45 μm membrane filter, and use the filtrate as the test solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and calculate the peak areas, A_T and A_S, of colchicoside for each solution; the amount of colchicoside is NMT 1.0% for the labeled amount of thiocolchicoside.

$$\text{Amount (mg) of colchicoside} = \text{Amount (mg) of colchicoside RS} \times \frac{A_T}{A_S} \times \frac{1}{1000}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: 16% acetonitrile

Flow rate: 2 mL/min

Dissolution Perform the test with 1 capsule of Thiocolchicoside Capsules at 100 revolutions per minute according to Method 2, using 500 mL of water as the dissolution medium. Take the dissolved solution after 45 minutes from the start of the test and filter. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add water to obtain a solution having known concentration of about 4 μg of thiocolchicoside per mL according to the labeled amount and to make exactly *V' mL*, and use this solution as the test solution. Separately, weigh accurately about 40 mg of thiocolchicoside RS and add water to make 100 mL. Pipet 2 mL of this solution, add water to make 200 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of thiocolchicoside, A_T and A_S, in each solution. The acceptable dissolution criterion is NLT 75% of Thiocolchicoside Capsules dissolved in 30 minutes.

$$\text{Dissolution rate (\%) with respect to the labeled amount of thiocolchicoside } (C_{27}H_{33}NO_{10}S) = W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C}$$

Ws: Amount (mg) of thiocolchicoside RS

C: Labeled amount (mg) of thiocolchicoside ($C_{27}H_{33}NO_{10}$) in 1 capsule

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 370 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of water and acetonitrile (84 : 16).

Flow rate: 1.5 mL/min

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the contents of 20 capsules of Thiocolchicoside Capsules. Weigh accurately about 4 mg of thiocolchicoside ($C_{27}H_{33}NO_{10}$), add water to make 100 mL, filter through a 0.45 μm membrane filter, and use the filtrate as the test solution. Separately, weigh accurately about 40 mg of thiocolchicoside RS and add water to make 100 mL. Pipet 10.0 mL of this solution, add water to make 100 mL, filter through 0.45 μm filters, and use the filtrate as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of thiocolchicoside, respectively.

$$\text{Amount (mg) of thiocolchicoside } (C_{27}H_{33}NO_{10}S) = \text{Amount (mg) of thiocolchicoside RS} \times \frac{A_T}{A_S} \times \frac{1}{10}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 370 nm).

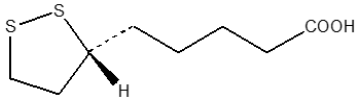
Column: A stainless steel column about 4 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: 16% acetonitrile

Flow rate: 2 mL/min

Packaging and storage Preserve in tight containers.

Thioctic Acid
티옥트산



and enantiomer

$C_8H_{14}O_2S_2$: 206.33

1,2-Dithiolane-3-pentanoic acid, [1077-28-7]

Thioctic Acid, when dried, contains NLT 97.0% and NMT 101.0% of thioctic acid ($C_8H_{14}O_2S_2$).

Description Thioctic Acid occurs as pale yellow or yellow crystals or a crystalline powder and is odorless.

It is freely soluble in dimethylformamide or chloroform, soluble in ethanol, acetone or ether and insoluble in wa-

ter.

Identification (1) Weigh 5 mg of Thioctic Acid, dissolve in 1 mL of ethanol, and use this solution as the test solution. Separately, dissolve 5 mg of thioctic acid RS in 1 mL of ethanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography, develop the plate with a mixture of 1-butanol, ammonia and ethanol (8 : 3 : 2) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light; the R_f values of the spots obtained from the test solution and standard solution are the same.

(2) To 5 mL of ethanol solution of Thioctic Acid (1 in 100), add 10 mL of dilute hydrochloric acid and 1 g of zinc powder. Shake vigorously for 20 minutes, and then filter. Continue adding 10% ammonia water until the white precipitates formed in this filtrate are dissolved, and then add 2 to 3 drops of sodium nitroprusside TS. It will soon exhibits a magenta color and then fade.

Melting point Between 59 and 63 °C.

Purity (1) ***Chloride***—Dissolve 0.2 g of Thioctic Acid in 100 mL of ethanol (6 in 10) mixture. Perform the test with 50 mL of this solution. Prepare the control solution with 0.2 mL of 0.01 mol/L hydrochloric acid solution (NMT 0.071%).

(2) ***Sulfate***—Take 50 mL of the solution from (1) and perform the test. Prepare the control solution with 0.4 mL of 0.005 mol/L sulfuric acid (NMT 0.192%).

(3) ***Heavy metals***—Weigh 1.0 g of Thioctic Acid, put in a crucible, heat it slowly below 500℃, add 5 mL of dilute hydrochloric acid to the residue, and evaporate to dryness on a steam bath. Dissolve the residue in 2 mL of dilute acetic acid. If necessary, filter and add water to make 50 mL, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Loss on drying NMT 1.0% (1.0 g, phosphorus pentoxide, 2 kPa, 18 hours).

Residue on ignition NMT 0.1% (0.5 g).

Assay Weigh accurately about 5 mg of Thioctic Acid, previously dried, add chloroform to make 100.0 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of thioctic acid RS dried in a sulfuric acid desiccator for 4 hours, and dissolve in chloroform to make 100.0 mL. Take accurately 10.0 mL of this solution, add chloroform to make 100.0 mL, and use this solution as the standard solution. Take 2.0 mL each of the test solution, standard solution, and chloroform, slowly evaporate to dryness on a steam bath at 70 °C, and cool. To the residue, add 2 mL of the solution prepared by 0.4 g of 2,6-dibromoquinonechlorimide dissolved in 95% ethanol to make 100 mL. After stoppering, allow to stand for 15 minutes, add 10 mL of potassium chloride and hydrochloric acid buffer at pH 2.2, and add 95% ethanol to make 25.0 mL. Determine the absorbances of A_S and A_T at 440 nm as directed under the Ultraviolet-visible Spectroscopy using the blank test solution as the control solution.

$$\text{Amount (mg) of thioctic acid } (C_8H_{14}O_2S_2) = \text{amount (mg) of thioctic acid RS} \times \frac{A_T}{A_S} \times \frac{1}{10}$$

Packaging and storage Preserve in well-closed containers.

Thioctic Acid Injection
티옥트산 주사액

Thioctic Acid Tablets contain NLT 90.0% and NMT 130.0% of the labeled amount of thioctic acid ($C_8H_{14}O_2S_2$: 206.33).

Method of preparation Prepare as directed under Injections, with Thioctic Acid.

Identification The retention times of the major peaks obtained from the test solution and standard solution under the Assay are the same.

pH Between 7.5 and 9.5.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Thioctic Acid Injection, equivalent to 50 mg of thioctic acid ($C_8H_{14}O_2S_2$) according to the labeled amount, add methanol to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of thioctic acid RS, proceed in the same manner as the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of thioctic acid in each solution.

$$\text{Amount (mg) of thioctic acid } (C_8H_{14}O_2S_2) = \text{Amount (mg) of thioctic acid RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of 0.1% phosphoric acid and acetonitrile (60 : 40).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in light-resistant, hermetic containers (in a cold place).

Thioctic Acid Tablets
티옥트산 정

Thioctic Acid Tablets contain NLT 90.0% and NMT 130.0% of the labeled amount of thioctic acid ($C_8H_{14}O_2S_2$: 206.33).

Method of preparation Prepare as directed under Tablets, with Thioctic Acid.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Dissolution Perform the test with 1 tablet of Thioctic Acid Tablets at 100 revolutions per minute according to Method 2, using 500 mL of pH 6.8 phosphate buffer solution as the dissolution medium. Take the dissolved solution after 45 minutes from the start of the test and filter. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add water to make *V'* mL of a solution containing about 0.4 mg of thioctic acid per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 40 mg of thioctic acid RS, dissolve in 10 mL of methanol, add the dissolution medium to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of thioctic acid in each solution. Meets the requirements if the dissolution rate of Thioctic Acid Tablets in 45 minutes is NLT 75%.

Dissolution rate (%) of the labeled amount of thioctic acid ($C_8H_{14}O_2S_2$)

$$= W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 500$$

W_S: Amount (mg) of thioctic acid RS

C: Labeled amount (mg) of thioctic acid ($C_8H_{14}O_2S_2$) in 1 tablet

pH 6.8 phosphate buffer solution—Dissolve 137.6 g of sodium dihydrogen phosphate monohydrate and 23.9 g of citric acid hydrate in water to make 5000 mL, and adjust the pH to 6.8.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (about 5 μm in particle diameter).

Mobile phase: Adjust the pH of a mixture of methanol, 0.005 mol/L potassium dihydrogen phosphate solution and acetonitrile (117 : 91 : 18) with phosphoric acid (8.3 in 100) to between 3.0 and 3.1.

Flow rate: 1.3 mL/min

System suitability

System performance: Proceed with 50 μL of the standard solution according to the above conditions; the symmetry factor is NMT 2.0.

System repeatability: Repeat the test 5 times with 50 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area of thioctic acid is NMT 2.0%.

0.005 mol/L potassium dihydrogen phosphate solution—Dissolve 1.36 g of potassium dihydrogen phosphate in water to make 2000 mL.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Thioctic Acid Tablets, and powder. Weigh accurately an amount of Thioctic Acid Tablets, equivalent to about 0.5 mg of thioctic acid ($C_8H_{14}O_2S_2$), according to the labeled amount, add methanol to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of thioctic acid RS, proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of thioctic acid in each solution.

Amount (mg) of thioctic acid ($C_8H_{14}O_2S_2$)

$$= \text{Amount (mg) of thioctic acid RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

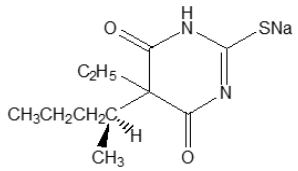
Column: A stainless steel column about 4 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of 0.1% phosphoric acid and acetonitrile (60 : 40).

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Thiopental Sodium
티오펜탈나트륨


and enantiomer

$C_{11}H_{17}N_2NaO_2S$: 264.32
Sodium 5-ethyl-4,6-dioxo-5-pentan-2-yl-1*H*-pyrimidine-2-thiolate [*71-73-8*]

Thiopental Sodium, when dried, contains NLT 97.0% and NMT 101.0% of thiopental sodium ($C_{11}H_{17}N_2NaO_2S$).

Description Thiopental Sodium occurs as a pale yellow powder and has a faint, characteristic odor.
It is very soluble in water, freely soluble in ethanol(95) and practically insoluble in ether.
A solution of Thiopental Sodium in 10 mL of water is alkaline.
It is hygroscopic.
Allow to stand an aqueous solution of Thiopental Sodium; it is gradually decomposed.

Identification (1) Dissolve 0.2 g of Thiopental Sodium in 5 mL of sodium hydroxide TS and add 2 mL of lead acetate TS; a white precipitate is formed. The precipitate dissolves when heated, while a black precipitate is gradually formed when re-boiled. Also, the precipitate responds to the Qualitative Analysis for sulfide.

(2) Dissolve 0.5 g of Thiopental Sodium in 15 mL of water, add 10 mL of dilute hydrochloric acid; a white precipitate is formed. Extract this four times with each 25 mL of chloroform. Combine the chloroform extracts, evaporate on a steam bath and dry at 105 °C for 2 hours; the melting point of the residue is between 157 and 162 °C.

(3) An aqueous solution of Thiopental Sodium (1 in 10) responds to the Qualitative Analysis (1) and (2) for sodium salt.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Thiopental Sodium in 10 mL of freshly boiled and cooled water; the resulting solution is clear and pale yellow.

(2) ***Heavy metals***—Dissolve 2.0 g of Thiopental Sodium in 76 mL of water, add 4 mL of dilute hydrochloric acid, shake to mix and filter through a glass filter (G4). To 40 mL of the filtrate, add 2 mL of ammonium acetate TS, and add water to make 50 mL. Use this solution as the test solution and perform the test. Prepare a control solution by adding 2 mL of dilute acetic acid, 2 mL of ammonium acetate TS and water to 2.0 mL of lead standard solution to make 50 mL (NMT 20 ppm).

(3) ***Neutral and basic substances***—Weigh accurately about 1.0 g of Thiopental Sodium, dissolve in 10 mL of water and 5 mL of sodium hydroxide TS, add 40 mL of chloroform and shake to mix well. Separate the chloroform layer, wash the layer twice with 5 mL each of water, filter and evaporate the filtrate on a steam bath to dryness. Dry the residue at 105 °C for 1 hour; the amount of the residue is NMT 0.50%.

(4) ***Related substances***—Dissolve 50 mg of Thiopental Sodium in 50 mL of the mobile phase and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to it make exactly 200 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the total area of the peaks of thiopental from the test solution is not greater than the peak area of thiopental from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 1 g of potassium dihydrogen phosphate in 1000 mL of water and adjust the pH to 3.0 with phosphoric acid. To 700 mL of this solution, add 300 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of thiopental is about 15 minutes.

System suitability

Test for required detectability: Take exactly 2 mL of the standard solution, and add the mobile phase to make exactly 10 mL. Confirm that the peak area of thiopental obtained from 20 μL of this solution is equivalent to 15% to 25% of that of thiopental obtained from the standard solution.

System performance: Dissolve 5 mg each of isopropyl p-hydroxybenzoate and propyl p-hydroxybenzoate in 50 mL of acetonitrile and add water to make 100 mL. Proceed with 20 μL of this solution under the above operating conditions; isopropyl p-hydroxybenzoate and propyl p-hydroxybenzoate are eluted in this order with the resolution being NLT 1.9.

Time span of measurement: About 1.5 times the retention time of thiopental.

Loss on drying NMT 2.0% (1 g, in vacuum, 80 °C, 4 hours).

Assay Weigh accurately about 0.5 g of Thiopental Sodium, previously dried, put into a separatory funnel, dissolve in 20 mL of water, add 5 mL of ethanol(95) and 10 mL of dilute hydrochloric acid, and extract with 50 mL of chloroform, Then, extract three times with 25 mL each of

chloroform. Combine the chloroform extracts, wash twice with 5 mL each of water and extract the washings twice with 10 mL each of chloroform. Combine the chloroform extracts and filter into an Erlenmeyer flask. Wash the filter paper three times with 5 mL each of chloroform. Combine the filtrate and the washings and add 10 mL of ethanol(95). Titrate with 0.1 mol/L potassium hydroxide-ethanol VS (indicator: 2 mL of alizarin yellow GG-thymolphthalein TS). However, the endpoint of the titration is when the color of the solution changes from yellow through pale blue to violet. Perform a blank test in the same manner with a solution of 30 mL of ethanol(95) in 160 mL of chloroform and make any necessary correction.

Each mL of 0.1 mol/L potassium hydroxide VS
= 26.43 mg of $C_{11}H_{17}N_2NaO_2S$

Packaging and storage Preserve in light-resistant, tight containers.

Thiopental Sodium for Injection
주사용 티오펜탈나트륨

Thiopental Sodium for Injection is a preparation for injection which is dissolved before use. Thiopental Sodium for Injection contains NLT 93.0% and NMT 107.0% of the labeled amount of thiopental sodium ($C_{11}H_{17}N_2NaO_2S$: 264.32).

Method of preparation Prepare as directed under Injections with Thiopental Sodium and dried sodium carbonate mixed at a mass ratio of 100 : 6.

Description Thiopental Sodium for Injection occurs as a pale yellow powder or a mass with a slightly characteristic odor.
It is very soluble in water and practically insoluble in dehydrated ether.
It is hygroscopic.

Identification (1) Dissolve 0.1 g of Thiopental Sodium for Injection in 10 mL of water, then add 0.5 mL of barium chloride TS; a white precipitate is formed. Collect the precipitate and add dilute hydrochloric acid dropwise: the precipitate dissolves with effervescence.

(2) Perform the test as directed under the Identification of Thiopental sodium.

pH Dissolve 1.0 g of Thiopental Sodium for Injection in 40 mL of water; the pH of this solution is between 10.2 and 11.2.

Purity Perform the test as directed under Purity for Thiopental sodium.

Loss on drying NMT 2.0% (1 g, in vacuum, 80 ℃, 4 hours)

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.3 EU per mg of thiopental sodium

Uniformity of dosage units Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

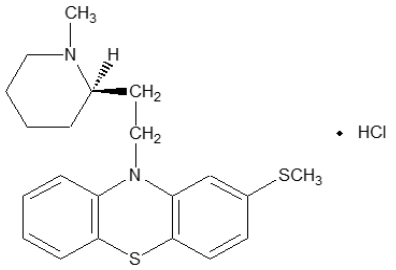
Insoluble particulate matter in injections Meets the requirements.

Assay Take 10 units of thiopental sodium for injection and carefully open each. Dissolve each content with water, wash each container with water, combine the washings with the former solution and add water to make exactly 1000 mL. Pipet 10 mL of this solution and add water to make exactly 100 mL. Pipet an amount (*V* mL) of this solution equivalent to about 15 mg of thiopental sodium ($C_{11}H_{17}N_2NaO_2S$), and add water to make exactly 1000 mL. Pipet 10 mL of this solution and add 15 mL of diluted dilute sodium hydroxide TS (1 in 100), then add water to make exactly 30 mL and use this solution as the test solution. Separately, weigh accurately about 46 mg of Thiopental RS, previously dried at 105 ℃ for 3 hours, dissolve in 50 mL of dilute sodium hydroxide TS and add water to make exactly 200 mL. Pipet 2 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 304 nm as directed under Ultraviolet-visible Spectroscopy.

Amount (mg) of thiopental sodium ($C_{11}H_{17}N_2NaO_2S$) in 1 unit of thiopental sodium for injection
$= \text{Amount (mg) of thiopental RS} \times \frac{A_T}{A_S} \times \frac{300}{V} \times 1.0904$

Packaging and storage Preserve in light-resistant, hermetic containers.

Thioridazine Hydrochloride
티오리다진염산염



and enantiomer

$C_{21}H_{26}N_2S_2 \cdot HCl$: 407.04
10-[2-(1-Methylpiperidin-2-yl)ethyl]-2-

methylsulfanylphenothiazinehydrochloride [*130-61-0*]

Thioridazine Hydrochloride, when dried, contains NLT 99.0% and NMT 101.0% of thioridazine hydrochloride ($C_{21}H_{26}N_2S_2 \cdot HCl$).

Description Thioridazine Hydrochloride occurs as a white to pale yellow, crystalline powder. It is odorless and has a bitter taste.
It is freely soluble in water, in methanol, acetic acid(100) or ethanol(95), sparingly soluble in acetic anhydride and practically insoluble in ether.
Dissolve 1.0 g of Its in 100 mL of water; the pH of the solution is between 4.2 and 5.2.
It is gradually colored by light.

Identification (1) Dissolve 10 mg of Thioridazine Hydrochloride in 2 mL of sulfuric acid; the resulting solution exhibits a deep blue color.

(2) Dissolve 10 mg of Thioridazine Hydrochloride in 2 mL of water and add 1 drop of tetraammonium cerium (IV) sulfate TS; the solution exhibits a blue color, and the color disappears the excess test solution is added.

(3) Determine the infrared spectra of Thioridazine Hydrochloride and thioridazine hydrochloride RS, previously dried, as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers

(4) To 5 mL of an aqueous solution of Thioridazine Hydrochloride (1 in 100), add 2 mL of ammonia TS, heat on a steam bath for 5 minutes, cool, and filter. Acidify the filtrate with dilute nitric acid: the solution responds to the Qualitative Analysis (2) for chloride.

Melting point Between 159 and 164 °C.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Thioridazine Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Selenium***—Weigh 0.1 g of Thioridazine Hydrochloride, add 0.1 g of magnesium oxide, mix, transfer to a combustion flask, and proceed as directed under the Oxygen Flask Combustion, using 25 mL of diluted nitric acid (1 in 30) as the absorbent. Use a 1 L volumetric flask as the combustion flask. After combustion, wash the stopper and the inner wall of the flask with 10 mL of water. Transfer the liquid from the flask to a 150-mL beaker, using 20 mL of water. Heat gently to boil, boil for 10 minutes, cool to room temperature, and use this solution as the test solution. Separately, pipet 3.0 mL of standard selenium stock solution, add 25 mL of diluted nitric acid (1 in 30) and 25 mL of water, and use this solution as the standard solution. Adjust the pH of the test solution and the standard solution to 2.0 ± 0.2 with diluted ammonia water(28) (1 in 2), add water to make exactly 60 mL, transfer it to a separatory funnel using 10 mL of water, and wash the separatory funnel with 10 mL of water. To each, add 0.2 g of hydroxylamine hydrochloride and stir to dissolve. Then, immediately add 5.0 mL of 2,3-diaminonaphthalene TS, put a stopper, stir to mix, and allow to stand at the room temperature for 100 minutes. To this, add 5.0 mL of cyclohexane, shake vigorously for 2 minutes, and allow to stand. When the layer is separated, remove the water layer, centrifuge cyclohexane extracts, remove water, and take the cyclohexane layer. With these solutions and a control solution prepared with water added to 25 mL of diluted nitric acid (1 in 30) in the same manner, perform the test as directed under the Ultraviolet-visible Spectroscopy. Determine the absorbance at the absorption maximum wavelength around 380 nm; the absorbance of the solution from the test solution is not greater than the absorbance from the standard solution (NMT 30 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Thioridazine Hydrochloride according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Dissolve 0.10 g of Thioridazine Hydrochloride in 10 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 20 mL, pipet 2 mL of this solution, add methanol to make exactly 10 mL and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, 2-propanol and ammonia water(28) (74 : 25 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 366 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 °C, 4 hours)

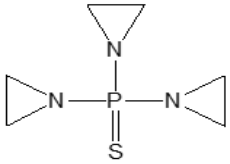
Residue on ignition NMT 0.1% (1 g)

Assay Weigh accurately about 0.35 g of Thioridazine Hydrochloride, previously dried, dissolve in 80 mL of a mixture of acetic anhydride and acetic acid(100) (1 : 1), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 40.704 mg of $C_{21}H_{26}N_2S_2 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Thiotepa
티오테파



$C_6H_{12}N_3PS$: 189.22

tris(Aziridin-1-yl)-sulfanylidene-λ*5*-phosphane [*52-24-4*]

Thiotepa, when dried, contains NLT 98.0% and NMT 101.0% of thiotepa ($C_6H_{12}N_3PS$).

Description Thiotepa occurs as colorless or white crystals or a crystalline powder and is odorless.
It is freely soluble in water, ethanol(95) or ether.
Dissolve 1.0 g of Its in 10 mL of water; the solution is neutral.

Identification (1) To 5 mL of an aqueous solution of Thiotepa (1 in 100), add 1 mL of ammonium molybdate TS and allow to stand; the resulting solution exhibits a dark blue color slowly when the solution is cold, or quickly when warm.

(2) To 5 mL of an aqueous solution of Thiotepa (1 in 100), add 1 mL of nitric acid; the resulting solution responds to the Qualitative Analysis (2) for phosphate.

(3) Dissolve 0.1 g of Thiotepa in a mixture of 1 mL of lead acetate TS and 10 mL of sodium hydroxide TS and boil; the gas evolved changes moistened red litmus paper to blue and the solution exhibits a grayish red color.

Melting point Between 52 and 57 °C.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Thiotepa in 20 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Thiotepa in a platinum crucible according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Dissolve 0.20 g of Thiotepa in 5 mL of water and add 1 mL of nitric acid and 1 mL of sulfuric acid. Proceed with this solution according to Method 2 and perform the test (NMT 10 ppm).

Loss on drying NMT 0.2% (1 g, in vacuum, silica gel, 4 hours).

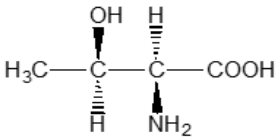
Residue on ignition NMT 0.1% (1 g, platinum crucible).

Assay Weigh accurately about 0.1 g of Thiotepa, previously dried, dissolve in 50 mL of a potassium thiocyanate solution (3 in 20), add exactly 25 mL of 0.05 mol/L sulfuric acid VS, and allow to stand for 20 minutes with occasional shaking. Titrate the excess sulfuric acid with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of methyl red TS). However, the endpoint of the titration is when the color of the solution changes from red to pale yellow. Perform a blank test in the same manner.

Each mL of 0.05 mol/L sulfuric acid VS
= 6.307 mg of $C_6H_{12}N_3PS$

Packaging and storage Preserve in a cold place, light-resistant, tight containers.

L-Threonine
L-트레오닌



$C_4H_9NO_3$: 119.12

(2*S*,3*R*)-2-Amino-3-hydroxybutanoic acid [*72-19-5*]

L-Threonine, when dried, contains NLT 98.5% and NMT 101.0% of L-threonine ($C_4H_9NO_3$).

Description L-Threonine occurs as crystals or a crystalline powder, which is odorless or has a slight characteristic odor and a slightly sweet taste.
It is freely soluble in formic acid, soluble in water, and practically insoluble in ethanol(95) or ether.

Identification Determine the infrared spectra of L-Threonine and L-threonine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -26.0° and -29.0° (1.5 g after drying, water, 25 mL, 100 mm).

pH Dissolve 0.20 g of L-Threonine in 20 mL of water; the pH of this solution is between 5.2 and 6.2.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of L-Threonine in 20 mL of water; the resulting solution is clear and colorless.

(2) ***Chloride***—Perform the test with 0.5 g of L-Threonine. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.021%).

(3) ***Sulfate***—Perform the test with 0.6 g of L-Threonine. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid (NMT 0.028%).

(4) ***Ammonium***—Perform the test with 0.25 g of L-Threonine. Prepare the control solution with 5.0 mL of ammonium standard solution (NMT 0.02%).

(5) ***Heavy metals***—Proceed with 1.0 g of L-Threonine according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(6) ***Iron***—Dissolve 0.333 g of L-Threonine in water to make 45 mL, add 2 mL of hydrochloric acid, and use this solution as the test solution. Add water to 1.0 mL of iron standard solution to make 45 mL, add 2 mL of hy-

drochloric acid, and use this solution as the standard solution. Add 50 mg of ammonium peroxydisulfate and 3 mL of 30% ammonium thiocyanate solution to each of the test solution and the standard solution and mix; the color obtained from the test solution is not more intense than that from the standard solution (NMT 30 ppm).

(7) ***Arsenic***—Dissolve 1.0 g of L-Threonine in 5 mL of dilute hydrochloric acid and use this solution as the test solution (NMT 2 ppm).

(8) ***Related substances***—Dissolve 0.30 g of L-Threonine in water to make exactly 50 mL and use this solution as the test solution. Pipet 1 mL of this solution and add water to make exactly 50 mL. Pipet 5 mL of this solution, add water to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, water and acetic acid(100) (3 : 1 : 1) (as the developing solvent) to a distance of about 10 cm, and dry the plate at 80 ℃ for 30 minutes. Spray evenly a solution of ninhydrin in acetone (1 in 50) on the plate, heat at 80 ℃ for 5 minutes; the spots other than the principal spot are not more intense than the spots from the standard solution.

Loss on drying NMT 0.2% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.12 g of L-Threonine, previously dried, and dissolve in 3 mL of formic acid, add 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 11.912 mg of $C_4H_9NO_3$

Packaging and storage Preserve in tight containers.

Thrombin
트롬빈

Thrombin is prepared by treating prothrombin derived from human or bovine blood with thromboplastin in the presence of calcium ions, sterilizing, and lyophilizing.

Thrombin contains NLT 80.0% and NMT 150.0% of the labeled units of Thrombin.

Each mg of Thrombine contains NLT 10 units of Thrombin.

Description Thrombin occurs as a white to pale yellow powder.
Dissolve an amount, equivalent to 500 units Thrombin, in isotonic sodium chloride injection; the resulting solution is clear within 1 minute or slight turbid while dissolving.

Loss on drying NMT 3.0% (50 mg, in vacuum, phosphorus pentoxide, 4 hours)

Sterility Meets the requirements.

Assay (1) ***Fibrinogen solution***—Weigh accurately about 30 mg of fibrinogen and dissolve in 3 mL of isotonic sodium chloride injection. Add about 3 units of Thrombin and frequently shake to mix until clots are sufficiently produced. Separately, take the precipitated clots and wash thoroughly with water until the washings yield no turbidity when silver nitrate TS is added. Dry at 105 ℃ for 3 hours, weigh the residue, and determine the percentage (%) of the clots. Based on the percentage (%) of the clots, dissolve separately fibrinogen in isotonic sodium chloride injection so that the amount of fibrinogen in the solution is 0.20% of the clots and adjust the pH of the solution between 7.0 and 7.4 by adding 0.05 mol/L sodium monohydrogen phosphate TS (if necessary, use 0.5 mol/L sodium monohydrogen phosphate TS), and add isotonic sodium chloride injection to make a 0.1% solution.

(2) ***Procedure***—Dissolve thrombin RS in isotonic sodium chloride injection to prepare 4 standard solutions, which contain 4.0, 5.0, 6.2 and 7.5 units of thrombin RS per mL, respectively. Pipet 0.10 mL of the standard solution, previously kept at between 20 and 30 ℃ (± 1 ℃), transfer into a small test tube, 10 mm in internal diameter and 100 mm in length. To the test tube, pipet 0.9 mL of the fibrinogen solution, previously kept at the same temperature as the standard solution. Start a stopwatch simultaneously, shake the tube gently to mix, and measure the time for the first appearance of clot. Repeat the procedure 5 times with each of the 4 standard solutions and determine the average values. If the difference between the maximum and the minimum values from the 5 measurements is NLT 10%, repeat the procedure. The concentration of the standard solution may be varied appropriately withing the range of 14 to 60 seconds of the clotting time. The measurement is performed at the same temperature described above. Next, weigh accurately the mass of the entire contents of a single container of Thrombin and dissolve in isotonic sodium chloride injection to obtain a solution containing about 5 units of Thrombin per mL. Take 0.10 mL of the solution, repeat the above procedure 5 times, measure the clotting time, and determine the average value. Plot the average value of the clotting times of the 4 standard solutions (vertical axis) against units of thrombin RS (horizontal axis), using units as the abscissa and clotting times as the ordinate on a logarithmic graph to create a calibration curve. Using the calibration curve, read the unit *U*, corresponding to the average clotting time of the test solution.

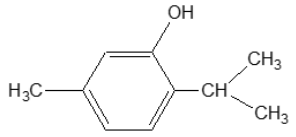
Units of a single container of Thrombin
$= U \times 10 \times V$

V: Number of mL of the volume in which the contents of a single container of Thrombin is dissolved

Separately, determine the units per mg of the contents.

Packaging and storage Preserve in hermetic containers below 10 ℃.

Thymol
티몰



$C_{10}H_{14}O$: 150.22

5-Methyl-2-propan-2-ylphenol [*89-83-8*]

Thymol contains NLT 98.0% and NMT 101.0% of thymol ($C_{10}H_{14}O$).

Description Thymol occurs as colorless crystals or a white crystalline mass. It has an aromatic odor and a burning taste.
It is very soluble in acetic acid(100), freely soluble in ethanol(95) or ether, and slightly soluble in water.
It sinks in water, but when warmed, it melts and rises to the surface of water.

Identification (1) To 1 mL of a solution of Thymol in acetic acid(100) (1 in 300), add 6 drops of sulfuric acid and 1 drop of nitric acid; the solution exhibits a bluish green color by reflected light and a purple color by transmitted light.

(2) To 1 g of Thymol, add 5 mL of sodium hydroxide solution (1 in 10), dissolve by heating on a steam bath, and continue heating for several minutes: the solution gradually exhibits a pale yellowish red color. Allow this solution to stand at room temperature; the color changes to dark yellowish brown. To this solution, add 2 to 3 drops of chloroform and shake to mix; the solution immediately exhibits a purple color.

(3) Triturate Thymol with an equal amount of camphor or menthol: the mixture liquefies.

Melting point Between 49 and 51 °C.

Purity (1) ***Non-volatile residue***—Volatilize 2.0 g of Thymol by heating on a steam bath and dry the residue at 105 °C for 2 hours: the mass is NMT 1.0 mg.

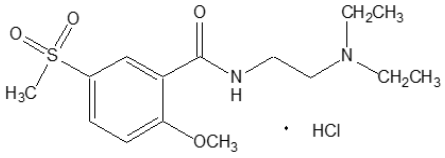
(2) ***Other phenols***—To 1.0 g of Thymol, add 20 mL of warm water, shake vigorously for 1 minute, and filter. To 5 mL of the filtrate, add 1 drop of iron(III) chloride TS; the solution exhibits a green color but no blue to violet color.

Assay Weigh accurately about 0.5 g of Thymol, dissolve in 10 mL of sodium hydroxide TS and add water to make exactly 100 mL. Pipet 10 mL of this solution, put it into an iodine bottle, add 50 mL of water and 20 mL of dilute sulfuric acid, and cool in iced water for 30 minutes. Then, add exactly 20 mL of 0.05 mol/L bromine solution, stopper immediately, allow to stand for 30 minutes in iced water with occasional shaking in the dark, add 14 mL of potassium iodide TS and 5 mL of chloroform, stopper, shake vigorously, and titrate the liberated iodine with 0.1 mol/L sodium thiosulfate VS (indicator: 3 mL of starch TS). However, near the endpoint of titration, stopper and shake vigorously. The endpoint is when the blue color in the chloroform layer disappears. Perform a blank test in the same manner.

Each mL of 0.05 mol/L bromine VS
= 3.756 mg of $C_{10}H_{14}O$

Packaging and storage Preserve in light-resistant, tight containers.

Tiapride Hydrochloride
티아프리드염산염



$C_{15}H_{24}N_2O_4S \cdot HCl$: 364.89

N-[2-(Diethylamino)ethyl]-2-methoxy-5-methylsulfonylbenzamidehydrochloride [*51012-33-0*]

Tiapride Hydrochloride contains NLT 98.5% and NMT 101.0% of tiapride hydrochloride ($C_{15}H_{24}N_2O_4S \cdot HCl$), calculated on the dried basis.

Description Tiapride Hydrochloride occurs as a white to pale yellowish white crystalline powder.
It is freely soluble in water, soluble in methanol and slightly soluble in ethanol(95).

Identification (1) Determine the infrared spectra of Tiapride Hydrochloride and tiapride hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) An aqueous solution of Tiapride Hydrochloride (2.5 in 50) responds to the Qualitative Analysis for chloride.

pH Dissolve 2.5 g of Tiapride Hydrochloride in 50 mL of water; the pH of this solution is between 4.0 and 6.0.

Purity (1) ***Clarity and color of solution***—Dissolve 2.5 g of Tiapride Hydrochloride in 50 mL of water; the solution is clear. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at the wavelength of 450 nm is NMT 0.030.

(2) ***Heavy metals***—Proceed with 1.0 g of Tiapride

Hydrochloride according to Method 1, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (20 ppm).

(3) ***Related substance I***—Dissolve 0.40 g of Tiapride Hydrochloride, accurately weighed, in methanol to make exactly 10 mL and use this solution as the test solution. Separately, dissolve 20.0 mg of tiapride related substance I RS {*N*,*N*-diethylethylen-1,2-diamine} in methanol to make exactly 50 mL. To 2.0 mL of this solution, add methanol to make exactly 20 mL and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of methyl-t-butyl ether, ethanol(99.5), and ammonia water(28) (40 : 10 : 2) as the developing solvent to a distance of about 12 cm, and air-dry the plate. Spray evenly with 0.2 w/v% ninhydrin 1-butanol solution and heat at 100 °C for 15 minutes; the spots of the related substance I from the test solution are not more intense than the spots from the standard solution (NMT 0.1%).

(4) ***Related substances***—Dissolve 0.1 g of Tiapride Hydrochloride, accurately weighed, in the mobile phase to make exactly 100 mL and use this solution as the test solution. To 1.0 mL of the test solution, add the mobile phase to make exactly 10 mL. To 1.0 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and calculate the areas of peaks; the area of peaks other than the major peak obtained from the test solution is not greater than the area of the major peak from the standard solution (0.1%), and the sum of the areas of these peaks is not greater than 3 times the area of the major peak from the standard solution (0.3%). However, disregard any peak with an area smaller than 0.5 times the area of the major peak from the standard solution (NMT 0.05%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 5.44 g of potassium dihydrogen phosphate and 80 mg of sodium ocatanesulphonate in 780 mL of water, adjust the pH to 2.7 with phosphoric acid, and add water to make 800 mL. To this solution, add 150 mL of methanol and 50 mL of acetonitrile.

Flow rate: 1.5 mL/min

System suitability

Dissolve 5.0 mg of tiapride hydrochloride RS and 5.0 mg of tiapride N-oxide RS in the mobile phase to make 100 mL. Proceed with 10 μL of this solution according to the above conditions; the resolution between the peaks of tiapride (the retention time is about 9 minutes) and tiapride N-oxide (the retention time is about 13 minutes) is NLT 4.0.

Loss on drying NMT 0.5% (1 g, 105 °C, constant mass).

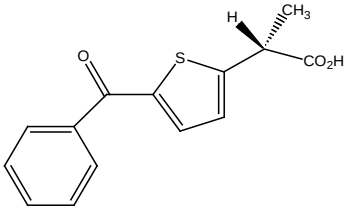
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Tiapride Hydrochloride, dissolve in 20 mL of acetic acid(100) and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Separately, perform a blank test, and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 36.489 mg of $C_{15}H_{24}N_2O_4S \cdot HCl$

Packaging and storage Preserve in well-closed containers.

Tiaprofenic Acid
티아프로펜산



and enantiomer

$C_{14}H_{12}O_3S$: 260.31

2-(5-Benzoylthiophen-2-yl)propanoic acid [*33005-95-7*]

Tiaprofenic Acid contains NLT 99.0% and NMT 101.0% of tiaprofenic acid ($C_{14}H_{12}O_3S$), calculated on the dried basis.

Description Tiaprofenic Acid occurs as a white crystalline powder.
It is very soluble in acetone, ethanol(95) or dichloromethane, and practically insoluble in water.

Identification Determine the infrared spectra of Tiaprofenic Acid and tiaprofenic acid RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 95 and 99 °C.

Optical rotation $[\alpha]_D^{20}$: Between -0.10° and +0.10° (0.5 g, ethyl acetate, 10 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 2.0 g of Tiaprofenic Acid in ethanol(95) to make 20 mL; the

resulting solution is clear and not more intense than a mixture of 5 mL of Matching fluids for color F and 95 mL of 1 w/v% hydrochloric acid.

(2) ***Heavy metals***—Proceed with 2.0 g of Tiaprofenic Acid according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 20.0 mg of Tiaprofenic Acid in the mobile phase to make exactly 20 mL, and use this solution as the test solution. Add the mobile phase to 1.0 mL of the test solution to make exactly 50 mL, and add the mobile phase to 1.0 mL of this solution to make exactly 10 mL. Use this solution as the standard solution (1). To 5.0 mL of the standard solution (1), add the mobile phase to make exactly 10 mL, and use this solution as the standard solution (2). Dissolve 10.0 mg of tiaprofenic acid related substance I RS [(2RS)-2-(5-benzoyl-thiopene-3-yl)propanosan] in the mobile phase to make 100 mL. Add the mobile phase to 1.0 mL of this solution to make exactly 50 mL, and use this solution as the standard solution (3). Add the standard solution (3) to 1.0 mL of the standard solution (1) to make exactly 2 mL, and use this solution as the standard solution (4). Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. The peak area of the related substance I obtained from the test solution is not greater than the corresponding peak area from the standard solution (3) (NMT 0.2%). The area of the peaks other than the major peak from the test solution and the peak area of the related substance It is not greater than the area of the major peak obtained from the standard solution (2) (0.1%), and the sum of the areas of peaks other than the major peak from the test solution and the peak of the related substance I, is not greater than 1.5 times the area of the major peak obtained from the standard solution (1) (0.3%). However, disregard the peaks smaller than 0.5 times the area of the major peak obtained from the standard solution (2).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 250 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of dichloromethane, hexane, acetic acid(100) and water (500 : 500 : 20 : 1). Add the water to acetic acid(100), mix, then add hexane and dichloromethane. Sonicate the mixture for 2 minutes. Do not degas with helium during analysis.

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 20 μL each of the test solution and standard solution (4) according to the above conditions; the relative retention times of related substance II, III and I to the retention time of tiaprofenic acid are 0.19, 0.48 and 0.86, respectively, and the resolution of the peaks between tiaprofenic acid and related substance I is NLT 3.0 Adjust the detection sensitivity so that the height of the major peak from the standard solution (4) is NLT 50% of the full scale.

Loss on drying NMT 0.5% (1.0 g, 60℃, NMT 0.9 kPa, 3 hours).

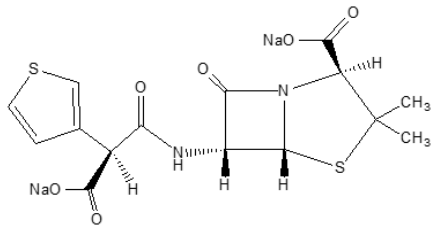
Residue on ignition NMT 0.1% (1.0 g).

Assay Weigh accurately about 0.25 g of Tiaprofenic Acid, dissolve in 25 mL of ethanol(95), add 25 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 0.5 mL of phenolphthalein TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mL of 0.1 mol/L sodium hydroxide VS
= 26.031 mg of $C_{14}H_{12}O_3S$

Packaging and storage Preserve in light-resistant, well-closed containers.

Ticarcillin Sodium
티카르실린나트륨



$C_{15}H_{14}N_2Na_2O_6S_2$: 428.40

Disodium(2*S*,5*R*,6*R*)-6-[[(2*R*)-2-carboxylato-2-thiophen-3-ylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate [*4697-14-7*]

Ticarcillin Sodium contains NLT 800 μg (potency) of ticarcillin ($C_{15}H_{16}N_2O_6S_2$: 384.43) per mg, calculated on the anhydrous basis.

Description Ticarcillin Sodium occurs as a white to pale yellowish white powder and has a characteristic odor.
It is very soluble in water, freely soluble in methanol, sparingly soluble in ethanol(95), and practically insoluble in ether.

Identification (1) Weigh accurately 40 mg of Ticarcillin Sodium and ticarcillin sodium RS, respectively, and dissolve in water to make exactly 100 mL. Add 0.1 mol/L methanol hydrochloric acid TS to 5 mL of each these solutions to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Determine the absorption spectra of the test solution and the standard solution at 200 nm to 300 nm as directed under the Ultraviolet-visible Spectroscopy, using 0.1 mol/L methanol hydrochloric acid TS as the control solution; it exhibits a maximum at the wavelength of

around 230 nm, and the absorption spectrum of each wavelength is the same as that of the reference standards.

(2) An aqueous solution of Ticarcillin Sodium (1 in 20) responds to the Qualitative Analysis for sodium.

Optical rotation $[\alpha]_D^{25}$: Between +172° and +187° (1 g, calculated on the anhydrous basis, water, 100 mL, 100 mm).

pH Dissolve 0.1 g of Ticarcillin Sodium in 10 mL of water; the pH of this solution is between 6.0 and 8.0.

Purity (1) ***Dimethylaniline***—Weigh accurately about 1.0 g of Ticarcillin Sodium, add 5 mL of 1 mol/L sodium hydroxide TS and 1 mL of the internal standard solution, centrifuge, if necessary, and use the clear supernatant as the test solution. Separately, weigh accurately about 50 mg of dimethylaniline, add 2.0 mL of hydrochloric acid, and add water to make 50 mL. Pipet 5.0 mL of this solution and add water to make exactly 250 mL. Pipet 1.0 mL of this solution, add 5.0 mL of 1 mol/L sodium hydroxide TS and 1.0 mL of the internal standard solution, centrifuge if necessary, and use the clear supernatant as the standard solution. Perform the test with 1 μL each of the test solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of dimethylaniline to the internal standard from the test solution and the standard solution, respectively (NMT 20 ppm).

$$\text{Content (ppm) of dimethylaniline} = \text{Amount (mg) of dimethylaniline taken} \times \frac{Q_T}{Q_S} \times \frac{Purity\ (\%)\ of\ dimethylaniline}{Amount\ (mg)\ of\ \text{Ticarcillin Sodium}} \times 4$$

Internal standard solution—Dissolve 50.0 mg of naphthalene in cyclohexane to make 50 mL. Take 5.0 mL of this solution, add cyclohexane to make 100 mL, and use this solution as the internal standard solution.

Operating conditions

Detector: A flame ionization detector

Column: A column about 2 mm in internal diameter and about 2 m in length, packed with diatomaceous earth for gas chromatography, which is coated with 50% phenyl-50% methylpolysiloxane for gas chromatography equivalent to 3% of the mass of the diatomaceous earth for gas chromatography.

Column temperature: 120 °C

Temperatures of the sample injection port and the detector: 150 °C.

Carrier gas: Nitrogen

Flow rate: 30 mL/min

(2) ***Ticarcillin content***—Weigh accurately about 40 mg each of Ticarcillin Sodium and ticarcillin sodium RS and dissolve each in water to make exactly 100 mL. Pipet 5.0 mL each of these solutions, add 0.1 mol/L methanol hydrochloric acid TS to make exactly 100 mL, and use these solutions as the test solution and the standard solution, respectively. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at 230 nm as directed under Ultraviolet-visible Spectroscopy, using the blank test solution as the control solution (NLT 80.0% and NMT 94.0%, calculated on the anhydrous basis).

$$\text{Content (\%) of ticarcillin} = \text{Concentration (\%) of ticarcillin in ticarcillin sodium RS} \times \frac{Amount\ (mg)\ of\ ticarcillin\ sodium\ RS}{Amount\ (mg)\ of\ sample} \times \frac{A_T}{A_S}$$

0.1 mol/L Hydrochloric acid-methanol TS—Add methanol to 0.8 mL of hydrochloric acid to make 100 mL.

Water NMT 6.0% (0.2 g, volumetric titration, direct titration).

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, the manufacturing process of sterile preparations which includes the terminal sterile process is exceptional.

Bacterial endotoxins Less than 0.05 EU per mg (potency) of ticarcillin when used in the manufacturing of sterile preparations.

Assay Weigh about 50 mg (potency) each of Ticarcillin Sodium and ticarcillin sodium RS, dissolve each in a phosphate buffer solution (pH 6.4) to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of the test solution and the standard solution, respectively.

$$\text{Potency (μg) of ticarcillin } (C_{15}H_{16}N_2O_6S_2) = \text{Potency (μg) of ticarcillin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column with an internal diameter of about 4 mm and a length of about 30 cm, packed with octadecylsilanized silica gel for liquid chromatography (3 to 10 μm in particle diameter).

Mobile phase: A mixture of phosphate buffer solution (pH 4.3) and acetonitrile (95 : 5).

Flow rate: 2 mL/min

System suitability

System performance: Proceed with the resolution test solution under the above operating conditions; the relative retention time of clavulanic acid and ticarcillin are 0.2 and 1.0, respectively, the resolutions are NLT 5.0; the number of theoretical plates and the symmetric factor are NLT 1000 and NMT 2.0, respectively.

System repeatability: Repeat the test 5 times with 20 μL each of the standard solutions according to the above operating conditions; the relative standard deviation of the peak area of ticarcillin is NMT 2.0%.

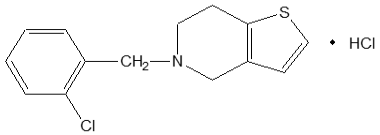
Phosphate buffer solution (pH 6.4)—Dissolve 6.9 g of sodium dihydrogen phosphate monohydrate in 900 mL of water, adjust with 10 mol/L sodium hydroxide to a pH of 6.4 ± 0.1, and add water to make 1000 mL.

Phosphate buffer solution (pH 4.3)—Dissolve 13.8 g of sodium dihydrogen phosphate monohydrate in 900 mL of water, adjust with 10 mol/L sodium hydroxide to a pH of 4.3 ± 0.1, and add water to make 1000 mL.

Resolution test solution—Weigh accurately about 25 mg (potency) of ticarcillin sodium RS, add 5 mL of phosphate buffer solution (pH 6.4) solution of clavulanic acid RS containing 0.15 mg per mL, and then add phosphate buffer solution (pH 6.4) to make exactly 25 mL.

Packaging and storage Preserve in tight containers (at 2 to 8 ℃).

Ticlopidine Hydrochloride
티클로피딘염산염



$C_{14}H_{14}ClNS \cdot HCl$: 300.25

5-[(2-Chlorophenyl)methyl]-4*H*,5*H*,6*H*,7*H*-thieno[3,2-c]pyridine hydrochloride [*53885-35-1*]

Ticlopidine Hydrochloride contains NLT 99.0% and NMT 101.0% of ticlopidine hydrochloride ($C_{14}H_{14}ClNS \cdot HCl$), calculated on the anhydrous basis.

Description Ticlopidine Hydrochloride occurs as a white to pale yellowish crystalline powder.
It is freely soluble in acetic acid(100), soluble in water or methanol, sparingly soluble in ethanol(99) and practically insoluble in ether.

Identification (1) Determine the absorption spectra of Ticlopidine Hydrochloride and ticlopidine hydrochloride RS according to the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) A solution of Ticlopidine Hydrochloride (1 in 20) responds to the Qualitative Analysis (2) for chloride.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Ticlopidine Hydrochloride according to Method 3, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Ticlopidine Hydrochloride according to Method 4, and perform the test (NMT 2 ppm).

(3) ***Related substances***—Dissolve 0.5 g of Ticlopidine Hydrochloride in 20 mL of methanol (1 in 20000) of hydrochloric acid, and use this solution as the test solution. Pipet 5 mL of this solution, add methanol (1 in 20000) of hydrochloric acid to make exactly 200 mL, and use this solution as the standard solution (1). Separately, pipet 1 mL of test solution, add methanol (1 in 20000) of hydrochloric acid to make exactly 50 mL, and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL of the test solution and standard solution (1) on a plate (1) made of silica gel with fluorescent indicator for thin-layer chromatography, and spot 10 μL of each test solution and standard solution (2) on a plate (2) made of silica gel for thin-layer chromatography. Next, develop the plate with the upper layer of a mixture of water, 1-butanol and acetic acid(100) (5 : 4 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray evenly a solution of ninhydrin in acetone (1 in 50) on the plate (1) and heat at 100 °C for 20 minutes; spots other than the principal spot from the test solution are not more intense than the spots from the standard solution (1). Allow the plate (2) to stand for 30 minutes in iodine steam; the spots other than the principal spot from the test solution are not more intense than those from the standard solution (2).

(4) ***Formaldehyde***—Dissolve 0.8 g of Ticlopidine Hydrochloride in 19.0 mL of water, add 1.0 mL of 4 mol/L sodium hydroxide TS, and shake well to mix. Centrifuge this solution and filter the upper layer. To 5.0 mL of the filtrate, add 5.0 mL of acetylacetone TS, mix, and warm at 40℃ for 5 minutes; the color of the resulting solution is not more intense than that of the following control solution.

Control solution—Weigh exactly 0.54g of formaldehyde solution, and add water to make exactly 1000 mL. Pipet 10 mL of this solution and add water to make exactly 1000 mL. Prepare before use. Add water to 8.0 mL of this solution to make 20.0 mL, and filter. Take 5.0 mL of the filtrate, add 5.0 mL of acetylacetone TS, and proceed in the same manner as below.

Water NMT 1.0% (0.3 g, volumetric titration, direct titration).

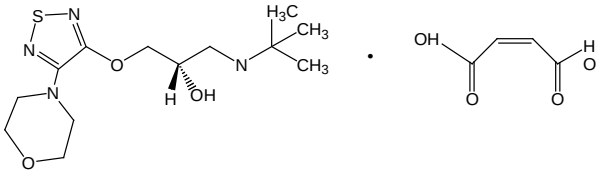
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Ticlopidine Hydrochloride, dissolve in 20 mL of acetic acid(100), add 40 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

1 mL of 0.1 mol/L perchloric acid VS
= 30.025 mg of $C_{14}H_{14}ClNS \cdot HCl$

Packaging and storage Preserve in well-closed containers.

Timolol Maleate
티몰롤말레산염



$C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$: 432.49
(*Z*)-But-2-Enedioic acid;(2*S*)-1-(*tert*-butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol
[*26921-17-5*]

Timolol Maleate, when dried, contains NLT 98.0% and NMT 101.0% of timolol maleate ($C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$).

Description Timolol Maleate occurs as a white to pale yellowish white powder.
It is freely soluble in acetic acid(100), and soluble in water or ethanol(99.5).
It dissolves in 0.1 mol/L hydrochloric acid TS.

Melting point—About 197 °C (with decomposition).

Identification (1) Determine the absorption spectra of solutions of Timolol Maleate and timolol maleate RS in 0.1 mol/L hydrochloric acid TS (3 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Timolol Maleate and timolol maleate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Add 1 drop of potassium permanganate TS to 5 mL of an aqueous solution of Timolol Maleate (1 in 500); the red color of the test solution disappears immediately.

pH Dissolve 1.0 g of Timolol Maleate in 20 mL of water; the pH of this solution is between 3.8 and 4.3.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Timolol Maleate in 20 mL of water; the resulting solution is clear. Also, perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at 440 nm is NMT 0.05.

(2) ***Heavy metals***—Proceed with 2.0 g of Timolol Maleate according to Method 4, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve about 30 mg of Timolol Maleate in 20 mL of the mobile phase and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to it make exactly 100 mL, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine each peak area by the automatic integration method; the peak area other than that of timolol and maleic acid from the test solution is not greater than 0.2 times the peak area of timolol from the standard solution. The total area of the peaks other than the peak of timolol and maleic acid from the test solution is not greater than 0.5 times the peak area of timolol from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 1.9 g of sodium 1-hexanesulfonate in 1800 mL of water, add 6.0 mL of triethylamine and 8.0 mL of formic acid, adjust the pH to 3.0 with formic acid, and add water to make 2000 mL. To 1400 mL of this solution, add 500 mL of methanol and 100 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of timolol is about 18 minutes.

System suitability

Test for required detectability: Take exactly 1 mL of the standard solution, and add the mobile phase to make exactly 10 mL. Confirm that the peak area of timolol obtained from 25 μL of this solution is equivalent to 7% to 13% of that from the standard solution.

System performance: Proceed with 25 μL of the standard solution according to the above conditions; the number of theoretical plates and the symmetry factor of the peak of timolol are NLT 1500 and NMT 2.5, respectively.

System repeatability: Repeat the test 6 times with 25 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of timolol is NMT 2.0%.

Time span of measurement: About 2 times the retention time of timolol after the solvent peak.

Isomer Perform the test using light-resistant containers. Weigh exactly 30 mg of Timolol Maleate, dissolve in 10 mL of a mixture of methylene chloride and isopropanol (10 : 30), and use this solution as the test solution. Dissolve 30 mg of timolol maleate RS in 10 mL of a solvent and use this solution as the standard solution (a). Dissolve 3 mg of timolol maleate enantiomer RS ({(2R)-1-[(1,1-dimethylethyl)amino}-3-{[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy} propane-2-) in 10 mL of the solvent, take 1.0 mL of this solution, add the solvent to make exactly 10mL, and use this solution as the standard solution (b). Take 1 mL of the standard solution (a) and add the

solvent to make 100 mL. Mix 1 mL of this solution and 1 mL of the standard solution (b) and use this solution as the standard solution (c). Add 100 mL of the solvent to 1.0 mL of the test solution and use this solution as the standard solution (d). Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions; the amount of timolol maleate enantiomer is not greater than that corresponding to the area of the major peak of the standard solution (d) (1.0%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 297 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with silica gel for liquid chromatography (cellulose tris (3,5-dimethylphenylcarbamate)) (5 μm in particle diameter).

Mobile phase: A mixture of diethylamine, 2-propanol and hexane (2 : 40 : 960).

Flow rate: 1 mL/min

Injection volume: 5 μL

Order of elution: Timolol maleate enantiomer is eluted the first in the order of elution.

System suitability

System performance: The peak retention times of the major peak of the test solution and the standard solution (a) are the same, and the resolution between the major peak of the standard solution (c) and the peak of timolol maleate enantiomer is NLT 4.

Loss on drying NMT 0.5% (1 g, in vacuum, 100 ℃, 3 hours).

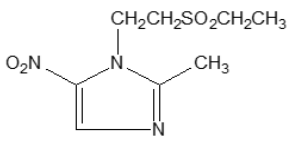
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.8 g of Timolol Maleate, previously dried, dissolve in 90 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 43.25 mg of $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$

Packaging and storage Preserve in tight containers.

Tinidazole
티니다졸



$C_8H_{13}N_3O_4S$: 247.27

1-(2-Ethylsulfonylethyl)-2-methyl-5-nitroimidazole

[*19387-91-8*]

Tinidazole, when dried, contains NLT 98.5% and NMT 101.0% of tinidazole ($C_8H_{13}N_3O_4S$).

Description Tinidazole occurs as a pale yellow crystalline powder.

It is soluble in acetic anhydride or acetone, sparingly solution in methanol, slightly soluble in ethanol(95) and practically insoluble in water.

Identification (1) Determine the absorption spectra of Tinidazole and tinidazole RS in methanol (1 in 50000) as directed Under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Determine the infrared spectra of Tinidazole and tinidazole RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 125 and 129 ℃.

Purity (1) ***Sulfate***—To 2.0 g of Tinidazole, add 100 mL of water, boil for 5 minutes, and cool. Then, add water to make 100 mL and filter. Take 25 mL of the filtrate, add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution with 0.45 mL of 0.005 mol/L sulfuric acid (NMT 0.043%).

(2) ***Heavy metals***—Proceed with 1.0 g of Tinidazole according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 2.0 g of Tinidazole according to Method 3 and perform the test (NMT 1 ppm).

(4) ***Related substances***—Dissolve 50 mg of Tinidazole in 2 mL of acetone and use this solution as the test solution. Pipet 1 mL of this solution, add acetone to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each 10 μL of the test solution and the standard solution on a plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate and diethylamine (19 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Heat the plate at 100 ℃ for 5 minutes, cool, and examine under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 1.0% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.35 g of Tinidazole, previously dried, dissolve in 50 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric

titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 24.73 mg of $C_8H_{13}N_3O_4S$

Packaging and storage Preserve in light-resistant, tight containers.

Tinidazole Tablets
티니다졸 정

Tinidazole Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of tinidazole ($C_8H_{13}N_3O_4S$: 247.27).

Method of preparation Prepare as directed under Tablets, with Tinidazole.

Identification (1) Determine the absorption spectra of solutions of Tinidazole Tablets and tinidazole RS in 0.001% methanol as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Extract Tinidazole Tablets, previously powdered, with methanol to obtain a solution containing 5 mg of tinidazole per mL, and use this solution as the test solution. Separately, add methanol to tinidazole RS to obtain a solution containing 5 mg per mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Paper Chromatography. Spot 50 μL each of the test solution and the standard solution on the Whatman paper, develop the paper with a mixture of water, acetic acid(100), 1-butanol and ethyl acetate (1 : 1 : 1 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 366 nm); the color and R_f value of the spots obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

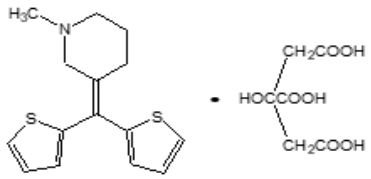
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Tinidazole Tablets, and powder. Weigh accurately an amount, equivalent to about 0.1 g of tinidazole ($C_8H_{13}N_3O_4S$), add about 70 mL of methanol, and shake for 10 minutes to mix. To this, add methanol to make 100 mL, and filter it. To 10.0 mL of the filtrate, add methanol to make 100 mL. Take 10.0 mL of this solution, add methanol to make 100 mL, and use this solution as the test solution. Separately, dry tinidazole RS in a desiccator (in vacuum, silica gel) for 4 hours. Weigh accurately 0.1 g of the dried matter, proceed in the same manner as in the preparation of the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using methanol as the control solution, and determine the absorbances, A_T and A_S, at the wavelength of 310 nm.

Amount (mg) of tinidazole ($C_8H_{13}N_3O_4S$)
= Amount (mg) of tinidazole RS× $\frac{A_T}{A_S}$

Packaging and storage Preserve in tight containers.

Tipepidine Citrate
티페피딘시트르산염



$C_{15}H_{17}NS_2 \cdot C_6H_8O_7$: 467.56
3(Di-2-thienylmethylene)-1-methyl-piperidine 2-hydroxy-1,2,3-propanetricarboxylate (1:1), [*14698-07-8*]

Tipepidine Citrate, when dried, contains NLT 99.0% and NMT 101.0% of tipepidine citrate ($C_{15}H_{17}NS_2 \cdot C_6H_8O_7$).

Description Tipepidine Citrate occurs as white to light yellow crystals or a crystalline powder, and has no or a slight odor and a bitter taste.
It is freely soluble in acetic acid(100), sparingly soluble in water or methanol, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and practically insoluble in anhydrous ether.

Identification (1) Add 10 mL of water to 0.1 g of Tipepidine Citrate, and heat to dissolve. After cooling, add sodium hydroxide TS until precipitate forms. Add chloroform to this solution, shake to mix, take the aqueous layer, and add ammonia TS to neutralize it; the resulting solution responds to the Qualitative Analysis (2) and (3) for citrate.

(2) Dissolve 1 mg of Tipepidine Citrate with 3 mL of acetic acid(100), and add 5 mL of ninhydrin-sulfuric acid (1 in 1000); the solution exhibits bluish-purple.

(3) To 0.1 g of Tipepidine Citrate, add 5 mL of water, dissolve by heating on a steam bath, and cool. Use this solution as the test solution. Add 1 to 2 drops of bromine TS to 2 mL of the test solution; the color of the test solution disappears immediately.

(4) To 2 mL of the test solution obtained from (3), add 5 mL of chloramine TS; yellow color appears or yellow precipitates are formed.

(5) Add 500 mL of water to 10 mg of Tipepidine Citrate, heat to dissolve, and cool. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at a wavelength between 245 nm and 249 nm.

Melting point Between 138 and 142 ℃.

Purity (1) ***Heavy metals***—Prepare the test solution with 2.0 g of Tipepidine Citrate according to Method 2 under the Heavy Metals, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Prepare the test solution with 1.0 g of Tipepidine Citrate according to Method 3 under the Arsenic, and perform the test (NMT 2 ppm).

(3) ***Related substances***—Weigh about 10 mg of Tipepidine Citrate, add the mobile phase to make exactly 20.0 mL, and use this solution as the test solution. Take 1.0 mL of the test solution, add the mobile phase to make 50.0 mL, and use this solution as the standard solution. Test using 20 μL of test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. The total peak areas other than tipepidine from the test solution is not larger than peak area of tipepidine from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column, 4 mm to 4.6 mm in internal diameter and 15 cm to 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of methanol and ammonium acetate solution (1 in 500) (4 : 1).

Flow rate: Adjust the flow rate so that the retention time of tipepidine is about 5 to 7 minutes.

Time span of measurement: About 2 times the retention time of tipepidine.

System suitability

System performance: Weigh 12 mg of Tipepidine Citrate and 4 mg of *o*-delphenyl, and dissolve in the mobile phase to make 50 mL. Proceed with 10 μL of this solution under the above operating conditions, using the resolution being NLT 2.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of the tipepidine in the chromatogram obtained from the standard solution is about 5% of the full scale of the recording paper.

Loss on drying NMT 1.0% (1 g, sulfuric acid, 24 hours).

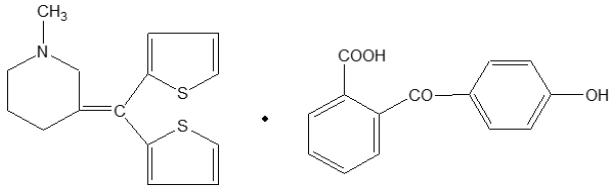
Residue on ignition NMT 0.10% (1 g).

Assay Weigh accurately about 0.9 g of Tipepidine Citrate, previously dried, dissolve in 40 mL of acetic acid(100) for non-aqueous titration, and titrate with 0.1 mol/L perchloric acid VS (indicator: 2 drops of methylrosanilinium chloride TS). the endpoint of the titration is when the purple color of this solution turns to blue and then finally to green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS
= 46.76 mg of C15H17NS2·C6H8O7

Packaging and storage Preserve in tight containers.

Tipepidine Hibenzate
티페피딘히벤즈산염



$C_{15}H_{17}NS_2 \cdot C_{14}H_{10}O_4$: 517.66

4-(2-Carboxybenzoyl)phenolate;3-(dithiophen-2-yl methylidene)-1-methylpiperidin-1-ium [*31139-87-4*]

Tipepidine Hibenzate, when dried, contains NLT 98.5% and NMT 101.0% of tipepidine hibenzate($C_{15}H_{17}NS_2 \cdot C_{14}H_{10}O_4$).

Description Tipepidine Hibenzate occurs as a white to pale yellow crystalline powder, and is odorless and tasteless.

It is freely soluble in acetic acid(100), slightly soluble in methanol or ethanol(95), very slightly soluble in water and practically insoluble in ether.

Identification (1) Dissolve 10 mg of Tipepidine Hibenzate in 5 mL of sulfuric acid; the resulting solution exhibits an orange color.

(2) Dissolve 0.3 g of Tipepidine Hibenzate in 10 mL of sodium hydroxide TS and 5 mL of water, and extract 2 times with 20 mL of chloroform. Wash the chloroform extract with 10 mL of water, and filter the chloroform layer. Evaporate the filtrate to dryness on a steam bath, and dissolve the residue by adding 0.5 mL of 1 mol/L hydrochloric acid TS and 5 mL of water. To 2 mL of this solution, add 5 mL of tin reinecke salt TS; a pale red precipitate is produced.

(3) Determine the absorption spectra of ethanol(99.5) solutions of Tipepidine Hibenzate and tipepidine hibenzate RS (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared spectra of Tipepidine Hibenzate and tipepidine hibenzate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 189 and 193 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Tipepidine Hibenzate in 10 mL of acetic acid(100); the

resulting solution is clear. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at 400 nm is NMT 0.16.

(2) ***Heavy metals***—Proceed with 2.0 g of Tipepidine Hibenzate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Tipepidine Hibenzate according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—(i) Dissolve 10 mg of Tipepidine Hibenzate in 20 mL of mobile phase, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to it make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area according to the automatic integration method; the total peak areas other than the peaks of hibenzic acid and tipepidine from the test solution is not greater than the peak area of tipepidine from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column, about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 - 10 μm in particle diameter).

Column temperature: A constant temperature of about 50 °C.

Mobile phase: A mixture of ammonium acetate solution (1 in 100) and tetrahydrofuran (32 : 13).

Flow rate: Adjust the flow rate so that the retention time of tipepidine is about 10 to 14 minutes.

System suitability

Detection sensitivity: Weigh accurately 2 mL of the standard solution and add the mobile phase to make exactly 20 mL. Verify that the peak area of tipepidine obtained from 20 μL of this solution is equivalent to 7% to 13% of the peak area of tipepidine obtained from the standard solution.

System performance: Dissolve 10 mg of Tipepidine Hibenzate and 3 mg of propyl *p*-hydroxybenzoate in 100 mL of the mobile phase. Proceed with 20 μL of this solution according to the above operating conditions; hibenzic acid, propyl *p*-hydroxybenzoate and tipepidine are eluted in this order with the resolution between peaks of tipepidine and propyl *p*-hydroxybenzoate being NLT 3.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of tipepidine is NMT 1.5%.

Time span of measurement: Range from after solvent peak until the tipepidine efflux.

(ii) Dissolve 10 mg of Tipepidine Hibenzate in 20 mL of the mobile phase and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to it make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the total peak areas other than hibenzic acid and tipepidine from the test solution is not larger than half the peak area of tipepidinee from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of methanol and ammonium acetate solution (1 in 500) (13 : 7).

Flow rate: Adjust the flow rate so that the retention time of tipepidine is about 10 minutes.

System suitability

Detection sensitivity: Weigh accurately 2 mL of the standard solution and add the mobile phase to make exactly 20 mL. Confirm that the peak area of tipepidine obtained from 20 μL of this solution is equivalent to 7% to 13% of the peak area of tipepidine obtained from the standard solution.

System performance: Dissolve 10 mg of Tipepidine Hibenzate and 3 mg of propyl p-hydroxybenzoate in 100 mL of the mobile phase. Proceed with 20 μL of this solution according to the above operating conditions, elute hibenzic acid, propyl *p*-hydroxybenzoate and tipepidine in this order with the resolution between tipepidine and propyl p-hydroxybenzoate being NLT 3.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of tipepidine is NMT 3.0%.

Time span of measurement: Range from after solvent peak until the tipepidine efflux.

Loss on drying NMT 0.5% (1 g, 60 ℃, in vacuum, phosphorus pentoxide, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 1 g of Tipepidine Hibenzate, previously dried, dissolve in 40 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 3 drops of methylrosanilinium chloride TS). However, the endpoint of the titration is when the violet color of this solution turns to the blue color and then finally to the green color. Perform a blank test in the same manner and make any necessary correction.

Each mL of 1 mol/L perchloric acid VS

= 51.766 mg of $C_{15}H_{17}NS_2 \cdot C_{14}H_{10}O_4$

Packaging and storage Preserve in light-resistant, well-closed containers.

Tipepidine Hibenzate Tablets
티페피딘히벤즈산염 정

Tipepidine Hibenzate Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of tipepidine hibenzate ($C_{15}H_{17}NS_2 \cdot C_{14}H_{10}O_4$: 517.66).

Method of preparation Prepare as directed under Tablets, with Tipepidine Hibenzate.

Identification (1) Weigh an amount of Tipepidine Hibenzate Tablets, previously powdered, equivalent to 44 mg of tipepidine hibenzate according to the labeled amount, add 5 mL of water, shake for 1 minute to mix, and add 10 mL of sodium hydroxide TS. Extract 2 times each with 20 mL of chloroform. Combine all extracts, wash with 10 mL of water, and then filter the chloroform layer. Evaporate the filtrate to dryness on a steam bath. To the residue, dissolve in 0.2 mL of 1 mol/L hydrochloric acid TS and 2 mL of water, and add 5 mL of Reinecke salt TS; a pale red precipitate is formed.

(2) Weigh an amount of Tipepidine Hibenzate Tablets, previously powdered, equivalent to 11 mg of tipepidine hibenzate according to the labeled amount, add 30 mL of ethanol(99.5), and warm for 10 minutes while occasionally shaking to mix. After cooling, add ethanol(99.5) to make 50 mL, and filter. To 1 mL of the filtrate, add ethanol(99.5) to make 20 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum absorption between 282 nm and 286 nm.

Dissolution Perform the test with 1 tablet of Tipepidine Hibenzate Tablets at 50 revolutions per minute according to Method 2, using 900 mL of water as the dissolution medium. Use the dissolved solution after 30 minutes from starting of the test as the test solution. Separately, weigh accurately about 0.11 g of tipepidine hibenzate RS, previously dried in a phosphorus pentoxide desiccator in vacuum at 60 ℃ for 3 hours, add diluted ethanol (3 in 4), and dissolve by occasionally warming. After cooling, add diluted ethanol (3 in 4) to make exactly 100 mL. Pipet 20 mL of this solution, add water to make 900 mL, and use this solution as the standard solution. Determine the absorbances, A_{T1} and A_{S1}, at 286 nm and A_{T2} and A_{S2}, at 360 nm of the test solution and the standard solution, respectively, as directed under Ultraviolet-visible Spectrophotometry.
Meets the requirements if the dissolution rate of Tipepidine Hibenzate Tablets in 30 minutes is NLT 80%.

Dissolution rate (%) of the labeled amount of tipepidine hibenzate ($C_{18}H_{17}NS_2 \cdot C_{14}H_{10}O_4$)

$$= W_S \times \frac{A_{T1} - A_{T2}}{A_{S1} - A_{S2}} \times \frac{20}{C}$$

W_S: Amount (mg) of the reference standards
C: Labeled amount (mg) of tipepidine hibenzate ($C_{15}H_{17}NS_2 \cdot C_{14}H_{10}O_4$) in 1 tablet

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following procedure.
Take 1 table of Tipepidine Hibenzate Tablets, add 5 mL of diluted acetic acid(100) (1 in 2) and 15 mL of methanol per 11 mg of tipepidine hibenzate, and warm for 15 minutes by shaking occasionally to mix. After cooling, add diluted methanol (1 in 2) to make V mL of a solution containing about 0.44 mg of tipepidine hibenzate per mL, then filter, discard 10 mL of the first filtrate, and pipet 5 mL of the subsequent filtrate. Add 5 mL of the internal standard solution, add diluted methanol (1 in 2) to make exactly 25 mL, and use this solution as the test solution. Perform the test as directed under the Assay below.

Amount (mg) of tipepidine hibenzate ($C_{15}H_{17}NS_2 \cdot C_{14}H_{10}O_4$)
$$= \text{Amount (mg) of tipepidine hibenzate RS} \times \frac{Q_T}{Q_S} \times \frac{V}{50}$$

Internal standard solution—A solution of dibucaine hydrochloride in methanol (1 in 2000).

Assay Weigh accurately the mass of NLT 20 Tipepidine Hibenzate Tablets, and powder. Weigh accurately an amount equivalent to about 22 mg of tipepidine hibenzate ($C_{15}H_{17}NS_2 \cdot C_{14}H_{10}O_4$), add 10 mL of diluted acetic acid(100) (1 in 2) and 30 mL of methanol, and warm for 10 minutes by shaking occasionally to mix. After cooling, add diluted methanol (1 in 2) to make exactly 50 mL, and filter. Discard the first 10 mL of the filtrate, and pipet 5 mL of the subsequent filtrate, add 5 mL of the internal standard solution, and then add diluted methanol (1 in 10) to make exactly 25 mL. Use this solution as the test solution. Separately, weigh accurately about 22 mg of tipepidine hibenzate RS, previously dried in a phosphorus pentoxide desiccator in vacuum at 60 ℃ for 3 hours, dissolve in 10 mL of diluted acetic acid(100) (1 in 2) and 30 mL of methanol, and add diluted methanol (1 in 2) to make exactly 50 mL. Pipet 5 mL of this solution, add exactly 5 mL of the internal standard solution, then add diluted methanol (1 in 5) to make 25 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak area ratios, Q_T and Q_S, of tipepidine to the peak area of the internal standard, respectively.

Amount (mg) of tipepidine hibenzate ($C_{18}H_{17}NS_2 \cdot C_{14}H_{10}O_4$)
$$= \text{Amount (mg) of tipepidine hibenzate RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of dibucaine hydrochloride in methanol (1 in 2000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column, about 4 to 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

Mobile phase: A mixture of a solution of sodium lauryl sulfate in diluted phosphoric acid (1 in 1000) (1 in 500), acetonitrile and 2-propanol (3 : 2 : 1).

Flow rate: Adjust the flow rate so that the retention time of tipepidine is about 7 minutes.

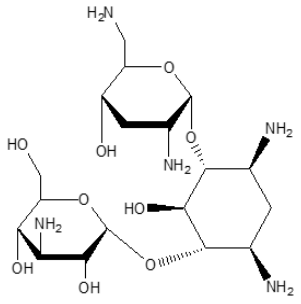
System suitability

System performance: Proceed with 20 μL of the standard solution under the above operating conditions; tipepidine and the internal standard are eluted in this order with the resolution being NLT 10.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the ratios of the peak area of tipepidine to the peak area of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Tobramycin
토브라마이신



$C_{18}H_{37}N_5O_9$: 467.51

(2*S*,3*R*,4*S*,5*S*,6*R*)-4-Amino-2-[(1*S*,2*S*,3*R*,4*S*,6*R*)-4,6-diamino-3-[(2*R*,3*R*,5*S*,6*R*)-3-amino-6-(aminomethyl)-5-hydroxyoxan-2-yl]oxy-2-hydroxycyclohexyl]oxy-6-(hydroxymethyl)oxane-3,5-diol [*32986-56-4*]

Tobramycin is an aminoglycoside substance having antibacterial activity produced by cultivating *Streptomyces tenebrarius.*

Tobramycin contains NLT 900 μg and NMT 1060 μg (potency) of tobramycin ($C_{18}H_{37}N_5O_9$) per mg, calculated on the anhydrous basis.

Description Tobramycin occurs as a white to pale yellowish white crystalline powder.

It is very soluble in water, freely soluble in formamide, very slightly soluble in methanol, and very slightly soluble in ethanol(95).

It is hygroscopic.

Identification (1) Dissolve 10 mg each of Tobramycin and tobramycin RS in 1 mL of water and use each solution as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 4 μL each of the test solution and the standard solution on a plate of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ammonia water, 1-butanol, and methanol (5 : 5 : 2) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray ninhydrin TS evenly on the plate, and heat it at 100 ℃ for 5 minutes; the R_f values of the spots obtained from the test and the standard solutions are the same.

(2) Determine ^1H as directed under the nuclear magnetic resonance spectrum using the heavy aqueous solution (1 in 125) of Tobramycin for nuclear magnetic resonance spectrum and sodium 3-trimethylsilylpropanesulfonate for nuclear magnetic resonance spectrum as an internal standard; it exhibits single-line signals A, C around δ 5.1 ppm, δ 2.6 to 4.0 ppm, and δ 1.0 to 7.0 ppm, respectively, and the area intensity ratio A : B : C of each signal is about 1 : 8 : 2.

Optical rotation $[\alpha]_D^{20}$: Between +138 and +148° (1 g, calculated on the anhydrous basis, water, 25 mL, 100 mm).

pH Dissolve 0.10 g of Tobramycin in 10 mL of water; the pH of this solution is between 9.5 and 11.5

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Tobramycin in 10 mL of water; the solution is clear, and colorless to pale yellow.

(2) ***Heavy metals***—Proceed with 1.0 g of Tobramycin according to Method 2 and perform the test. Prepare the control solution with 3.0 mL of the lead standard solution (NMT 30 ppm).

(3) ***Related substances***—Dissolve 80 mg of Tobramycin in 10 mL of diluted ammonia water(28) (1 in 250) and use this solution as the test solution. Pipet 1 mL of this solution, add diluted ammonia water(28) (1 in 250) to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ammonia water(28), ethanol(95) and 2-butanone (1 : 1 : 1) as the developing solvent to a distance of about 10 cm, air-dry the plate, and heat it at 110 ℃ for 10 minutes. Immediately, spray a mixture of water and sodium hypochlorite TS (4 : 1) on the plate, air dry it, and then spray the potassium iodide starch TS again; the spots other than the principal spots obtained from the test solution are not intense than the spots obtained from the standard solution.

Water NMT 11.0% (0.1 g, volumetric titration, direct titration). However, use a mixture of formamide for water determination and methanol for water determination (3 : 1) instead of methanol for water determination.

Residue on ignition NMT 1.0% (0.5 g).

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxin Less than 2.0 EU per mg of tobramycin (potency) when used in the manufacturing of sterile preparations.

Assay Dissolve about 50 mg (potency) each of Tobramycin and tobramycin RS, weighed accurately, in water to make exactly 250 mL, and use these solutions as the test solution and the standard solution. Take exactly 4.0 mL each of the test solution and standard solution and put them in each 50-mL volumetric flask, and add 10 mL of 2,4-dinitrofluorobenzene solution and 10 mL of 2-amino-2-hydroxymethyl-1,3-propanediol solution, and shake to mix, and leave on a steam bath at 60 ± 2 ℃ for 50 ± 5 minutes, and allow to stand at room temperature for 10 minutes. Add about 20 mL of acetonitrile, cool at room temperature, make exactly 50 mL with acetonitrile, filter it through a membrane filter with a pore diameter of NMT 0.5 μm, and use the solutions as the test solution, standard solution, and derivative solution, respectively. Take exactly 20 μL each of the test solution, standard solution, and derivative solution, and perform the test as directed under the Liquid Chromatography under the following conditions, and determine the peak areas A_T and A_S of tobramycin in each solution.

$$\text{Potency (μg) of Tobramycin } (C_{18}H_{37}N_5O_9) = \text{Potency (μg) of tobramycin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 365 nm).

Column: A stainless steel column about 4 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: Dissolve 2.0 g of 2-amino-2-hydroxymethyl-1,3-propanediol in 800 mL of water. Add 20 mL of sulfuric acid solution, 0.5 mol/L, into this solution, and add acetonitrile to make exactly 2000 mL.

Flow rate: 1.2 mL/min

System suitability

System performance: Weigh accurately 5 mg of *p*-naphtholbenzein to make exactly 20 mL with acetonitrile. Then, take 2 mL of this solution, add the standard solution and the derivative solution to make 10 mL, and use this solution as the system suitability solution. Inject the system suitability solution; the relative retention time of *p*-naphtholbenzein with respect to tobramycin is about 0.6, and the resolution is NLT 4.0.

Packaging and storage Preserve in tight containers.

Tobramycin Injection
토브라마이신 주사액

Tobramycin Injection contains NLT 90.0% and NMT 110.0% of the labeled amount of tobramycin ($C_{18}H_{37}N_5O_9$: 467.52).

Method of preparation Prepare as directed under Injections, with Tobramycin.

Description Tobramycin Injection occurs as a colorless to a pale yellow, clear liquid.

Identification Weigh accurately about 10 mg (potency) of Tobramycin Injection, add water to make exactly 1 mL, and use this solution as the test solution. Separately, weigh accurately 10 mg (potency) of tobramycin RS, add water to make exactly 1 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Thin Layer Chromatography. Spot 4 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of ammonia water, 1-butanol and methanol (5 : 5 : 2) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly ninhydrin TS on the plate and heat the plate at 100 ℃ for 5 minutes; the R_f values of the spots obtained from the test solution and the standard solution are the same.

pH Between 5.0 and 7.0.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.50 EU per mg (potency) of tobramycin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Perform the test as directed in the Assay under Tobramycin. Prepare the test solution by taking an amount of Tobramycin Injection equivalent to about 50 mg (potency) according to the labeled potency and dissolving in water to make exactly 250 mL.

Packaging and storage Preserve in hermetic containers.

Tobramycin Ophthalmic Ointment
토브라마이신 안연고

Tobramycin Ophthalmic Ointment contains NLT 90.0% and NMT 120.0% of the labeled amount of tobramycin ($C_{18}H_{37}N_5O_9$: 467.52).

Method of preparation Prepare as directed under Ophthalmic Solutions, with Tobramycin.

Identification Perform the test according to the Identification (1) of Tobramycin. Weigh an appropriate amount of Tobramycin Ophthalmic Ointment, put in a separatory funnel, and dissolve in 10 mL of chloroform. Add water, shake to mix, and allow to stand until the two liquid layers are completely separated. Take the water layer, and dilute it with water to obtain a solution containing 3 mg (potency) per mL, and use this solution as the test solution. Separately, weigh an appropriate amount of tobramycin RS, dissolve in water to obtain a solution containing 3 mg (potency) per mL, and use this solution as the standard solution. The drop volume of the test solution and the standard solution is 5 μL.

Water NMT 1.0% (1.0 g, volumetric titration, direct titration).

Sterility Meets the requirements.

Foreign metallic matter Meets the requirements.

Assay Proceed as directed under the Assay under Tobramycin. However, weigh accurately an appropriate amount of Tobramycin Ophthalmic Ointment to place in a separatory funnel, and add 50 mL of ether. Extract 3 times with 25 mL of sterile purified water, combine the extracts, and add sterile purified water to make exactly 100 mL. Take an appropriate amount of this solution and dilute with sterile purified water to obtain a solution containing 0.2 mg (potency) per mL, and use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Tobramycin Ophthalmic Solution
토브라마이신 점안액

Tobramycin Ophthalmic Solution contains NLT 90.0% and NMT 120.0% of the labeled amount of tobramycin ($C_{18}H_{37}N_5O_9$: 467.52).

Method of preparation Prepare as directed under Ophthalmic Solutions, with Tobramycin.

Identification Perform the test according to the Identification (1) of Tobramycin. However, weigh an appropriate amount of Tobramycin Ophthalmic Solution and tobramycin RS, dissolve in water to make a solution containing 3 mg (potency) per mL, and use this solution as the test solution and standard solution, respectively.

pH Between 7.0 and 8.0.

Sterility Meets the requirements.

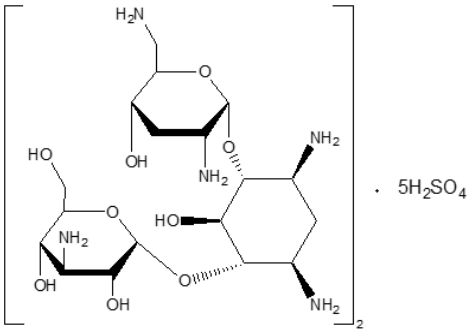
Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in ophthalmic solutions Meets the requirements.

Assay Proceed as directed under the Assay under Tobramycin. However, take an amount of Tobramycin Ophthalmic Solution, equivalent to about 50 mg (potency), according to the labeled potency, dissolve it in water to make exactly 250 mL, and use this solution as the test solution.

Packaging and storage Preserve in tight containers.

Tobramycin Sulfate
토브라마이신황산염



$(C_{18}H_{37}N_5O_9)_2.5H_2SO_4$: 1425.43

(2*S*,3*R*,4*S*,5*S*,6*R*)-4-Amino-2-[(1*S*,2*S*,3*R*,4*S*,6*R*)-4,6-diamino-3-[(2*R*,3*R*,5*S*,6*R*)-3-amino-6-(aminomethyl)-5-hydroxyoxan-2-yl]oxy-2-hydroxycyclohexyl]oxy-6-(hydroxymethyl)oxane-3,5-diol;sulfuric acid [*49842-07-1*]

Tobramycin Sulfate contains NLT 634 μg and NMT 739 μg (potency) of tobramycin ($C_{18}H_{37}N_5O_9$: 467.52) per mg, calculated on the anhydrous basis.

Description Tobramycin Sulfate occurs as a white to pale yellowish powder.
It is freely soluble in water, slightly soluble in ethanol(95), and practically insoluble in chloroform or ether.
It is hygroscopic.

Identification (1) Perform the test according to the Iden-

tification for Tobramycin. However, Dissolve about 60 mg (potency) each of Tobramycin Sulfate and tobramycin RS, weighed respectively, in water to make a solution containing 6 mg (potency) per mL, and use these solutions as the test solution and the standard solution.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

(3) Tobramycin Sulfate responds to the Qualitative Analysis for sulfate.

pH Dissolve 0.4 g of Tobramycin Sulfate (potency) in 10 mL of water; the pH is between 6.0 and 8.0.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Tobramycin Sulfate according to Method 2 and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(2) ***Related substances***—Dissolve 50 mg of Tobramycin Sulfate, weighed accurately, in 7 mL of water, adjust the pH to 5.5 with 1 mol/L sulfuric acid, then add water to make 10 mL and use this solution as the test solution. Pipet 1 mL of the test solution, add water to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 1 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography and develop the thin later plate with a mixture of sodium chloride solution (29.2 in 100), alcohol and water (50 : 30 : 20) as the developing solvent to a distance of about 15 cm, and dry the thin-layer chromatographic plate by using hot air, and then heat it at 110 ℃ for 10 minutes. Spray diluted sodium hypochlorite solution TS (1 in 5) on the hot thin-layer chromatographic plate and add a drop of potassium iodide starch TS to the lower part of the circular line of the thin-layer chromatographic plate and blow cold air until a very light blue color appears. Evenly spray potassium iodide starch solution on the thin-layer chromatographic plate; it exhibits bluish-purple spots. Spots other than the principal spot obtained from the test solution are not more intense than the spots obtained from the standard solution (NMT 1.0%).

Water NMT 2.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 1.0% (1 g).

Sterility It meets the requirements when used in the manufacturing of sterile preparations. However, it is excluded in cases where there is a terminal sterilization process in the manufacturing of sterile preparations.

Bacterial endotoxins Less than 2.0 EU per mg of tobramycin (potency) when used in the manufacturing of sterile preparations.

Assay Weigh accurately 50 mg of Tobramycin Sulfate and tobramycin RS (potency), dissolve each in the water phase to make exactly 250 mL, and use these solutions as the test solution and the standard solution. Take exactly 4.0 mL each of the test solution and the standard solution, add them in each 50-mL volumetric flask, add 10 mL of 2,4-dinitrobenzene TS and 10 mL of 2-amino-2-hydroxymethyl-1,3-propanediol TS, and shake to mix for 60 minutes, and leave in a ±2 °C on a steam bath for 50±5 minutes and allow to stand at room temperature for 10 minutes. Add about 20 mL of acetonitrile, cool at room temperature, make exactly 50 mL with acetonitrile, filter it through a membrane filtration method with a pore diameter of NMT 0.5 μm, and use these solutions as the test solution, the standard solution, and the derivative solution, respectively. Take exactly 20 μL each of the test solution, the standard solution, and the derivative solution, and perform the test as directed under the Liquid Chromatography under the following conditions, and determine the peak areas, A_T and A_S, of Tobramycin in each solution.

$$\text{Potency (μg) of tobramycin } (C_{18}H_{37}N_5O_9) = \text{Potency (μg) of tobramycin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 365 nm).

Column: A stainless steel column about 4 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: Dissolve 2.0 g of 2-amino-2-hydroxymethyl-1,3-propanediol in 800 mL of water. Add 20 mL of 1 mol/L sulfuric acid solution into this solution, and add acetonitrile to make exactly 2000 mL.

Flow rate: 1.2 mL/min

System performance: Weigh accurately 5 mg of *p*-naphtholbenzein to make exactly 20 mL with acetonitrile, and then, take 2 mL of this solution, and add the standard solution and the derivative solution to make 10 mL, and use this solution as the system suitability solution. Inject the system suitability solution; the relative retention time of *p*-naphtholbenzein with respect to tobramycin is about 0.6, and the resolution is NLT 4.0.

Packaging and storage Preserve in tight containers.

Tobramycin Sulfate Injection
토브라마이신황산염 주사액

Tobramycin Sulfate Injection contains NLT 90.0% and NMT 120.0% of the labeled amount of tobramycin ($C_{18}H_{37}N_5O_9$: 467.52).

Method of preparation Prepare as directed under Injections, with Tobramycin Sulfate.

Description Tobramycin Sulfate Injection occurs as col-

orless to yellowish white, clear liquid.

Identification (1) Dissolve about 60 mg (potency) each of Tobramycin Sulfate Injection and tobramycin RS in water to obtain solutions having known concentrations of 6 mg (potency) per mL, and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot an appropriate amount each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol, strong ammonia water and chloroform (60 : 30 : 25) as the developing solvent, and air-dry the plate. Spray evenly a mixture of 100 mL of a solution of 1% ninhydrin in butanol and 1 mL of pyridine on the plate and heat the plate at 110 ℃ for 10 minutes; the R*f* values of the spots obtained from the test solution and the standard solution are the same.

(2) The retention times of the major peaks from the test solution and the standard solution obtained in the Assay are the same.

pH Between 3.0 and 6.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 2.0 EU per mg (potency) of tobramycin.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Weigh accurately 50 mg (potency) of Tobramycin Sulfate Injection, add water to make 250 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg (potency) of tobramycin RS, add water to make exactly 250 mL, and use this solution as the standard solution. Pipet 4.0 mL each of the test solution and the standard solution, place in each 50 mL-volumetric flask, add 10 mL of 2,4-dinitrofluorobenzene TS and 10 mL of tris(hydroxymethyl)aminomethane TS, and shake to mix. Allow each to stand on a steam bath at 60 ± 2 ℃ for 50 ± 5 minutes and then at the room temperature for 10 minutes. Add about 20 mL of acetonitrile to each, cool to the room temperature, add acetonitrile to each to make exactly 50 mL, and filter through a membrane filter of 0.5 μm in pore diameter. Perform the test with 20 μL each of the resulting solutions as directed under the Liquid Chromatography according to the following conditions, and calculate peak areas, A_T and A_S, of tobramycin in the solutions, respectively.

Potency of (μg) tobramycin ($C_{18}H_{37}N_5O_9$)

$$= \text{Potency (μg) of tobramycin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 365 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (10 μm in particle diameter).

Mobile phase: Dissolve 2.0 g of tris(hydroxymethyl)aminomethane in 800 mL of water. To this solution, add 20 mL of 1 mol/L sulfuric acid and add acetonitrile to make exactly 2000 mL.

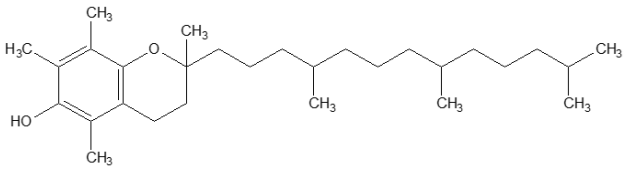
Flow rate: 1.2 mL/min

System suitability

System performance: Weigh accurately 5 mg of *p*-naphtholbenzein, add acetonitrile to make exactly 100 mL, and use this solution as the resolution measurement solution. Inject a mixture of the resolution measurement solution and the standard solution; the relative retention time of *p*-naphtholbenzein with respect to tobramycin is about 0.6 with the resolution between the two peaks being NLT 4.0.

Packaging and storage Preserve in hermetic containers.

Tocopherol
토코페롤



Vitamin E

dl-α-Tocopherol $C_{29}H_{50}O_2$: 430.71

(2*R*)-2,5,7,8-Tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-ol [*10191-41-0*]

Tocopherol contains NLT 96.0% and NMT 102.0% of *dl*-α-tocopherol ($C_{29}H_{50}O_2$).

Description Tocopherol occurs as a yellow to reddish brown, clear, viscous liquid, which is odorless.
It is miscible with ethanol(99.5), acetone, ether, chloroform or vegetable oil.
It is freely soluble in ethanol(95), and practically insoluble in water.
It has no optical rotation.
It is oxidized by the action of air and light, turning dark red.

Identification (1) Dissolve 10 mg of Tocopherol in 10 mL of ethanol(99.5), add 2 mL of nitric acid, and heat at 75 ℃ for 15 minutes; the resulting solution exhibits a red to orange color.

(2) Determine the infrared spectra of Tocopherol

and tocopherol RS as directed under the liquid film method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Refractive index n_D^{20}: Between 1.503 and 1.507.

Specific gravity d_{20}^{20}: Between 0.947 and 0.955.

Absorbance $E_{1cm}^{1\%}$ (292 nm): Between 71.0 and 76.0 (10 mg, ethanol(99.5), 200 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Tocopherol in 10 mL of ethanol(99.5); the solution is clear and the color is not more intense than the control solution C.

(2) ***Heavy metals***—Proceed with 1.0g of Tocopherol according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

Assay Weigh accurately about 50 mg each of Tocopherol and tocopherol RS, dissolve each in ethanol(99.5) to make them exactly 50 mL, and use these solutions as the test solution and the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak heights, H_T and H_S of tocopherol from each of the solutions.

$$\text{Amount (mg) of tocopherol } (C_{29}H_{50}O_2) = \text{amount (mg) of tocopherol RS} \times \frac{H_T}{H_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 292 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of methanol and water (49 : 1).

Flow rate: Adjust the flow rate so that the retention time of tocopherol is about 10 minutes.

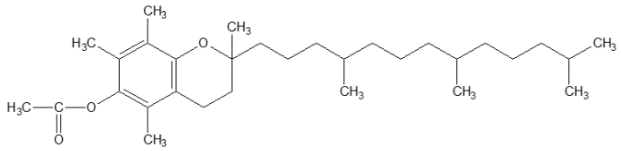
System suitability

System performance: Dissolve 50 mg each of Tocopherol and tocopherol acetate in 50 mL of ethanol(99.5). Proceed with 20 μL of this solution under the above operating conditions; tocopherol and tocopherol acetate are eluted in this order with the resolution being NLT 2.6.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak height of tocopherol is NMT 0.8%.

Packaging and storage Preserved in light-resistant, tight containers, as well-filled or under the nitrogen atmosphere.

Tocopherol Acetate
토코페롤아세테이트



Vitamin E Acetate

dl-α-Tocopherol Acetate $C_{31}H_{52}O_3$: 472.74

[(2*R*)-2,5,7,8-Tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-yl]acetate [*7695-91-2*]

Tocopherol Acetate contains NLT 96.0% and NMT 102.0% of *dl*-α-tocopherol acetate ($C_{31}H_{52}O_3$).

Description Tocopherol Acetate occurs as a colorless to yellow, clear, viscous liquid, and is odorless.
It is miscible with ethanol(99.5), acetone, hexane, ether, chloroform or vegetable oil.
It is freely soluble in ethanol(95), and practically insoluble in water.
It shows no optical rotation.
It is affected by air and light.

Identification (1) Dissolve 50 mg of Tocopherol Acetate in 10 mL of ethanol(99.5) mL, add 2 mL of nitric acid, and heat at 75 ℃ for 15 minutes; the resulting solution exhibits a red to orange color.

(2) Determine the infrared spectra of Tocopherol Acetate and tocopherol acetate RS as directed under the liquid film method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Refractive index n_D^{20}: Between 1.494 and 1.499.

Specific gravity d_{20}^{20}: Between 0.952 and 0.966.

Absorbance $E_{1cm}^{1\%}$ (284 nm): Between 41.0 and 45.0 (10 mg, ethanol(99.5), 100 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Tocopherol Acetate in 10 mL of ethanol(99.5); the solution is clear and its color is not more intense than the following control solution.

Control solution—To 0.5 mL of the colorimetric stock solution of iron(III) chloride, add 0.5 mol/L hydrochloric acid TS to make 100 mL.

(2) ***Heavy metals***—Carbonize 1.0 g of Tocopherol Acetate by gentle heating. After cooling, add 10 mL of a solution of magnesium nitrate in ethanol(95) (1 in 10), and ignite the ethanol to burn. After cooling, add 1 mL of sulfuric acid, proceed according to Method 4 and perform

the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***α-tocopherol***—Dissolve 0.10 g of Tocopherol Acetatein exactly 10 mL of hexane, and use this solution as the test solution. Separately, weigh 50 mg of tocopherol RS and add hexane to make exactly 100 mL. Pipet 1 mL of this solution, add hexane to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of toluene and acetic acid(100) (19 : 1) to a distance of about 10 cm, and air-dry the plate. Spray evenly a solution of iron(III) chloride ethanol(99.5) (1 in 500), again spray evenly a solution of 2,2'-dipyridyl ethanol(99.5) (1 in 200), and allow to stand for 2 - 3 minutes; the spot obtained from the test solution, of which location corresponds to that of the spot from the standard solution, is neither larger nor more intense than the spot from the standard solution.

Assay Weigh accurately about 50 mg each of Tocopherol Acetate and tocopherol acetate RS, dissolve in ethanol(99.5) respectively to make them exactly 50 mL, and use these solutions as the test solution and the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak heights, H_T and H_S of tocopherol acetate from each of the solutions.

$$\text{Amount (mg) of tocopherol acetate } (C_{31}H_{52}O_3) = \text{amount (mg) of tocopherol acetate RS} \times \frac{H_T}{H_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 284 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of methanol and water (49 : 1).

Flow rate: Adjust the flow rate so that the retention time of tocopherol acetate is about 12 minutes.

System suitability

System performance: Dissolve 50 mg each of Tocopherol Acetate and tocopherol RS in 50 mL of ethanol(99.5). Proceed with 20 μL of this solution under the above operating conditions; tocopherol and tocopherol acetate are eluted in this order with the resolution being NLT 2.6.

System repeatability: Repeat the test 5 times with 20 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak height of tocopherol acetate is NMT 0.8%.

Packaging and storage Preserve in light-resistant, tight containers.

50% Tocopherol Acetate Powder
토코페롤아세테이트 2배산

50% Tocopherol Acetate Powder, when dried, contains NLT 50.0% of tocopherol acetate ($C_{31}H_{52}O_3$: 472.74).

Method of preparation Prepare by finely dispersing Tocopherol Acetate in a diluent such as gelatin. 50% Tocopherol Acetate Powder is a drug substance.

Description 50% Tocopherol Acetate Powder occurs as a white to pale yellow powder.

Identification (1) Dissolve 0.1 g of 50% Tocopherol Acetate Powder in 10 mL of anhydrous ethanol(99.5), add 2 mL of nitric acid and heat for 15 minutes at 75 °C; the solution exhibits a red to orange color.

(2) Weigh accurately an amount equivalent to 50 mg of tocopherol acetate, add 5 mL of 0.01 mol/L hydrochloric acid, and mix by sonicating on a 60 °C water bath. To this solution, add 5 mL of anhydrous ethanol(99.5) and 10 mL of cyclohexane, shake for 1 minute, centrifuge for 5 minutes, and use the supernatant as the test solution. Separately, dissolve 50 mg of tocopherol acetate RS in 10 mL of cyclohexane and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of cyclohexane and diethyl ether (80 : 20) as the developing solvent to about 15 cm, air-dry the plate at room temperature, and expose it to ultraviolet light (main wavelength: 254 nm); the R_f value and the color of the spots obtained from the test solution and the standard solution are the same.

Loss on drying NMT 6.0% (1 g, 105 °C, 4 hours).

Assay Weigh accurately 0.1 g of 50% Tocopherol Acetate Powder, previously dried, place in a 50-mL volumetric flask and add 1 mL of water to suspend. Then add anhydrous ethanol(99.5) to make exactly 50 mL and use this solution as the test solution. Separately, weigh accurately about 0.1 g of tocopherol acetate RS, add anhydrous ethanol(99.5) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of tocopherol acetate, A_T and A_S, in each solution.

$$\text{Amount (mg) of tocopherol acetate } (C_{31}H_{52}O_3)$$

= Amount (mg) of tocopherol acetate RS × A_T / A_S

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 284 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: Mixture of methanol and water (49 : 1).

Flow rate: 1.6 mL/min

System suitability

System performance: Dissolve 50.0 mg each of tocopherol acetate and tocopherol in 50 mL of anhydrous ethanol. Proceed with 20 μL of this solution according to the above conditions; tocopherol and tocopherol acetate are eluted in this order with the resolution being NLT 2.6.

System repeatability: Repeat the test 6 times with the standard solution according to the above conditions; the relative standard deviation of the peak area of tocopherol acetate is NMT 0.8%.

Packaging and storage Preserve in light-resistant, tight containers.

Tocopherol Acetate and Magnesium Oxide Capsules
토코페롤아세테이트·산화마그네슘 캡슐

Tocopherol Acetate and Magnesium Oxide Capsules contain NLT 90.0% and NMT 150.0% of the labeled amount of tocopherol acetate ($C_{31}H_{52}O_3$: 472.74) and NLT 90.0% and NMT 110.0% of the labeled amount of magnesium in the magnesium oxide (Mg : 24.31).

Method of preparation Prepare as directed under Capsules, with Tocopherol Acetate and Magnesium Oxide.

Identification (1) ***Tocopherol acetate***—Perform the test with Tocopherol Acetate and Magnesium Oxide Capsules as directed under the Analysis for Vitamins.

(2) ***Magnesium in the magnesium oxide***—Perform the test with Tocopherol Acetate and Magnesium Oxide Capsules as directed under the Analysis for Minerals.

Disintegration Meets the requirements.

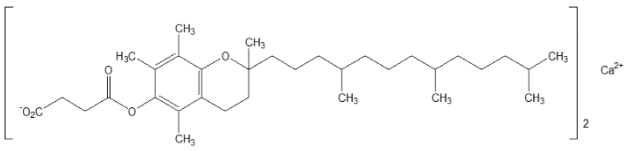
Uniformity of dosage units Meets the requirements.

Assay (1) ***Tocopherol acetate*—**Weigh accurately the mass of the contents of NLT 20 capsules of Tocopherol Acetate and Magnesium Oxide Capsules and perform the test as directed under the Analysis for Vitamins.

(2) ***Magnesium in the magnesium oxide*—**Weigh accurately the mass of the contents of NLT 20 capsules of Tocopherol Acetate and Magnesium Oxide Capsules and perform the test as directed under the Analysis for Minerals

Packaging and storage Preserve in tight containers.

Tocopherol Calcium Succinate
토코페롤숙시네이트칼슘



Vitamin E Calcium Succinate

$C_{66}H_{106}CaO_{10}$: 1099.62

Calcium 4-oxo-4-[[(2*R*)-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-3,4-dihydro-chromen-6-yl]oxy]butanoate [*14638-18-7*]

Tocopherol Calcium Succinate, when dried, contains NLT 96.0% and NMT 102.0% of *dl*-α-tocopherol calcium succinate ($C_{66}H_{106}CaO_{10}$).

Description Tocopherol Calcium Succinate occurs as a white to yellowish white powder, which is odorless.
It is freely soluble in chloroform or carbon tetrachloride, and practically insoluble in water, ethanol(95) or acetone.
Add 7 mL of acetic acid(100) to 1 g of Tocopherol Calcium Succinate, and shake to mix; it dissolves, and produces a turbidity after being allowed to stand for a while.
It dissolves in acetic acid(100).
It has no optical rotation.

Identification (1) Dissolve to 50 mg of Tocopherol Calcium Succinate with 1 mL of acetic acid(100), add 9 mL of ethanol(99.5), and mix. Add 2 mL of fuming nitric acid, and heat at 75 ℃ for 15 minutes; the solution exhibits a red to orange color.

(2) Dissolve 80 mg each of Tocopherol Calcium Succinate and tocopherol calcium succinate RS, previously dried, in 0.2 mL of chloroform, and determine the infrared spectra of these solutions as directed under the liquid film method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 5 g of Tocopherol Calcium Succinate in 30 mL of chloroform, add 10 mL of hydrochloric acid, shake to mix for 20 minutes, take the water layer, and neutralize with ammonia TS; the solution responds to the Qualitative Analysis for calcium salt.

Absorption $E_{1cm}^{1\%}$ (286 nm): Between 36.0 and 40.0 (10 mg, chloroform 100 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Tocopherol Calcium Succinate in 10 mL of chloroform; the resulting solution is clear and it's color is not more intense than the following control solution.

Control solution—To 0.5 mL of the colorimetric stock solution of iron(III) chloride, and add 0.5 mol/L hydrochloric acid TS to make 100 mL.

(2) ***Alkali***—Add 10 mL of ether, 2 mL of water, 1 drop of phenolphthalein TS and 0.10 mL of 0.1 mol/L hydrochloric acid TS to 0.20 g of Tocopherol Calcium Succinate, and shake to mix; the water layer does not exhibit a red color.

(3) ***Chloride***—Dissolve 0.10 g of Tocopherol Calcium Succinate in 4 mL of acetic acid(100), add 20 mL of water and 50 mL of ether, shake well to mix, and collect the water layer. Add 10 mL of water into the ether layer, shake to mix, and collect the water layer. Combine the water layers, and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution in the same manner as in the test solution using 0.60 mL of 0.01 mol/L of hydrochloric acid instead of Tocopherol Calcium Succinate (NMT 0.212%).

(4) ***Heavy metals***—Proceed with 1.0 g of Tocopherol Calcium Succinate according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(5) ***Arsenic***—Proceed with 1.0 g of Tocopherol Calcium Succinate according to Method 3 and perform the test (NMT 2 ppm).

(6) ***α-tocopherol***—Dissolve 0.10 g of Tocopherol Calcium Succinate with chloroform to make exactly 10 mL, and use this solution as the test solution. Separately, dissolve 50 mg of tocopherol RS with chloroform to make exactly 100 mL. Pipet 1 mL of this solution, add chloroform to make exactly 10 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of toluene and acetic acid(100) (19 : 1) to a distance of about 10 cm, and air-dry the plate. Spray evenly a solution of iron(III) chloride hexahydrate in ethanol(99.5) (1 in 500) on the plate, again spray evenly a solution of 2,2'-dipyridyl in ethanol(99.5) (1 in 200), and allow to stand for 2 - 3 minutes; the spot obtained from the test solution, of which location corresponds to that of the spot from the standard solution, is neither larger nor more intense than the spot from the standard solution.

Loss on drying NMT 2.0% (1 g, in vacuum, phosphorus pentoxide, 24 hours).

Assay Weigh accurately about 50 mg each of Tocopherol Calcium Succinate and tocopherol succinate RS, previously dried, disslove with a mixture of ethanol(99.5) and diluted acetic acid(100) (1 in 5) (9 : 1) to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak heights, H_T and H_S, of tocopherol succinate from these solutions.

$$\text{Amount (mg) of tocopherol calcium succinate } (C_{66}H_{106}CaO_{10}) = \text{Amount (mg) of tocopherol succinate RS} \times \frac{H_T}{H_S} \times 1.0358$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 284 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of methanol, water and acetic acid(100) (97 : 2 : 1).

Flow rate: Adjust the flow rate so that the retention time of tocopherol succinate is about 8 minutes.

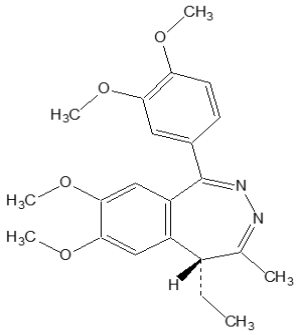
System suitability

System performance: Weigh 50 mg each of tocopherol succinate and tocopherol, and dissolve in a mixture of ethanol(99.5) and diluted acetic acid(100) (1 in 5) (9 : 1) to make 50 mL. Proceed with 20 μL of this solution according to the above operating conditions; tocopherol succinate and tocopherol are eluted in this order with a resolution being 2.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak height of tocopherol succinate is NMT 0.8%.

Packaging and storage Preserve in light-resistant, tight containers.

Tofisopam
토피소팜



and enantiomer

$C_{22}H_{26}N_2O_4$: 382.45

1-(3,4-Dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5*H*-2,3-benzodiazepine [*22345-47-7*]

Tofisopam, when dried, contains NLT 98.0% and NMT 101.0% of tofisopam ($C_{22}H_{26}N_2O_4$).

Description Tofisopam occurs as a pale yellowish white crystalline powder.

It is freely soluble in acetic acid(100), soluble in acetone, sparingly soluble in ethanol(95), slightly soluble in ether, and practically insoluble in water.
A solution of Tofisopam in ethanol(95) (1 in 100) shows no optical rotation.

Identification (1) Determine the absorption spectra of solutions of Tofisopam and tofisopam RS in ethanol(95) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit the same intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Tofisopam and tofisopam RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 155 and 159 ℃.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Tofisopam according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Proceed with 1.0 g of Tofisopam according to Method 3 and perform the test (NMT 2 ppm).

(3) ***Related substances***—Dissolve 50 mg of Tofisopam in 10 mL of acetone and use this solution as the test solution. Add the acetone to 1.0 mL of this solution to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of ethyl acetate, acetone, methanol and formic acid (24 : 12 : 2 : 1) (as the developing solvent) to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot obtained from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, silica gel, 60 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Tofisopam, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L hydrochloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 38.25 mg of $C_{22}H_{26}N_2O_4$

Packaging and storage Preserve in light-resistant, tight containers.

Tofisopam Tablets
토피소팜 정

Tofisopam Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of tofisopam ($C_{22}H_{26}N_2O_4$: 382.45).

Method of preparation Prepare as directed under Tablets, with Tofisopam.

Identification Weigh an amount, equivalent to 50 mg of tofisopam according to the labeled amount of Tofisopam Tablets, add 10 mL of acetone, shake to dissolve, and filter. Use the filtrate as the test solution. Separately, weigh 25 mg of tofisopam RS, dissolve in 5 mL of acetone, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography Next, develop the plate with a mixture of ether, acetic acid(100) and ethanol(95) (30 : 9 : 5) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

Purity ***Related substances*—**The test solution obtained in the Identification is used as the test solution. Dilute 0.2 mL of the test solution with 10 mL of ethanol(95) and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the above Identification. The spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution (NMT 2%).

Disintegration Meets the requirements.

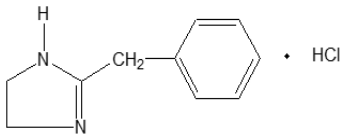
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Tofisopam Tablets and powder. Weigh accurately an amount, equivalent to about 50 mg of tofisopam ($C_{22}H_{26}N_2O_4$), add 50 mL of ethanol(95), shake to mix, and add ethanol(95) to make exactly 100 mL. Centrifuge a portion of this solution, pipet 1 mL of the supernatant, add ethanol(95) to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of tofisopam RS and add ethanol(95) to make exactly 100 mL. Pipet 1 mL of this solution, add ethanol(95) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using ethanol as a control solution, and determine the absorbances, A_T and A_S, at the wavelength of 310 nm.

Amount (mg) of tofisopam ($C_{22}H_{26}N_2O_4$)
= Amount (mg) of tofisopam RS × (A_T / A_S)

Packaging and storage Preserve in well-closed containers.

Tolazoline Hydrochloride
톨라졸린염산염



$C_{10}H_{12}N_2$·HCl: 196.68
2-Benzyl-4,5-dihydro-1*H*-imidazolehydrochloride
[*59-97-2*]

Tolazoline Hydrochloride contains NLT 98.0% and NMT 101.0% of tolazoline hydrochloride ($C_{10}H_{12}N_2$·HCl), calculated on the dried basis.

Description Tolazoline Hydrochloride occurs as a white to grayish white crystalline powder.
It is freely soluble in water or ethanol(95).
An aqueous solution of Tolazoline Hydrochloride appears weekly acidic on the litmus paper.

Identification (1) Determine the infrared spectra of Tolazoline Hydrochloride and tolazoline hydrochloride RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit a maximum at the same wavenumbers.

(2) Proceed the test according to the Related substances; the R_f value of the principal spot from the identification solution is the same as the R_f value of the spot from the standard solution (1).

Melting point Between 172.0 and 176.0 ℃.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Tolazoline Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Weigh accurately an appropriate amount of Tolazoline Hydrochloride, dissolve in methanol to make a solution containing 20 mg per mL, and use this solution as the test solution. Take an appropriate amount of the test solution, dissolve in methanol to make a solution containing 100 μg per mL, and use this solution as the identification test solution. Separately, weigh accurately an appropriate amount of tolazoline hydrochloride RS (previously dried in vacuum for 4 hours with silica gel), dissolve in methanol to make a solution containing 100 μg per mL, and use this solution as the standard solution (1). Pipet 4 mL, 3 mL, 2 mL and 1 mL each of this solution, add methanol to make 5 mL, respectively, and use these solutions as the standard solutions (2), (3), (4) and (5). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution, the identification solution and the standard solutions (1) - (5) on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of methanol and ammonia TS (95 : 5) (as a developing solvent) to a distance of about 15 cm, and dry the plate for at least 30 minutes. Expose the plate to chlorine gas for 5 minutes at most, and air-dry until the chlorine gas disappears. Spray the coloring agent, and determine the sum of the intensities by comparing the intensities of all spots other than the principal spot from the test solution with the intensities of the spots from each of the standard solutions; it is NMT 1.0%.

Coloring agent—Dissolve 0.5 g of potassium iodide in 50 mL of water, separately, dissolve 1.5 g of soluble starch in 50 mL of boiling water; mix each 10 mL of these solutions before use, and add 3 mL of ethanol(95).

Loss on drying NMT 0.2% (1 g, in vacuum, silica gel, 4 hours).

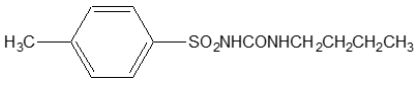
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Tolazoline Hydrochloride, dissolve in 100 mL of acetic acid(100), add 25 mL of mercury(II) acetate TS, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 19.668 mg of $C_{10}H_{12}N_2$·HCl

Packaging and storage Preserve in well-closed containers.

Tolbutamide
톨부타미드



$C_{12}H_{18}N_2O_3S$: 270.35
3-Butyl-1-[(4-methylbenzene)sulfonyl]urea [*64-77-7*]

Tolbutamide, when dried, contains NLT 99.0% and NMT 101.0% of tolbutamide ($C_{12}H_{18}N_2O_3S$).

Description Tolbutamide occurs as white crystals or a crystalline powder which is odorless or has a slight characteristic odor, and is tasteless.
It is soluble in ethanol(95), slightly soluble in ether, and practically insoluble in water.

Identification (1) Take 0.2 g of Tolbutamide, add 8 mL of diluted sulfuric acid (1 in 3), and boil under a reflux condenser for 30 minutes. Cool the solution in iced water,

collect the separated crystals by filtration, recrystallize from water, and dry at 105 ℃ for 3 hours; the melting point is between 135 and 139℃.

(2) Add 20 mL of sodium hydroxide solution (1 in 5) to the filtrate of (1) to make alkaline, and heat; it gives a ammonia-like odor.

Melting point Between 126 and 132 ℃.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Tolbutamide in 10 mL of 0.5 mol/L ammonia water; the solution is clear than milky white color.

(2) ***Acidity***—To 3.0 g of Tolbutamide, add 150 mL of water, warm at 70 ℃ for 5 minutes, allow to stand in iced water for 1 hour, and filter. To 25 mL of the filtrate, add 2 drops of methyl red TS and 0.20 mL of 0.1 mol/L sodium hydroxide TS; the solution exhibits a yellow color.

(3) ***Chloride***—To 40 mL of the filtrate obtained in (1), add 6 mL of dilute nitric acid and water to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid (NMT 0.011%).

(4) ***Sulfate***—To 40 mL of the filtrate obtained in (1), add 1 mL of dilute hydrochloric acid and water to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid (NMT 0.021%).

(5) ***Heavy metals***—Proceed with 2.0 g of Tolbutamide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(6) ***Selenium***—Mix 0.1 g of Tolbutamide and 0.1 g of magnesium oxide, transfer the mixture to a combustion flask, and combust as directed under the Oxygen Flask Combustion, using 25 mL of diluted nitric acid (1 in 30) as an absorbent. Use a combustion flask with a volume of 1 L, combust, wash the stopper and the inner wall of the flask with 10 mL of water, and use 20 mL of water to move the solution in the combustion flask into a 150-mL beaker. Heat lightly until it boils, boil for 10 minutes, allow it to cool down at room temperature, and use this solution as the test solution. Separately, pipet 3.0 mL of standard selenium stock solution, add 25 mL of diluted nitric acid (1 in 30) and 25 mL of water, and use this solution as the standard solution. Adjust the pH of each of the test and standard solutions to 2.0 ± 0.2 with diluted ammonia water(28) (1 in 2), add water to dilute exactly to 60 mL, and transfer the solution to a separatory funnel with 10 mL of water. Then, wash the separatory funnel with 10 mL of water. To each, add 0.2 g of hydroxylamine hydrochloride, stir to dissolve, add immediately 5.0 mL of 2,3-diaminonaphthalene TS, put a stopper, stir to mix, and allow to stand at the room temperature for 100 minutes. Add 5.0 mL of cyclohexane, shake hard for 2 minutes, and allow to stand. If the layers are separated, remove the water layer, centrifuge cyclohexane extracts to remove water, and take the cyclohexane layer. With these solutions and a control solution prepared with 25 mL of water added to 25 mL of diluted nitric acid (1 in 30) in the same way, perform the test as directed under the Ultraviolet-visible Spectroscopy. Determine the absorbance at the absorbance maximum wavelength of about 380 nm; the absorption of the solution from the test solution is not larger than the absorption from the standard solution (NMT 30 ppm).

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

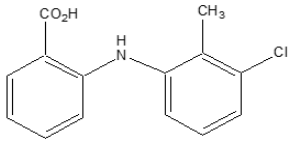
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Tolbutamide, previously dried, dissolve in 30 mL of neutralized ethanol, add 20 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of phenolphthalein TS).

Each mL of 0.1 mol/L sodium hydroxide VS
= 27.035 mg of $C_{12}H_{18}N_2O_3S$

Packaging and storage Preserve in well-closed containers.

Tolfenamic Acid
톨페남산



$C_{14}H_{12}ClNO_2$: 261.70
2-(3-Chloro-2-methylanilino)benzoic acid [*13710-19-5*]

Tolfenamic Acid, when dried, contains NLT 99.0% and NMT 101.0% of tolfenamic acid ($C_{14}H_{12}ClNO_2$).

Description Tolfenamic Acid occurs as a white or pale yellow crystalline powder.
It is soluble in *N,N*-dmethylformamide, sparingly soluble in ethanol(95) or dichloromethane, and practically insoluble in water.
It is soluble in dilute sodium hydroxide TS.

Melting point—About 213 °C.

Identification (1) Dissolve 10 mg each of Tolfenamic Acid and tolfenamic acid RS in a mixture of methanol and 1 mol/L hydrochloric acid (99 : 1) to make 100 mL, and to 5.0 mL of this solution, add a mixture of methanol and 1 mol/L hydrochloric acid (99 : 1) to make exactly 50 mL. Determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Tolfenamic Acid and tolfenamic acid RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 25 mg each of Tolfenamic Acid and tolfenamic acid RS in methanol to make 10 mL, and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of acetone, heptane and acetic acid(100) (70 : 30 : 1) (as the developing solvent) to a distance of about 15 cm, and air-dry the plate. Expose the plate under ultraviolet light (main wavelength: 254nm); the color and R_f values of the principal spots obtained from the test solution and the standard solution are the same.

Purity (1) ***Copper***—Put 1.0 g of Tolfenamic Acid into a porcelain crucible, moisten with sulfuric acid, and heat over a flame carefully for 30 minutes. Increase the temperature slowly to about 650 ℃, ignite until completely carbonized, cool, dissolve the residue in 0.1 mol/L hydrochloric acid TS to make 25.0 mL, and use this solution as the test solution. Prepare the standard solution by diluting the copper standard stock solution if necessary. Perform the test with the test solution and the standard solutions as directed under the Atomic Absorption Spectroscopy, and determine the copper concentration in the test solution and quantify (10 ppm).

Gas: Air–acetylene
Lamp: Copper hollow cathode lamp
Wavelength: 324.8 nm

(2) ***Related substances***—Dissolve 50.0 mg of Tolfenamic Acid in 5 mL of ethanol(95), add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, dissolve 25 mg each of tolfenamic acid related substances I (2-chlorobenzoic acid) and tolfenamic acid related substances II (3-chloro-2-methylaniline) in 5 mL of ethanol(95), add the mobile phase to make exactly 50 mL, and use this solution as the standard solution (1). Add the mobile phase to 1.0 mL of the test solution to make exactly 50 mL, and add the mobile phase to 1.0 mL of this solution to make exactly 10 mL. Use this solution as the standard solution (2). Perform the test with 20 μL each of the test solution and the standard solution (1) and (2) as directed under the Liquid Chromatography according to the following operating conditions. The peak area of the related substance I from the test solution is not greater than that from the standard solution (1) (0.1%), and the peak area of the related substance II is not greater than 0.5 times that from the standard solution (1) (0.05%). The area of any peak other than the major peak obtained from the test solution is not greater than the area of the major peak from the standard solution (2) (0.1%) and the sum of the peak areas other than the major peak obtained from the test solution is not greater than 5 times the area of the major peak from the standard solution (2) (0.5%). However, exclude any peak with an area less than 0.1 times the area of the major peak from the standard solution (2).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 232 nm).

Column: A stainless steel column 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of ethanol(95), water and acetic acid(100) (650 : 320 : 2).

Flow rate: 0.8 mL/min

System suitability

System performance: Proceed with each of the test solution and the standard solution (1) under the above conditions; the relative retention time of the related substance I and II to the retention time of tolfenamic acid (about 15 minutes) is 0.25 and 0.34, respectively, and the resolution between these two peaks are NLT 2.5.

Loss on drying NMT 0.5% (1 g, 105 ℃, constant mass).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Tolfenamic Acid, previously dried, add 100 mL of ethanol(95), sonicate to dissolve, and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 0.1 mL of phenol red TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 26.171 mg of $C_{14}H_{12}ClNO_2$

Packaging and storage Preserve in light-resistant, well-closed containers.

Tolfenamic Acid Capsules
톨페남산 캡슐

Tolfenamic Acid Capsules contain NLT 95.0% and NMT 105.0% of tolfenamic acid ($C_{14}H_{12}ClNO_2$: 261.70).

Method of preparation Prepare as directed under Capsules, with Tolfenamic Acid.

Identification Take the contents of 1 capsule of Tolfenamic Acid Capsules and add 0.1 mol/L sodium hydroxide to make 100 mL. Agitate this solution for 30 minutes, take 1.0 mL of this solution, and add 0.1 mol/L sodium hydroxide to make 100 mL. Filter this solution and determine the absorption spectrum of the filtrate as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelengths between 283 nm and 289 nm.

Disintegration Meets the requirements.

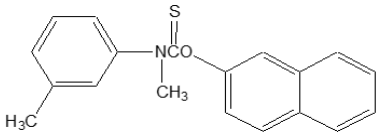
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the contents of NLT 20 capsules of Tolfenamic Acid Capsules. Weigh accurately about 0.3 g of tolfenamic acid ($C_{14}H_{12}ClNO_2$), dissolve in dimethylformamide, previously neutralized, and titrate with 0.1 mol/L of tetrabutylammonium hydroxide VS. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L of tetrabutylammonium hydroxide VS
= 26.170 mg of $C_{14}H_{12}ClNO_2$

Packaging and storage Preserve in well-closed containers.

Tolnaftate
톨나프테이트



$C_{19}H_{17}NOS$: 307.41

N-Methyl-*N*-(3-methylphenyl)-1-(naphthalen-2-yloxy)methanethioamide [*2398-96-1*]

Tolnaftate, when dried, contains NLT 98.0% and NMT 101.0% of tolnaftate ($C_{19}H_{17}NOS$).

Description Tolnaftate occurs as a white powder and is odorless.
It is freely soluble in chloroform, sparingly soluble in ether, slightly soluble in methanol or ethanol(95), and practically insoluble in water.

Identification (1) Take 0.2 g of Tolnaftate, add 20 mL of potassium hydroxide-ethanol TS and 5 mL of water, and heat under a reflux condenser for 3 hours. After cooling, take 10 mL of the solution, add 2 mL of acetic acid(100) and 1 mL of lead acetate TS in this order, and shake to mix; a black precipitate is formed.

(2) Determine the absorption spectra of solutions of Tolnaftate and tolnaftate RS in methanol (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Tolnaftate and tolnaftate RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 111 and 114 ℃ (after drying).

Purity (1) ***Heavy metals***—Weigh 1.0 g of Tolnaftate, and heat gently to carbonize. After cooling, add 5 mL of nitric acid and 1 mL of sulfuric acid, and heat until white fumes appear. After cooling, add another 2 mL of nitric acid, heat until white fumes appear, cool, add 2 mL of nitric acid and 0.5 mL of perchloric acid, heat gently until white fumes appear, repeat this procedure 2 times, and heat until white fumes are no longer evolved. Ignite the residue at between 500 and 600 ℃ for 1 hour to incinerate. Proceed as directed in Method 2 to make 50 mL, use this solution as the test solution, and perform the test. Prepare the control solution in the same manner as in the test solution with 11 mL of nitric acid, 1 mL of sulfuric acid, 1 mL of perchloric acid and 2 mL of hydrochloric acid, and add 2.0 mL of lead standard solution and water to make 50 mL (NMT 20 ppm).

(2) ***Related substances***—Dissolve 0.50 g of Tolnaftate in 10 mL of chloroform, and use this solution as the test solution. Pipet 2 mL of this solution and add chloroform to make exactly 100 mL. Pipet 5 mL of this solution, add chloroform to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Then, develop the plate with toluene (as the developing solvent) to a distance of about 10 cm, and air-dry the plate. Allow the plate to stand in iodine vapor for 5 minutes, examine under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot from the test solution are not more intense than the spot from the standard solution.

Loss on drying NMT 0.5% (1 g, 65 ℃, at the pressure not exceeding 0.67 kPa, 3 hours).

Residue on ignition Weigh accurately 2.0 g of Tolnaftate and heat gently to carbonize. Next, moisten with 1 mL of sulfuric acid, heat gently until white fumes are no longer evolved, and ignite at between 450 and 550 ℃ for about 2 hours to a constant mass; the residue is NMT 0.1%.

Assay Weigh accurately about 50 mg each of Tolnaftate and tolnaftate RS, previously dried, add each 200 mL of methanol, dissolve while warming on a steam bath, cool, and add methanol to make exactly 250 mL. Pipet 5 mL each of these solutions, add methanol to each to make exactly 100 mL, and use these solutions as the test solution and the standard solution. Determine the absorbance A_T and A_S, of the test solution and the standard solution, respectively, at 257 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of tolnaftate ($C_{19}H_{17}NOS$)
$= \text{amount (mg) of tolnaftate RS} \times \frac{A_T}{A_S}$

Packaging and storage Preserve in tight containers.

Tolnaftate Cream
톨나프테이트 크림

Tolnaftate cream contains NLT 90.0% and NMT 110.0% of the labeled amount of tolnaftate ($C_{19}H_{17}NOS$: 307.42).

Method of preparation Prepare as directed under Creams, with Tolnaftate.

Identification Take 10 mL of the chloroform solution immediately before the final solution obtained in the Assay under Tolnaftate Cream, evaporate to dryness on a steam bath, then dissolve in 1 mL of ethanol(95), and use this solution as the test solution. Separately, dissolve 10 mg of tolnaftate RS in 1 mL of ethanol(95), and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel (with fluorescence indicator) for thin-layer chromatography. Next, develop the plate with toluene (as the developing solvent) to a distance of about 12 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values of the spots obtained from the test solution and the standard solution are the same.

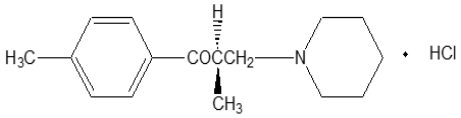
Assay Weigh accurately an amount of Tolnaftate Cream, equivalent to about 10 mg of tolnaftate ($C_{19}H_{17}NOS$), transfer to a separatory funnel, and extract with 75 mL of chloroform. Wash the chloroform layer with 25 mL of 0.1 mol/L sodium hydroxide TS twice, with 25 mL of 0.1 mol/L hydrochloric acid twice, and with 25 mL of water. Filter the chloroform layer using cotton washed with chloroform, then add chloroform to make exactly 100 mL. Pipet 5 mL of this solution, add chloroform to make exactly 50 mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of tolnaftate RS (previously dried in vacuum at 65℃ for 3 hours), dissolve in chloroform to obtain a solution containing 10 μg per mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at 258 nm as directed under Ultraviolet-visible Spectroscopy, using chloroform as the control solution.

$$\text{Amount (mg) of tolnaftate } (C_{19}H_{17}NOS) = C \times \frac{A_T}{A_S}$$

C: Concentration (μg/mL) of the standard solution

Packaging and storage Preserve in tight containers.

Tolperisone Hydrochloride
톨페리손염산염



and enantiomer

$C_{16}H_{23}NO \cdot HCl$: 281.82

2-Methyl-1-(4-methylphenyl)-3-piperidin-1-ylpropan-1-one hydrochloride [*3644-61-9*]

Tolperisone Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of tolperisone hydrochloride ($C_{16}H_{23}NO \cdot HCl$).

Description Tolperisone Hydrochloride occurs as a white crystalline powder and has a slight characteristic odor.

It is very soluble in acetic acid(100), freely soluble in water and ethanol(95), soluble in acetic anhydride, slightly soluble in acetone, and practically insoluble in ether.

It is hygroscopic.

Dissolve 1.0 g of Tolperisone Hydrochloride in 20 mL of water; the pH of the solution is between 4.5 and 5.5.

Melting point—Between 167 and 174 ℃.

Identification (1) Dissolve 0.2 g of Tolperisone Hydrochloride in 2 mL of ethanol(95) mL, add 2 mL of 1,3-dinitrobenzene TS and 2 mL of sodium hydroxide TS, and heat; the resulting solution exhibits a red color.

(2) To 5 mL of an aqueous solution of Tolperisone Hydrochloride (1 in 20), add 2 to 3 drops of iodine TS; a reddish brown precipitate is formed.

(3) Dissolve 0.5 g of Tolperisone Hydrochloride in 5 mL of water, add 2 mL of ammonia TS, and filter. Pipet 5 mL of the filtrate, add dilute nitric acid to make acid; the solution responds to the Qualitative Analysis for chloride.

Absorbance $E_{1cm}^{1\%}$ (257 nm): Between 555 and 585 (5 mg after drying, ethanol(95), 500 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Tolperisone Hydrochloride in 10 mL of water; the solution is clear and colorless.

(2) ***Sulfate*—**Perform the test with 4.0 g of Tolperisone Hydrochloride. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid (NMT 0.005%).

(3) ***Heavy metals***—Proceed with 1.0 g of Tolperisone Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Piperidine hydrochloride***—Weigh 0.20 g of Tolperisone Hydrochloride, dissolve in water to make exactly 10 mL, and use this solution as the test solution. Separately, weigh 20 mg of piperidine hydrochloride RS, dissolve in water to make exactly 1000 mL, and use this solution as the standard solution. Take exactly 5.0 mL

each of the test solution and the standard solution into a separatory funnel, respectively, add 0.1 mL of copper sulfate solution (1 in 20), 0.1 mL of ammonia water(28) and exactly 10 mL of a mixture of isooctane and carbon disulfide (3 : 1) in each funnel, and shake vigorously for 30 minutes to mix. Allow to stand, separate immediately isooctane-carbon disulfide layer, and dehydrate with anhydrous sodium sulfate. Perform the test with these solutions as directed under the Ultraviolet-visible Spectroscopy; the absorbance of the test solution at 438 nm is not greater than that of the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, silica gel, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Tolperisone Hydrochloride, previously dried, dissolve in 70 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 28.182 mg of $C_{16}H_{23}NO \cdot HCl$

Packaging and storage Preserve in well-closed containers.

Tolperisone Hydrochloride Tablets
톨페리손염산염 정

Tolperisone Hydrochloride Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of tolperisone hydrochloride ($C_{16}H_{23}NO \cdot HCl$: 281.82).

Method of preparation Prepare as directed under Tablets, with Tolperisone Hydrochloride.

Identification (1) Weigh an amount, equivalent to 0.2 g of tolperisone hydrochloride according to the labeled amount of Tolperisone Hydrochloride Tablets, add 10 mL of water, shake well to mix, and filter. To this solution, add 2 mL of Nessler's TS; the solution turns to a yellowish white color and, when allowed to stand, it forms a yellowish white, oil-phase precipitate.

(2) Weigh an amount, equivalent to 0.2 g of tolperisone hydrochloride according to the labeled amount of Tolperisone Hydrochloride Tablets, add 10 mL of water, shake well to mix, and filter. Evaporate the filtrate to concentration in vacuum, add 2 mL of ethanol to the residue, and heat to filter the insolubles. To this solution, add 2 mL of 1,3-dinitrobenzene TS, add sodium hydroxide TS, and heat; the solution exhibits a red color.

(3) Weigh an amount, equivalent to 0.5 g of tolperisone hydrochloride according to the labeled amount of Tolperisone Hydrochloride Tablets, add 20 mL of water, and shake well to mix. To this, add 2 mL of ammonia TS and filter. Take 10 mL of this solution, add dilute nitric acid to acidify, and add silver nitrate TS; a white precipitate is formed.

Disintegration Meets the requirements.

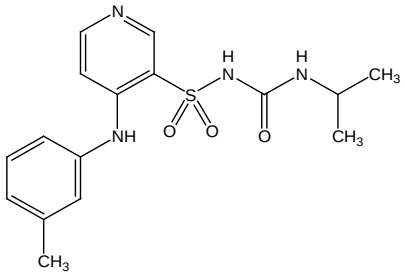
Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Tolperisone Hydrochloride Tablets and powder it. Weigh accurately an amount, equivalent to about 30 mg of tolperisone hydrochloride ($C_{16}H_{23}NO \cdot HCl$), and put in a separatory funnel. Dissolve in 40 mL of 0.1 mol/L hydrochloric acid TS, add n-hexane, and shake to mix. Separate the n-hexane layer and wash it with 20 mL of 0.1 mol/L hydrochloric acid TS. Combine the washings with the previously separated 0.1 mol/L hydrochloric acid TS layer, and add 0.1 mol/L hydrochloric acid TS to make 100 mL. Filter this solution with a filter paper and discard the about 50 mL of the first filtrate, pipet 2.0 mL of the remaining filtrate, and add 0.1 mol/L hydrochloric acid TS to make exactly 50 mL. Use this solution as the test solution. Separately, weigh accurately about 0.15 g of tolperisone hydrochloride RS, previously dried (in vacuum, silica gel, for 3 hours), and add 0.1 mol/L hydrochloric acid TS to make exactly 50 mL. Pipet 10.0 mL of this solution, place in a separatory funnel, add 30 mL of 0.1 mol/L hydrochloric acid TS, and proceed in the same manner as the preparation of the test solution. Use the resulting solution as the standard solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using 0.1 mol/L hydrochloric acid TS as the control solution, and determine the absorbances, A_T and A_S, respectively, at the wavelength of 262 nm.

Amount (mg) of tolperisone hydrochloride ($C_{16}H_{23}NO \cdot HCl$)
= Amount (mg) of tolperisone hydrochloride RS $\times \frac{A_T}{A_S} \times \frac{1}{5}$

Packaging and storage Preserve in light-resistant, well-closed containers.

Torsemide
토르세미드



$C_{16}H_{20}N_4O_3S$: 348.42

1-[4-(3-Methylanilino)pyridin-3-yl]sulfonyl-3-propan-2-ylurea [*56211-40-6*]

Torsemide contains NLT 98.0% and NMT 102.0% of torsemide ($C_{16}H_{20}N_4O_3S$), calculated on the anhydrous basis.

Description Torsemide occurs as a white crystalline powder.
It is slightly soluble in ethanol(95) or methanol and very slightly soluble in acetone or chloroform and practically insoluble in water or ether.

Identification (1) Determine the infrared spectra of Torsemide and torsemide RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Torsemide according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Use the test solution in the Assay as the test solution. Pipet 1 mL of this solution, and add the mobile phase to make exactly 100 mL. Pipet 2 mL of this solution, add the mobile phase to it make exactly 10 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration and determine the amount of each related substances; torsemide-related substance I with a relative retention time of 0.4 with respect to Torsemide obtained from the test solution is NMT 0.5%, and torsemide-related substance II with a relative retention time of 1.9 is NMT 0.3%, and torsemide-related material III with a relative retention time of 0.5 is NMT 0.2%. Additionally, each unknown related substance is more than 0.1%, the total sum of each unknown related substance is NMT 0.2%, and total related substances are less than 1.0%. However, exclude any peaks smaller than 0.05%.

$$\text{Content (\%) of related substances} = \frac{A_T}{A_S} \times rf \times \frac{1}{5}$$

A_T: Peak area of each related substance obtained from the test solution

A_S: Peak area of torsemide obtained from the standard solution

rf: The correction factor of each related substance for Torsemide peak

Torsemide-related substances I: 0.80

Torsemide-related substances II: 1.16

Torsemide-related substances III and other related substances: 1.00

Operating conditions

For the test solution, detector, mobile phase, and flow rate, proceed as directed in the operating conditions under the Assay.

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 ℃.

System suitability

Test for required detectability: Pipet 5 mL of the standard solution, and add the mobile phase to make exactly 20 mL. Proceed with 20 μL of this solution according to the above conditions; confirm that the signal-to-noise ratio of torsemide peak is NLT 10.

System performance: Proceed with 20 μL of the standard solution according to the above conditions; the symmetry factor for torsemide peak is between 0.8 and 2.0.

System repeatability: Perform the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of torsemide is not more that 10.0%.

Water NMT 1.0% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Dissolve about 38 mg of Torsemide, weighed accurately, in 30 mL of methanol, sonicate it for at least 8 minutes, then add 45 mL of 0.02 mol/L potassium dihydrogen phosphate buffer solution, and add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, dissolve about 19 mg of torsemide RS, weighed accurately, in 15 mL of methanol, sonicate it for NLT 8 minutes, add 22.5 mL of 0.02 mol/L potassium dihydrogen phosphate buffer solution, and add the mobile phase to make exactly 50 mL. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of Torsemide from each solution, A_T and A_S,

respectively.

$$\text{Amount (mg) of torsemide } (C_{16}H_{20}N_4O_3S) = 100 \times C \times \frac{A_T}{A_S}$$

C: Concentration of torsemide in the standard solution (mg/mL)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 288 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (7 μm in particle diameter).

Mobile phase: A mixture of 0.02 mol/L potassium dihydrogen phosphate buffer solution and methanol (3 : 2).

Flow rate: 1.5 mL/min

System suitability

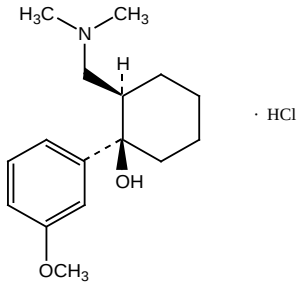
System performance: Proceed with 20 μL of the standard solution according to the above conditions; the symmetry factor of the peak of torsemide is NMT 2.0.

System repeatability: Perform the test 5 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of peak areas of torsemide is NMT 2.0%.

Potassium dihydrogen phosphate buffer solution, 0.02 mol/L—Dissolve 2.7 g of potassium dihydrogen phosphate in 900 mL of water, add phosphoric acid to adjust the pH to 3.5, and add water to make 1000 mL.

Packaging and storage Preserve in well-closed containers.

Tramadol Hydrochloride
트라마돌염산염



and enantiomer

$C_{16}H_{25}NO_2 \cdot HCl$: 299.84

(1*R*,2*R*)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol hydrochloride [*36282-47-0*]

Tramadol Hydrochloride contains NLT 99.0% and NMT 101.0% of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$), calculated on an anhydrous basis.

Description Tramadol Hydrochloride occurs as a white crystalline powder.

It is freely soluble in water or methanol and very slightly soluble in acetone.

Identification (1) Determine the infrared spectra of Tramadol Hydrochloride and tramadol hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Perform the test with related substances I under the Purity as directed under the Thin Layer Chromatography; the R_f value of the principal spots obtained from the test solution (2) and the standard solution (1) are the same.

(3) An aqueous of Tramadol Hydrochloride (1 in 50) responds to the Qualitative Analysis (2) for chloride.

Melting point Between 180 and 184 ℃.

Optical rotation $[\alpha]_D^{20}$: Between −10° and + 0.10° (1.0 g, water, 20 mL, 100 mm).

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Tramadol Hydrochloride in 20 mL of water; the resulting solution is clear and colorless.

(2) ***Acidity or alkalinity***—Dissolve 1.0 g of Tramadol Hydrochloride in 20 mL of water, take 10 mL of this solution, and add 0.1 mL of methyl red TS and 0.2 mL of 0.01 mol/L hydrochloric acid; the resulting solution exhibits a red color. Add 0.01 mol/L sodium hydroxide solution until the solution exhibits a yellow color; NMT 0.4 mL of 0.1 mol/L sodium hydroxide solution is consumed.

(3) ***Heavy metals***—Proceed with 1.0 g of Tramadol Hydrochloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Related substances I***—Dissolve 0.10 g of Tramadol Hydrochloride in 2 mL of methanol, and use this solution as the test solution (1). Pipet 1 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the test solution (2). Separately, dissolve 50 mg of tramadol hydrochloride RS in methanol to make 10 mL, and use this solution as the standard solution (1). Weigh 10 mg of tramadol related substances I RS {(2*RS*)-2-[(dimethylamino)methyl]cyclohexanone}, dissolve in 10 mL of methanol, pipet 1 mL of this solution, add methanol to make 10 mL, and use this solution as the standard solution (2). Weigh 5 mg of tramadol related substances II RS {(1*RS*,2*SR*)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol}, dissolve in 1 mL of the standard solution (1), and use this solution as the standard solution (3). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution, the standard solutions (2) and (3) on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, put the thin layer into one side of the double developing chamber containing ammonia wa-

ter(28), saturate for 20 minutes to develop more than 2/3 of the thin layer. On the other side, develop the plate with a mixture of toluene, 2-propanol, strong ammonia water (80 : 19 : 1) (as a developing solvent) to a distance of about 10 cm and air-dry the plate. Expose the plate to the iodine vapor for 1 hour, and then to the ultraviolet light (254 nm); the spot of the related substances I from the test solution (1) is not more intense or greater than that of the standard solution (2) (0.2%). This test is valid when the two spots from the standard solution (3) are clearly separated.

(5) ***Related substances***— Weigh 0.15 g of Tramadol Hydrochloride, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the test solution. To 2.0 mL of the test solution, and add the mobile phase to make 10 mL. To 1.0 mL of this solution, add the mobile phase to make 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of each solution according to the automatic integration method. The related substances II from the test solution are not greater than the major peak area from the standard solution (0.2%), the area of peaks other than the major peak is not greater than 0.5 times of the major peak area from the standard solution (0.1%), and the sum of the peak areas other than major peak is not greater than 2 times the peak area from the standard solution (0.4%). However, exclude any peak having an area smaller than 0.1 times the major peak area obtained from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for alkali inactivated liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of trifluoroacetic acid and water (0.2 : 100), and a mixture of acetonitrile (705 : 295).

Flow rate: 1.0 mL/min

System suitability

System performance: Dissolve 5 mg of tramadol related substances II RS in 4.0 mL of the test solution, and add the mobile phase to make 100 mL. Proceed with 20 μL of this solution according to the above conditions; the resolution between the peaks of related substances II and tramadol is NLT 2.0.

Water NMT 0.5% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.18 g of Tramadol Hydrochloride, dissolve in 25 mL of acetic acid(100), add 10 mL of acetic anhydride to mix, and titrate 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 29.984 mg of $C_{16}H_{25}NO_2 \cdot HCl$

Packaging and storage Preserve in light-resistant, well-closed containers.

Tramadol Hydrochloride Capsules
트라마돌염산염 캡슐

Tramadol Hydrochloride Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$: 299.84).

Method of preparation Prepare as directed under Capsules, with Tramadol Hydrochloride.

Identification With the contents of Tramadol Hydrochloride Capsules, weigh an amount equivalent to about 50 mg of tramadol hydrochloride according to the labeled amount. Add 10 mL of methanol, shake well to mix, filter, and use the filtrate as the test solution. Separately, dissolve about 50 mg of tramadol hydrochloride RS in 10 mL of methanol and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of methanol, acetone and formic acid (50 : 50 : 1) as the developing solvent and air-dry the plate. Spray evenly Dragendorff's TS on the plate; the R_f values and the colors of the spots obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 capsule of Tramadol Hydrochloride Capsules at 50 revolutions per minute according to Method 2, using 900 mL of water as the dissolution medium. Take the medium 30 minutes after the start of the test and filter. Discard the first 10 mL of the filtrate and pipet V mL of the subsequent filtrate. Add water to make exactly V' mL so that the solution contains about 50 μg of tramadol hydrochloride per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 50 mg of tramadol hydrochloride RS and add water to make 100 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of tramadol hydrochloride in each solution. It meets the requirements when the dissolution rate of Tramadol Hydrochloride Capsules in 30 minutes is NLT 80%.

Dissolution rate (%) wiht respect to the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$)

$$= W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 90$$

W_S: Amount of tramadol hydrochloride RS (mg)

C: Labeled amount (mg) of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) in 1 capsule

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octylcylsilaniaed silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of trifluoroacetic acid TS (0.2) and acetonitrile (705 : 295).

Flow rate: 1.0 mL/min

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the contents of NLT 20 capsules of Tramadol Hydrochloride Capsules. Weigh accurately about 10 mg of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$), add water to make 100 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 100 mg of tramadol hydrochloride RS, and add water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and determine the peak areas, A_T and A_S, of tramadol hydrochloride RS, respectively, in each solution.

Amount (mg) of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$)

$$= \text{Amount (mg) of tramadol hydrochloride RS} \times \frac{A_T}{A_S} \times \frac{1}{10}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30 °C.

Mobile phase: A mixture of 0.2% trifluoroacetic acid TS and acetonitrile (705 : 295).

Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL of the standard solution under the above operating conditions; the relative standard deviation of the peak area of tramadol hydrochloride is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Tramadol Hydrochloride Injection
트라마돌염산염 주사액

Tramadol Hydrochloride Injection contains NLT 95.0% and NMT 105.0% of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$: 299.84).

Method of preparation Prepare as directed under Injections, with Tramadol Hydrochloride.

Identification Take an amount of Tramadol Hydrochloride Injection, equivalent to about 50 mg of tramadol hydrochloride according to the labeled amount, add 10 mL of methanol, shake to mix, and use this solution as the test solution. Separately, weigh accurately about 50 mg of tramadol hydrochloride RS, dissolve in 10 mL of methanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of methanol, acetone and formic acid (50 : 50 : 1) as the developing solvent to a distance of about 15 cm, and air-dry the plate. Spray evenly Dragendorff's TS onto the plate; the R_f values and colors of the spots obtained from the test solution and the standard solution are the same.

pH Between 5.3 and 7.3.

Sterility Meets the requirements.

Bacterial endotoxins Less than 3 EU per mg of tramadol hydrochloride.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

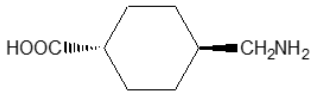
Assay Pipet Tramadol Hydrochloride Injection in the amount equivalent to 0.1 g of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) according to the labeled amount, and add water to make exactly 200 mL. Pipet 5 mL of this solution, add water to make exactly 50 mL, and use the resulting solution as the test solution. Separately, weigh accurately about 0.1 g of tramadol hydrochloride RS, add 830 μL of sodium acetate solution (0.4 in 100), and add water to make exactly 200 mL. Pipet 5 mL of this solution, add water to make exactly 50 mL, and use the resulting solution as the standard solution. Separately, to

830 μL of sodium acetate solution (0.4 in 100), add water to make exactly 200 mL, proceed with this solution in the same manner as the preparation of the test solution, and use the resulting solution as the blank test solution. Perform the test with the test solution and the standard solution as directed under the Ultraviolet-visible Spectroscopy, using the blank test solution as a control solution, and determine the absorbances, A_T and A_S, respectively, at the wavelength of 272 nm.

Amount (mg) of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$)
= Amount (mg) of tramadol hydrochloride RS × (A_T / A_S)

Packaging and storage Preserve in hermetic containers.

Tranexamic Acid
트라넥삼산



$C_8H_{15}NO_2$: 157.21
4-(Aminomethyl)cyclohexane-1-carboxylic acid [*1197-18-8*]

Tranexamic Acid, when dried, contains NLT 98.0% and NMT 101.0% of tranexamic acid ($C_8H_{15}NO_2$).

Description Tranexamic Acid occurs as white crystals or a powder.
It is freely soluble in water and practically insoluble in ethanol(99.5).
It dissolves in sodium hydroxide TS.

Identification Determine the infrared spectra of Tranexamic Acid and tranexamic acid RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit the same intensities of absorption at the same wave numbers.

pH Dissolve 1.0 g of Tranexamic Acid in 20 mL of water; the pH of this solution is between 7.0 and 8.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Tranexamic Acid in 10 mL of water; the solution is clear and colorless.

(2) ***Chloride***—Perform the test with 1.0 g of Tranexamic Acid. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid (NMT 0.014%).

(3) ***Heavy metals***—Dissolve 2.0 g of Tranexamic Acid in water to make 20 mL, and use this solution as the test stock solution. Add 2 mL of hydrochloric acid-ammonium acetate buffer solution, pH 3.5, to 12 mL of the test stock solution and shake to mix. Add 1.2 mL of Thioacetamide TS, shake immediately to mix, and use this solution as the test solution. Separately, proceed in the same manner with a mixture of 1 mL of lead standard solution, 2 mL of the test stock solution and 9 mL of water and use this solution as the standard solution. Proceed in the same manner with a mixture of 10 mL of water and 2 mL of the test stock solution and use this solution as the control solution. Confirm that the color of the standard solution is slightly intense than that of the control solution. Compare the colors between the test solution and the standard solution 2 minutes after the preparation of the solutions; the color of the test solution is not more intense than that of the standard solution (NMT 10 ppm).

(4) ***Arsenic***—Dissolve 1.0 g of Tranexamic Acid in 10 mL of water and use this solution as the test solution to perform the test (NMT 2 ppm).

(5) ***Related substances***—Dissolve 0.20 g of Tranexamic Acid in 20 mL of water and use this solution as the test solution. Pipet 5 mL of this solution, add water to make exactly 100 mL, pipet 1 mL of this resulting solution, add water to make exactly 10 mL, and use this solution as the standard solution. With 20 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions and determine the peak areas from the respective solutions according to the automatic integration method; the area determine by multiply the peak area obtained from the test solution with the relative retention time of 1.5 by the correction factor of 1.2 is not greater than 2/5 of the peak area of the tranexamic acid from the standard solution, and the peak area obtained from the test solution with the relative retention time of 2.1 is not greater than 1/5 of the peak area of the tranexamic acid from the standard solution. In addition, each peak area other than tranexamic acid and the above peaks from the test solution are not greater than 1/5 times the peak area of tranexamic acid from the standard solution. However, multiply the correction factor of 0.005 for the peak area with the relative retention time of 1.1, and the correction factor of 0.006 for the peak area with the relative retention time of 1.3, respectively. The sum of peak areas other than tranexamic acid from the test solution is not greater than the peak area of tranexamic acid from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

System performance: Proceed as directed under the system suitability under the Assay.

Test for required detectability: Pipet 5 mL of the standard solution and add water to make exactly 25 mL. Verify that the peak area of tranexamic acid obtained from 20 μL of this solution is equivalent to between 14% and 26% of the peak area of tranexamic acid obtained from the standard solution.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of tranexamic acid is NMT 7%.

Time span of measurement: About 3 times the

retention time of tranexamic acid after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 ℃, 2 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg each of Tranexamic Acid and tranexamic acid RS, previously dried, dissolve each in water to make exactly 25 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area, A_T and A_S of tranexamic acid from each of the solutions.

$$\text{Amount (mg) of tranexamic acid } (C_8H_{15}NO_2) = \text{amount (mg) of tranexamic acid RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 6.0 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Mobile phase: Dissolve 11.0 g of anhydrous sodium dihydrogen phosphate in 500 mL of water and add 5 mL of triethylamine and 1.4 g of sodium lauryl sulfate. Adjust the pH to 2.5 with phosphoric acid and phosphoric acid solution (1 in 10) and add water to make 600 mL. Add 400 mL of methanol to this solution.

Flow rate: Adjust the flow rate so that the retention time of tranexamic acid is about 20 minutes.

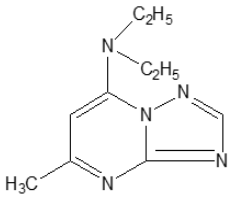
System suitability

System performance: Take 5 mL of the standard solution, add 1 mL of the solution prepared by dissolving 10 mg of 4-(aminomethyl)benzoic acid in water to make 100 mL, and add water to make 50 mL. Proceed with 20 μL of this solution according to the above conditions; tranexamic acid and 4-(aminomethyl)benzoic acid are eluted in this order with the resolution between the peaks being NLT 5.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of tranexamic acid is NMT 0.6%.

Packaging and storage Preserve in well-closed containers.

Trapidil
트라피딜



$C_{10}H_{15}N_5$: 205.26

N,*N*-Diethyl-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-amine [*15421-84-8*]

Trapidil, when dried, contains NLT 98.5% and NMT 101.0% of trapidil ($C_{10}H_{15}N_5$).

Description Trapidil occurs as a white to pale yellowish white crystalline powder.
It is very soluble in water or methanol, and freely soluble in ethanol(95), acetic anhydride or acetic acid(100), and sparingly soluble in ether.
Dissolve 1.0 g of Trapidil in 100 mL of water; the pH of the solution is between 6.5 and 7.5.

Identification (1) Take 5 mL of an aqueous solution of Trapidil (1 in 50) and add 3 drops of Dragendorff's TS; the solution exhibits an orange color.

(2) Determine the absorption spectra of solutions of Trapidil and trapidil RS (1 in 125000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Melting point Between 101 and 105 ℃.

Absorbance $E_{1cm}^{1\%}$ (307 nm): Between 860 and 892 (20 mg after drying, water, 2500 mL).

Purity (1) ***Clarity and color of solution***—Dissolve 2.5 g of Trapidil in 10 mL of water; the resulting solution is colorless to pale yellow and clear.

(2) ***Chloride***—Perform the test with 0.5 g of Trapidil. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid (NMT 0.018%).

(3) ***Ammonium***—Weigh 50 mg of Trapidil, put in a glass-stoppered Erlenmeyer flask, add 10 drops of sodium hydroxide TS to moisten, and put a stopper. Allow to stand at 37 ℃ for 15 minutes; the gas evolved does not change the color of a moistened red litmus paper to blue.

(4) ***Heavy metals***—Dissolve 1.0 g of Trapidil in 40 mL of water, and add 1.5 mL of dilute hydrochloric acid, 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 2 mL of dilute acetic acid and water to 1.0 mL of lead standard solution to make 50 mL (NMT 10 ppm).

(5) ***Arsenic***—Proceed with 1.0 g of Trapidil according to Method 1 and perform the test (NMT 2 ppm).

(6) ***Related substances***—Dissolve 0.10 g of Trapidil in 4 mL of methanol and use this solution as the test solution. Pipet 1.0 mL of this solution and add methanol to make exactly 20 mL, pipet 1 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform

the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of chloroform, ethanol(95) and acetic acid(100) (85 : 13 : 2) (as the developing solvent) to a distance of about 10 cm, and air-dry the plate. Allow the plate to stand for 60 minutes in iodine steam; the spots other than the principal spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (1 g, in vacuum, silica gel, 60 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Trapidil, previously dried, and dissolve in 20 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 20.526 mg of $C_{10}H_{15}N_5$

Packaging and storage Preserve in tight containers.

Trazodone Hydrochloride Capsules
트라조돈염산염 캡슐

Trazodone Hydrochloride Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of trazodone hydrochloride ($C_{19}H_{22}ClN_5O$·HCl : 408.33).

Method of preparation Prepare as directed under Capsules, with Trazodone Hydrochloride.

Identification Weigh an amount equivalent to 25 mg of trazodone hydrochloride according to the labeled amount, add 5 mL of water, and shake to dissolve. To this solution, add 20 mL of ethanol, mix, filter and use the filtrate as the test solution. Separately, weigh 25 mg of trazodone hydrochloride RS, dissolve in 5 mL of water, add 20 mL of ethanol, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography (with a fluorescent indicator). Develop the plate with a mixture of acetone, hexane, and ammonia water (10 : 10 : 1) as the developing solvent, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm), the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

Dissolution Perform the test with 1 capsule of Trazodone Hydrochloride Capsules at 50 revolutions per minute according to Method 2, using 900 mL of water as the dissolution medium. Take the dissolved solution after 30 minutes from the start of the test and filter. Discard the first 10 mL of the filtrate and pipet V mL of the subsequent filtrate. Add water to make exactly V' mL so that the solution contains about 20 μg of trazodone hydrochloride per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 20 mg of trazodone hydrochloride RS and add water to make 100 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions. Determine the peak areas, A_T and A_S, of trazodone hydrochloride in each solution. Meets the requirements if the dissolution rate of Trazodone Hydrochloride Capsules in 30 minutes is NLT 75%.

Dissolution rate (%) with respect to the labeled amount of trazodone hydrochloride ($C_{19}H_{22}ClN_5O$·HCl)

$$= W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C} \times 90$$

Ws: Amount (mg) of trazodone hydrochloride RS
C: Labeled amount (mg) of trazodone hydrochloride ($C_{19}H_{22}ClN_5O$·HCl) in 1 capsule

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 246 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 250 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of methanol and 0.01 mol/L ammonium phosphate (pH 6.0) (75 : 25).

Flow rate: 1.0 mL/min

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of the contents of NLT 20 capsules of Trazodone Hydrochloride Capsules. Weigh accurately about 5 mg of trazodone hydrochloride ($C_{19}H_{22}ClN_5O$·HCl), add water to make 100 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 50 mg of acetone, and add water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography, and calculate the peak areas, A_T and A_S, of trazodone in each solution.

Amount (mg) of trazodone hydrochloride ($C_{19}H_{22}ClN_5O$·HCl)

$$= \text{Amount (mg) of trazodone hydrochloride RS} \times \frac{A_T}{A_S} \times \frac{1}{10}$$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 246 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: A mixture of methanol and 0.01 mol/L ammonium phosphate dibasic buffer solution (pH 6.0) (75 : 25).

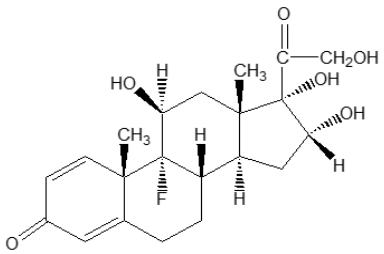
Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution under the above conditions; the relative standard deviation of the peak areas of trazodone is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Triamcinolone
트리암시놀론



$C_{21}H_{27}FO_6$: 394.43

(1*R*,2*S*,10*S*,11*S*,13*R*,14*S*,15*S*,17*S*)-1-Fluoro-13,14,17-trihydroxy-14-(2-hydroxyacetyl)-2,15-dimethyltetracyclo[8.7.0.0^{2,7}.0^{11,15}]heptadeca-3,6-dien-5-one [*124-94-7*]

Triamcinolone, when dried, contains NLT 97.0% and NMT 103.0% of triamcinolone ($C_{21}H_{27}FO_6$).

Description Triamcinolone occurs as a white crystalline powder and is odorless.

It is freely soluble in *N*,*N*-dimethylformamide, slightly soluble in methanol, ethanol(95), or acetone and practically insoluble in water, 2-propanol, or ether.

Melting point—About 264 °C (with decomposition).

Identification (1) Dissolve 1 mg of Triamcinolone in 6 mL of ethanol(95), add 5 mL of 2,6-di-*t*-butylcresol TS and 5 mL of sodium hydroxide TS, and heat on a steam bath for 30 minutes under a reflux condenser; the solution exhibits a purple color.

(2) To 10 mL of Triamcinolone, add 5 mL of water and 1 mL of Fehling's TS and heat: a red precipitate is formed.

(3) Proceed with 10 mg of Triamcinolone as directed under the Oxygen Flask Combustion, using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as the absorbent; the solution responds to the Qualitative Analysis for fluoride.

(4) Determine the infrared spectra of Triamcinolone and triamcinolone RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy, respectively; both spectra exhibit similar intensities of absorption at the same wavenumbers. If there exist any differences in the two spectra, dissolve each 0.1 g of Triamcinolone and triamcinolone RS in 7 mL of a mixture of 2-propanol and water (2 : 1) by warming. Cool the solutions with ice, filter the extracted crystals, wash with 10 mL of water 2 times, and dry. Repeat the test with residues in the same manner.

Optical rotation $[\alpha]_D^{20}$: Between +65° and +71° (0.1 g after drying, *N*,*N*-dimethylformamide, 10 mL, 100 mm).

Purity ***Heavy metals***—Proceed with 0.5 g of Triamcinolone according to Method 2 and perform the test. Prepare the control solution with 1.5 mL of lead standard solution (NMT 30 ppm).

Loss on drying NMT 2.0% (0.5 g, in vacuum, phosphorus pentoxide, 60 ℃, 3 hours).

Residue on ignition NMT 0.3% (0.5 g, platinum crucible).

Assay Weigh accurately about each 20 mg of Triamcinolone and triamcinolone RS, previously dried, and dissolve in a solution of L-ascorbic acid in methanol (1 in 1000) to make exactly 50 mL. Pipet each 5 mL of these solutions, add 5 mL of the internal standard solution, and add a solution of L-ascorbic acid in methanol (1 in 1000) to make exactly 20 mL each. Use these solutions as the test solution and the standard solution, respectively. Perform the test with 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and calculate the peak height ratios, Q_T and Q_S, of triamcinolone to that of the internal standard.

$$\text{Amount (mg) of triamcinolone } (C_{21}H_{27}FO_6) = \text{Amount (mg) of triamcinolone RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—Dissolve 15 mg of methyl *p*-hydroxybenzoate in a solution of L-ascorbic acid in methanol (1 in 1000) to make 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and 15 to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Column temperature: A constant temperature of

about 25 °C.

Mobile phase: A mixture of water and acetonitrile (3 : 1).

Flow rate: Adjust the flow rate so that the retention time of triamcinolone is about 10 minutes.

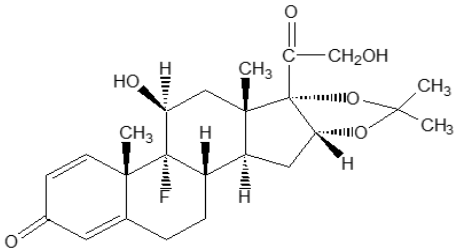
System suitability

System performance: Perform the test with 10 μL of the standard solution according to the above operating conditions; triamcinolone and the internal standard are eluted in this order with the resolution being NLT 2.0.

System repeatability: Proceed with 10 μL of the standard solution under the above operating conditions and repeat the test 6 times; the relative standard deviation of the peak height ratio of triamcinolone to that of the internal standard is NMT 1.5%.

Packaging and storage Preserve in light-resistant, tight containers.

Triamcinolone Acetonide
트리암시놀론아세토니드



$C_{24}H_{31}FO_6$: 434.50

(4a*S*,4b*R*,5*S*,6a*S*,6b*S*,9a*R*,10a*S*,10b*S*)-4b-Fluoro-6b-glycoloyl-5-hydroxy-4a,6a,8,8-tetramethyl-4a,4b,5,6,6a,6b,9a,10,10a,10b,11,12-dodecahydro-2*H*-naphtho[2',1':4,5]indeno[1,2-d][1,3]dioxol-2-one

[*76-25-5*]

Triamcinolone Acetonide, when dried, contains NLT 97.0% and NMT 103.0% of Triamcinolone Acetonide ($C_{24}H_{31}FO_6$).

Description Triamcinolone Acetonide occurs as a white, crystalline powder and is odorless.

It is sparingly soluble in ethanol(99.5), acetone or 1,4-dioxane, slightly soluble in methanol or ethanol(95), and practically insoluble in water or ether.

Melting point—About 290 °C (with decomposition).

Identification (1) Dissolve 2 mg of Triamcinolone Acetonide in 40 mL of ethanol(95), add 5 mL of 2,6-di-*t*-butylcresol TS and 5 mL of sodium hydroxide TS and heat on a steam bath for 20 minutes under a reflux condenser: the solution exhibits a green color.

(2) To 10 mg of Triamcinolone Acetonide, add 5 mL of water and 1 mL of Fehling's TS and heat: a red precipitate is formed.

(3) Proceed with 10 mg of Triamcinolone Acetonide as directed under the Oxygen Flask Combustion using a mixture of 0.5 mL of 0.01 mol/L sodium hydroxide TS and 20 mL of water as the absorbent; the solution responds to the Qualitative Analysis for fluoride.

(4) Determine the absorption spectra of Triamcinolone Acetonide and triamcinolone acetonide RS in ethanol(95) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(5) Determine the infrared spectra of Triamcinolone Acetonide and triamcinolone acetonide RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy, respectively; both spectra exhibit similar intensities of absorption at the same wavenumbers. If there exist any differences in the two spectra, dissolve each 0.1 g of Triamcinolone Acetonide and triamcinolone acetonide RS in 20 mL of ethanol(95), evaporate to dryness, and repeat the test with the residues in the same manner.

Optical rotation $[\alpha]_D^{20}$: Between +118° and +130° (0.05 g calculated on the dried basis, *N*,*N*-dimethylformamide, 10 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 0.5 g of Triamcinolone Acetonide according to Method 2 and perform the test. Prepare the control solution with 1.5 mL of lead standard solution (NMT 30 ppm).

(2) ***Related substances***—Dissolve 40 mg of Triamcinolone Acetonide in 4 mL of acetone and use this solution as the test solution. Pipet 1 mL of this solution, add acetone to make exactly 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform and methanol (93 : 7) (as the developing solvent) to a distance of about 10 cm and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); any spots other than the principal spot obtained from the test solution is not more intense than the spots from the standard solutions.

Loss on drying NMT 2.0% (0.5 g, in vacuum, phosphorus pentoxide, 60 ℃, 3 hours).

Residue on ignition NMT 0.2% (0.5 g, platinum crucible).

Assay Weigh accurately each 20 mg of Triamcinolone Acetonide and triamcinolone acetonide RS, previously dried, and dissolve in methanol to make exactly 50 mL, respectively. Pipet each 10 mL of these solutions, add exactly 10 mL of the internal standard solution and the mobile phase to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with each 20 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following con-

ditions and calculate the peak height ratios, Q_T and Q_S, of triamcinolone acetonide from the test solution to the peak height of the internal standard.

$$\text{Amount (mg) of triamcinolone acetonide } (C_{24}H_{31}FO_6) = \text{Amount (mg) of triamcinolone acetonide RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of Prednisolone in methanol (1 in 5000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of water and acetonitrile (3 : 1).

Flow rate: Adjust the flow rate so that the retention time of Triamcinolone Acetonide is about 13 minutes.

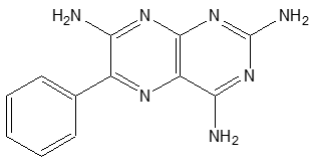
System suitability

System performance: Proceed with 10 μL of the standard solution under the above operating conditions; the internal standard and triamcinolone acetonide are eluted in this order with the resolution being NLT 6.

System repeatability: Perform the test 6 times with each 10 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak height ratio of triamcinolone acetonide to the peak height of the internal standard is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Triamterene
트리암테렌



$C_{12}H_{11}N_7$: 253.26

6-Phenylpteridine-2,4,7-triamine [*396-01-0*]

Triamterene, when dried, contains NLT 98.5% and NMT 101.0% of Triamterene ($C_{12}H_{11}N_7$).

Description Triamterene occurs as a yellow crystalline powder. It is odorless and tasteless.

It is sparingly soluble in dimethylsulfoxide, very slightly soluble in acetic acid(100) and practically insoluble in water, ethanol(95) or ether.

It dissolves in nitric acid or sulfuric acid but does not dissolve in dilute nitric acid, dilute sulfuric acid or dilute hydrochloric acid.

Identification (1) To 10 mg of Triamterene, add 10 mL of water, heat, cool, and filter; the filtrate exhibits a purple fluorescence. To 2 mL of the filtrate, add 0.5 mL of hydrochloric acid; the fluorescence disappears.

(2) The filtrate obtained in (1) responds to the Qualitative Analysis for primary aromatic amines.

(3) Dissolve each 10 mg of Triamterene and triamterene RS in 100 mL of acetic acid(100). To each 10 mL of these solutions, add water to make 100 mL. Determine the absorption spectra of these solutions as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

Purity (1) ***Heavy metals*—**Proceed with 1.0 g of Triamterene according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Arsenic*—**Proceed with 1.0 g of Triamterene according to Method 3 and perform the test (NMT 2 ppm).

(3) ***Related substances*—**Dissolve 0.10 g of Triamterene in 20 mL of dimethylsulfoxide. Pipet 2 mL of this solution, add methanol to make exactly 50 mL, and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 200 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each 5 μL of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, ammonia TS and methanol (9 : 1: 1) (as the developing solvent) to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 365 nm); any spot other than the principal spot obtained from the test solution is not more intense than the spot from the standard solution.

Loss on drying NMT 0.5% (1 g, 105 ℃, 4 hours).

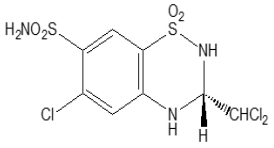
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.15 g of Triamterene, previously dried, dissolve in 100 mL of acetic acid(100) by warming, cool, and titrate with 0.05 mol/L perchloric acid VS (indicator: 2 drops of methylrosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction.

$$\text{Each mL of 0.05 mol/L perchloric acid VS} = 12.663 \text{ mg of } C_{12}H_{11}N_7$$

Packaging and storage Preserve in well-closed containers.

Trichlormethiazide
트리클로르메티아지드



and enantiomer

$C_8H_8Cl_3N_3O_4S_2$: 380.66

6-Chloro-3-(dichloromethyl)-1,1-dioxo-3,4-dihydro-2*H*-1λ6,2,4-benzothiadiazine-7-sulfonamide [*133-67-5*]

Trichlormethiazide, when dried, contains NLT 97.5% and NMT 102.0% of Trichlormethiazide ($C_8H_8Cl_3N_3O_4S_2$).

Description Trichlormethiazide occurs as a white powder.

It is freely soluble in *N*,*N*-dimethylformamide or acetone, slightly soluble in acetonitrile or ethanol(95), and practically insoluble in water.

A Solution of Trichlormethiazide in acetone (1 in 50) shows no optical rotation.

Melting point—About 270 °C (with decomposition).

Identification (1) Determine the absorption spectra of solutions of Trichlormethiazide and trichlormethiazide RS in ethanol(95) (3 in 250000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Trichlormethiazide and trichlormethiazide RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Perform the test with Trichiormethiazide as directed under the Flame Coloration (2); a green color appears.

Purify (1) ***Chloride***—Dissolve 1.0 g of Trichlormethiazide in 30 mL of acetone and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution to perform the test. Prepare the control solution by adding 30 mL of acetone, 6 mL of dilute nitric acid and water to 1.0 mL of 0.01 mol/L hydrochloric acid to make 50 mL (NMT 0.036%).

(2) ***Sulfate***—Dissolve 1.0 g of Trichlormethiazide in 30 mL of acetone and add 1 mL of dilute hydrochloric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 30 mL of acetone, 1 mL of dilute hydrochloric acid and water to 1.0 mL of 0.005 mol/L sulfuric acid to make 50 mL (NMT 0.048%).

(3) ***Heavy metals***—Proceed with 1.0 g of Trichlormethiazide according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Selenium***—Weigh 0.2 g of Trichlormethiazide and combust as directed under the Oxygen Flask Combustion with 25 mL of diluted nitric acid (1 in 30) as an absorbent. Use a 1 L combustion flask as the combustion flask. After combustion, wash the stopper and the inner wall of the flask with 10 mL of water, and transfer the liquid inside the flask to a 150-mL beaker using 20 mL of water. Then, heat gently to boil, boil for 10 minutes, cool to room temperature, and use this solution as the test solution. Separately, pipet 6.0 mL of the standard selenium stock solution, add 25 mL of diluted nitric acid (1 in 30) and 25 mL of water, and use this solution as the standard solution. Add diluted ammonia water(28) (1 in 2) to the test solution and standard solution, respectively, adjust the pH to 2.0 ± 0.2, and dilute by adding water to make exactly 60 mL. Transfer into a separatory funnel using 10 mL of water, and wash the separatory funnel with 10 mL of water. To each solution, add 0.2 g of hydroxylamine hydrochloride, stir to dissolve, then immediately add 5.0 mL of 2,3-diaminonaphthalene TS, and put a stopper. Stir to mix and allow to stand at room temperature for 100 minutes. To the resulting mixture, add 5.0 mL of cyclohexane, shake vigorously for 2 minutes, and allow to stand. If layers are separated, discard the water layer, centrifuge the cyclohexane extract to remove water, and take the cyclohexane layer. With these solutions and the control solution prepared in the same way with 25 mL of water added to 25 mL of diluted nitric acid (1 in 30), perform the test as directed under the Ultraviolet-visible Spectroscopy. Determine the absorbance at the absorption maximum wavelength of about 380 nm; the absorbance obtained from the test solution is not greater than that from the standard solution (NMT 30 ppm).

(5) ***Arsenic***—Proceed with 0.6 g of Trichlormethiazide according to Method 5 and perform the test. For this test, use 20 mL of *N*,*N*-dimethylformamide. (NMT 3.3 ppm).

(6) ***Related substances***—Dissolve 25 mg of Trichlormethiazide in 50 mL of acetonitrile and use this solution as the test solution. With 10 μL of the test solution, perform the test as directed under the Liquid Chromatography according to the following operating conditions. Determine each peak area by the automatic integration method and calculate the amount of related substances by the percentage peak area method; the amount of 4-amino-6-chlorobenzene-1,3-disulfonamide, having the relative retention time of about 0.3 with respect to trichlormethiazide, is NMT 2.0%, and the total amount of the related substances is NMT 2.5%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 268 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with phenyl silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: A mixture of diluted phosphoric acid (1 in 1000) and acetonitrile (3 : 1).

Mobile phase B: A mixture of acetonitrile and diluted phosphoric acid (1 in 1000) (3 : 1).

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 10	100	0
10 - 20	100 → 0	0 → 100

Flow rate: 1.5 mL/min

System suitability

Test for required detectability: Pipet 1 mL of the test solution, add acetonitrile to make exactly 50 rnL, and use this solution as the system suitability solution. Pipet 1 mL of the system suitability solution and add acetonitrile to make exactly 20 mL. Confirm that the peak area of trichlormethiazide obtained from 10 μL of this solution is 3.5 to 6.5% of that of trichlormethiazide obtained from 10 mL of the system suitability solution.

System performance: To 5 mL of the system suitability solution, add 5 mL of water, warm on a steam bath at 60 °C for 30 minutes, cool, and proceed with 10 μL of this solution according to the above operating conditions; 4-amino-6-chlorobenzene-1,3-disulfonamide and trichlormethiazide are eluted in this order, the relative retention time of 4-amino-6-chlorobenzene-1,3-disulfonamide with respect to trichlormethiazide is about 0.3, and the number of theoretical plates and the symmetry factor of the trichlormethiazide peak are NLT 5000 and NMT 1.2, respectively.

System repeatability: Perform the test 3 times with 10 μL of the system suitability solution according to the above operating conditions; the relative standard deviation of the peak area of Trichlormethiazide is NMT 2.0%.

Time span of measurement: About 2.5 times the retention time of trichlormethiazide after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 °C, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about each 25 mg of Trichlormethiazide and trichlormethiazide RS, previously dried, and dissolve in exactly 20 mL of the internal standard solution. Pipet each 1 mL of these solutions, add acetonitrile to make exactly 20 mL, and use these solutions as the test solution and the standard solution. Perform the test with 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions and calculate the peak area ratio, Q_T and Q_S, of trichlormethiazide to that of the internal standard.

$$\text{Amount (mg) of trichlormethiazide } (C_8H_8Cl_3N_3O_4S_2) = \text{Amount (mg) of triamcinolone RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of 3-nitropheno in acetonitrile (1 in 800).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 268 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with phenyl silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of diluted phosphoric acid (1 in 1000) and acetonitrile (3:1).

Flow rate: Adjust the flow rate so that the retention time of trichlormethiazide is about 8 minutes.

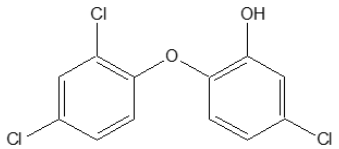
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions and perform the test; the internal standard and trichlormethiazide are eluted in this order with the resolution being NLT 2.0.

System repeatability: Perform the test 6 times with each 10 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area ratio of trichlormethiazide to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.

Triclosan
트리클로산



$C_{12}H_7Cl_3O_2$: 289.54

5-Chloro-2-(2,4-dichlorophenoxy)phenol [*3380-34-5*]

Triclosan contains NLT 97.0% and NMT 103.0% of triclosan ($C_{12}H_7Cl_3O_2$), calculated on the anhydrous basis.

Description Triclosan occurs as a white crystalline powder.

It is freely soluble in methanol, ethanol(95) or acetone, sparingly soluble in hexane and practically insoluble in water.

Melting point—About 57 °C.

Identification (1) Determine the infrared spectra of Triclosan and triclosan RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test

solution corresponds to that of the standard solution, as obtained in the Assay.

Purity (1) ***Clarity and color of solution***—Dissolve 1.40 g of Triclosan in 10 mL of acetone; the resulting solution is clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Triclosan according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 20 ppm).

(3) ***Related substances*—**Perform the test with 0.5 μL of the test solution in the Assay as directed under the Gas Chromatography according to the following operating conditions. Inject the test solution, increase the column temperature to 140 °C at a rate of 20 °C per minute, and then increase to 240 °C at a rate of 4 °C per minute. Maintain this temperature for NLT 5 minutes, measure the peak area of chromatogram obtained from the above, and calculate the amount of each related substance by the percentage peak area method; each related substance is NMT 0.1% and the amount of total related substance is NMT 0.5%.

Operating conditions

For the detector, column, mobile phase, flow rate, and system compatibility solution, proceed as directed in the operating conditions under the Assay.

(4) ***Monochlorophenols and 2,4-dichlorophenol*—**Weigh accurately 0.25 g of Triclosan, dissolve in 20 mL of acetonitrile, add water to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately 5 mg of 4-chlorophenol and 1 mg of 2,4-dichlorophenol, respectively, dissolve in 50 mL of acetonitrile, and add water to make exactly 100 mL. Pipet 1.0 mL of this solution, add a mixture of acetonitrile and water (1 : 1) to make 100 mL, and use this solution as the standard solution. Perform the test with each 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the peak areas of 4-chlorophenol and 2,4-dichlorophenol obtained from the test solution are not larger than those from the standard solution.

Operating conditions

Detector: An electrochemical detector (electrode 1: −0.45 V, electrode 2: −0.75 V).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 to 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and phosphate buffer solution (1: 1).

Flow rate: 1.0 mL/min

System suitability

System repeatability: Perform the test 5 times with 20 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of 2,4-dichlorophenol is NMT 9.0%.

Phosphate buffer solution—Dissolve 1.38 g of anhydrous sodium dihydrogen phosphoric acid and 1.42 g of sodium monohydrogen phosphoric acid in water to make 1000 mL.

(5) ***1,3,7-trichlorodibenzo-p-dioxin, 2,8-dichlorodibenzo-p-dioxin, 2,8-dichlorodibenzofuran and 2,4,8-trichlorodibenzofuran*—**Weigh accurately 2.0 g of Triclosan, transfer into a stoppered centrifuge tube, add 5 mL of 2 mol/L potassium hydroxide TS, and shake for 10 minutes to dissolve. Add 3 mL of *n*-hexane, shake for 10 minutes, allow to stand, and transfer the organic solvent layer to a suitable container. Add 3 mL of *n*-hexane to the aqueous layer, shake for 10 minutes, and allow to stand for the organic layer to be separated. Combine the organic layer with the extract above, and discard the aqueous layer. Add 3 mL of 2 mol/L potassium hydroxide TS to the combined organic solvent, shake for 10 minutes, and allow to stand. Then, take the organic solvent layer and discard the aqueous layer. Again, add 3 mL of 2 mol/L potassium hydroxide TS to the organic solvent layer, shake for 10 minutes, and allow to stand. Transfer the organic solvent layer to a suitable container and evaporate to dryness under a stream of nitrogen. Dissolve the residue in 1.0 mL of methanol and use this solution as the test solution. Separately, weigh accurately 5 mg of 2,8-dichlorodibenzofuran and 10 mg of 2,4,8-trichlorodibenzofuran, put into a 100-mL volumetric flask, add accurately amounts, equivalent to 5 mg of 1,3,7-trichlorodibenzo-*p*-dioxin and 10 mg of 2,8-dichlorodibenzo-*p*-dioxin, and dissolve in methanol to make exactly 100 mL. Pipet 1.0 mL of this solution, add methanol to make exactly 100 mL, and use this solution as the standard solution. Perform the test with each 20 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas from each solution; the peak areas of 2,8-dichlorodibenzofuran, 2,8-dichlorodibenzo-*p*-dioxin, 2,4,8-trichlorodibenzofuran, and 1,3,7-trichlorodibenzo-*p*-dioxin from the test solution are not larger than each corresponding peak area from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of acetonitrile, water and acetic acid(100) (70 : 30 : 0.1).

Flow rate: 1.5 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution according to the above operating conditions and perform the test; the relative retention times of 2,8-dichlorodibenzofuran, 2,8-dichlorodibenzo-*p*-dioxin,

2,4,8-trichlorobenzofuran, and 1,3,7-trichlorodibenzo-*p*-dioxin are about 0.59, 0.71, 0.88, and 1.0, respectively.

System repeatability: Perform the test 5 times with 20 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of 2,8-dichloro-dibenzo-*p*-dioxin is NMT 15.0%.

(6) ***2,3,7,8-tetrachlorodibenzo-p-dioxin and 2,3,7,8-tetrachlorodibenzofuran (extremely toxic)***—Weigh accurately 30 g of Triclosan, transfer into a separatory funnel, add 30 μL of the internal standard solution, dissolve in 200 mL of 1 mol/L sodium hydroxide TS, and extract 4 times with each 30 mL of *n*-hexane. Combine all the extracts and wash with 20 mL of water. Extract the washings with 15 mL of *n*-hexane. Combine the extracts, add about 3 g of anhydrous sodium sulfate to the combined extracts, and allow to stand for 30 minutes. Quantitatively transfer into an appropriate round-bottom flask, and distill using a distillation apparatus until about 1 mL of distillate remains. Transfer the distillate to the top of chromatographic column A, and elute with 50 mL of n-hexane. Collect the eluate on top of chromatograph column B, elute with 30 mL of a mixture of n-hexane and dichloromethane (98 : 2), and discard the eluate. Again, elute with 40 mL of a mixture of n-hexane and dichloromethane (1 : 1), and collect the eluates in a round-bottom flask. Distill the combined eluates, using a distillation apparatus, until about 1 mL remains. Evaporate this solution to concentrate to the volume of 50 μL with a stream of nitrogen, evaporate to dryness at room temperature, dissolve 10 μL of 2,2,4-trimethylpentane, and use this solution as the test solution. Perform the test with 1 μL of the test solution as directed under the Gas Chromatography with a high-resolution mass spectrometer, and determine the peak areas at mass-to-charge ratios of 319.90, 321.89, 331.88, 333.93, 303.90, 305.90 and 317.94. The peak area for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin at a mass-to-charge ratio of 319.90 is not larger than the peak area of the internal standard at a mass-to-charge ratio of 331.88; the peak area for 2,3,7,8-tetrachloro dibenzofuran at a mass-to-charge ratio of 303.90 is not larger than the peak area of the internal standard at a mass-to-charge ratio of 315.94.

Operating conditions

Detector: A high-resolution mass spectrometer (electron impact ionization).

Column: A capillary column, about 0.25 mm in internal diameter and about 60 m in length, coated with cyanopolysiloxane.

Mobile phase: helium

Column temperature: Maintain at 80 °C for 1 minute, raise the temperature to 220 °C at a rate of 20 °C per minute, raise the temperature to 270 °C at a rate of 2 °C per minute, and maintain at 270 °C for 20 minutes.

Signal-to-noise ratio: NLT 50 at a mass-to-charge ratio of 321.89.

Stationary phase A—Place about 10 g of silica gel in a suitable container and add about 3 mL of 1 mol/L sodium hydroxide TS.

Stationary phase B—Place about 60 g of silica gel in a suitable container and add about 74 mL of sulfuric acid.

Chromatography column A—Transfer 5.1 g of the stationary phase A, 0.5 g of silica gel, 6.2 g of the stationary phase B, 3.2 g of sodium sulfuric acid in a chromatography column with an internal diameter of 10 mm, wash by adding 50 mL of *n*-hexane, and discard the eluate.

Chromatography column B—Transfer 2.5 g of alumina and 2.5 g of sodium sulfate decahydrate in a chromatography column with an internal diameter of 6 mm, wash by adding 30 mL of *n*-hexane, and discard the eluate.

Internal standard solution—Weigh accurately a suitable amount of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, ^{13}C-labeled 2,3,7,8-tetrachlorodibenzofuran, ^{13}C-labeled nonane and dissolve in a suitable amount of 2,2,4-trimethylpentane to obtain a solution containing about 1.0 pg of each per μL.

Water NMT 0.1% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately each 40 mg of Triclosan and triclosan RS, dissolve in dichloromethane to make exactly 10 mL, respectively, and use these solutions as the test solution and the standard solution, respectively. Perform the test with each 0.5 μL of test solution and standard solution as directed under the Gas Chromatography according to the following operating conditions; determine the peak areas, A_T and A_S, of Triclosan obtained from the solutions.

$$\text{Amount (mg) of Triclosan } (C_{12}H_7Cl_3O_2) = \text{Amount (mg) of triclosan RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: A flame ionization detector

Column: About 0.53 mm in internal diameter and and about 15 m in length, packed with 50% of phenyl and 50% methylpolysiloxan.

Injection port temperature: Maintain at 34 °C and raise rapidly to 200 °C immediately after the injection.

Column temperature: After the injection, increase the column temperature to 140 °C at a rate of 20 °C per minute, then increase the temperature to 240 °C at a rate of 4 °C per minute, and maintain at 270 °C for 5 minutes or longer.

Detector temperature: 260 °C

Carrier gas: Helium (6 psi)

System suitability

System repeatability: Perform the test 5 times with 0.5 μL of the standard solution according to the above operating conditions. The relative standard deviation of the area of the Triclosan peak is NMT 2.0%.

Packaging and storage Preserve in light-resistant, tight containers.

Trifluridine Ophthalmic Solution
트리플루리딘 점안액

Trifluridine Ophthalmic Solution contains NLT 90.0% and NMT 110.0% of the labeled amount of trifluridine ($C_{10}H_{11}O_5N_2F_3$: 296.20).

Method of preparation Prepare as directed under Ophthalmic Ointments, with Trifluridine.

Identification Use Trifluridine Ophthalmic Solution as the test solution. Weigh 0.1 g of trifluridine RS, add water to make 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescence indicator for thin-layer chromatography. Next, develop the plate with a mixture of chloroform and ethanol (8 : 2) as the developing solvent, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values of the spots from the test solution and the standard solution are the same.

Sterility Meets the requirements.

Particulate contamination: Visible particles Meets the requirements.

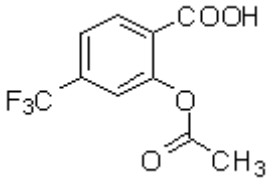
Insoluble particulate matter in ophthalmic solutions Meets requirements.

Assay Pipet an amount of Trifluridine Ophthalmic Solution, equivalent to about 50 mg of trifluridine ($C_{10}H_{11}O_5N_2F_3$), and add water to make exactly 50 mL. Take 5.0 mL of this solution, add 0.1 mol/L hydrochloric acid to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of trifluridine RS, and add water to make 50 mL. Take 5.0 mL of this solution, add 0.1 mol/L hydrochloric acid to make 50 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at 260 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of trifluridine } (C_{10}H_{11}O_5N_2F_3) = \text{Amount (mg) of trifluridine RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers.

Triflusal
트리플루살



$C_{10}H_7F_3O_4$: 248.16
2-Acetyloxy-4-(trifluoromethyl)benzoic acid [*322-79-2*]

Triflusal contains NLT 98.5% and NMT 101.5% of triflusal ($C_{10}H_7F_3O_4$), calculated on the dried basis.

Description Triflusal occurs as a white powder.
It is very soluble in ethanol(95), freely soluble in dichloromethane and practically insoluble in water.

Melting point—About 118 ℃ (with decomposition).

Identification (1) Determine the infrared spectra of Triflusal and triflusal RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Clarity and color of solution*—**Dissolve 1.0 g of Triflusal in ethanol(95) to make 20 mL; the solution is clear.

(2) ***Heavy metals*—**Weigh 2.0 g of Triflusal, dissolve in 9 mL of ethanol(95) and add water to make 20 mL. To this solution, add 2 mL of dilute acetic acid and a mixture of ethanol(95) and water (9 : 6) to make 50 mL, and perform the test using this solution as the test solution. Prepare the control solution by adding 2.0 mL of dilute acetic acid and the mixture of ethanol(95) and water (9: 6) to 2.0 mL of the lead standard solution to make 50 mL (NMT 10 ppm).

(3) ***Triflusal related substance I*—**Weigh accurately 0.1 g of Triflusal, dissolve in the mobile phase to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately 40 mg of triflusal related substance I (2-acetoxyterephthalic acid) RS and dissolve in the mobile phase to make exactly 100 mL. To this solution, add the mobile phase to make exactly 100 mL and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. The peak area of 2-acetoxyterephthalic acid obtained from the test solution is not greater than the area of the major peak obtained from the standard solution (NMT 0.1%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 250 nm).

Column: A stainless steel column, 4.6 mm in inter-

nal diameter and 25 cm in length, packed with aminopropylsilyl silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and 0.05 mol/L phosphate buffer (pH 4.5) (75 : 25).

Flow rate: 1.2 mL/min

System suitability

Perform the test with 20 μL of a mixture containing the same volume of the test solution and the standard solution according to the above operating conditions; the retention time of Triflusal and 2-acetoxyterephthalic acid is about 2.4 and 5 minutes, respectively.

(4) ***Triflusal related substance II***—Dissolve 0.1 g of Triflusal in 15 mL of ethanol(95), add 15 mL of cold water and 0.5 mL of 5 w/v% ammonium iron(III) sulfate, and allow to stand for 1 minute; the resulting solution is not more intense than the following control solution.

Control solution—Dissolve 10.0 mg of Triflusal related substance II [4-(trifluoromethylsalicylic acid)] in ethanol(95) to make exactly 100 mL. To 3 mL of the solution, add 0.1 mL of 0.5 w/v% ammonium iron(III) sulfate, 12 mL of ethanol(95) and 15 mL of water.

Loss on drying NMT 0.5% (1 g, in vacuum, phosphorus pentoxide).

Residue on ignition NMT 0.1% (1 g, platinum crucible).

Assay Weigh accurately about 0.2 g of Triflusal, dissolve in 50 mL of ethanol(95), and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 24.82 mg of $C_{10}H_7F_3O_4$

Packaging and storage Preserve in tight containers below 25 ℃.

Triflusal Capsules
트리플루살 캡슐

Triflusal Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of triflusal ($C_{10}H_7F_3O_4$: 248.16).

Method of preparation Prepare as directed under Capsules, with Triflusal.

Identification Weigh an amount of Triflusal Capsules, equivalent to 0.1 g of triflusal, add acetonitrile to make 100 mL, and use this solution as the test solution. Separately, weigh 0.1 g of triflusal RS, add acetonitrile to make 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of hexane, acetone, and acetic acid(100) (10 : 4 : 1) as the developing solvent and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); the R_f values of the spots obtained from the test solution and the standard solution are the same.

Uniformity of dosage units Meets the requirements.

Dissolution Take 1 capsule of Triflusal Capsules and perform the test at 100 revolutions per minute according to Method 1, using 900 mL of a mixture of 5 L of pH 4.5 acetic acid buffer solution and 2,500 mL of 1-propanol as the dissolution medium. Filter the dissolved solution 45 minutes after the start of the test. To 5.0 mL of the filtrate, add dissolution medium to make 20 mL, and use this solution as the test solution. Separately, weigh accurately about 33 mg of triflusal RS and add the dissolution medium to make 100 mL. Take 5.0 mL of this solution, add the dissolution medium to make 20 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 270 nm as directed under the Ultraviolet-visible Spectroscopy.
It meets the requirements if the dissolution rate of Triflusal Capsules in 45 minutes is NLT 70%.

Purity Weigh accurately the mass of the contents of NLT 20 capsules of Triflusal Capsules. Weigh accurately an amount equivalent to about 0.15 g (potency) of triflusal, add acetonitrile to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg of 4-(trifluoromethyl)salicylic acid RS and add acetonitrile to make 100 mL. Take 3.0 mL of this solution, add acetonitrile to make 25 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 324 nm as directed under the Ultraviolet-visible Spectroscopy with acetonitrile as a control solution.

$$\text{Content (\%) of 4-(trifluoromethyl)salicylic acid} = \frac{\text{Amount (mg) of the reference standard}}{\text{Amount (mg) of the sample}} \times \frac{A_T}{A_S} \times 12$$

Assay Weigh accurately the mass of the contents of NLT 20 capsules of Triflusal Capsules. Weigh accurately an amount equivalent to about 0.1 g of triflusal ($C_{10}H_7F_3O_4$), add the mobile phase to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately about 0.1 g of triflusal RS, add the mobile phase to make 25 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and

determine the peak areas, A_T and A_S, of triflusal in each solution.

$$\text{Amount (mg) of triflusal } (C_{10}H_7F_3O_4) = \text{Amount (mg) of triflusal RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 250 nm).

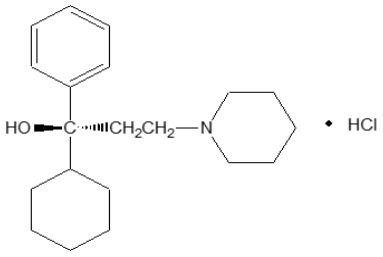
Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with aminopropylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetonitrile and 0.05 mol/L phosphate buffer solution (pH 4.5) (75 : 25).

Flow rate: 1.2 mL/min

Packaging and storage Preserve in tight containers.

Trihexyphenidyl Hydrochloride
트리헥시페니딜염산염



and enantiomer

$C_{20}H_{31}NO \cdot HCl$: 337.93

1-Cyclohexyl-1-phenyl-3-piperidin-1-ylpropan-1-ol hydrochloride [*52-49-3*]

Trihexyphenidyl Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of trihexyphenidyl hydrochloride ($C_{20}H_{31}NO \cdot HCl$).

Description Trihexyphenidyl Hydrochloride ($C_{20}H_{31}NO \cdot HCl$) occurs as a white crystalline powder. It is odorless and has a bitter taste.

It is soluble in ethanol(95), sparingly soluble in acetic acid(100), slightly soluble in water, very slightly soluble in acetic anhydride and practically insoluble in ether.

Melting point—About 250 °C (with decomposition).

Identification (1) Determine the infrared spectra of Trihexyphenidyl Hydrochloride and trihexyphenidyl hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) To 1 g of Trihexyphenidyl Hydrochloride, add 100 mL of water, dissolve by warming, and cool. The solution responds to the Qualitative Analysis (2) for chloride.

pH Dissolve 1.0 g of Trihexyphenidyl Hydrochloride in 100 mL of water by warming; the pH of the solution is between 5.0 and 6.0.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Trihexyphenidyl Hydrochloride in 100 mL of water by warming; the solution is colorless and clear.

(2) ***Heavy metals***—Dissolve 1.5 g of Trihexyphenidyl Hydrochloride in 60 mL of water by warming on a steam bath at 80 °C, cool, and filter. To 40 mL of the filtrate, add 2 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. Prepare the control solution by adding 2.0 mL of dilute acetic acid and water to 2.0 mL of the lead standard solution to make 50 mL (NMT 20 ppm).

(3) ***Related substances***—Weigh accurately 20 mg of Trihexyphenidyl Hydrochloride, dissolve in 10 mL of the mobile phase, and use this solution as the test solution. To 1.0 mL of the test solution, add the mobile phase to make 200 mL. Pipet 10 mL of this solution, add the mobile phase to make 50 mL, and use this solution as the standard solution (1). Separately, weigh accurately about 10 mg of trihexyphenidyl related substance I {1-phenyl-3-(pyperidin-1-yl)propan-1-one} RS, dissolve in 10 mL of the mobile phase, and use this solution as the standard solution (2). Pipet 1.0 mL of the standard solution (2), add the mobile phase to make 100 mL, and use this solution as the standard solution (3). Pipet 1 mL of the standard solution (2) and 1 mL of the test solution, add the mobile phase to make 100 mL, and use this solution as the standard solution (4). Perform the test with each 20 μL of the test solution and the standard solutions (1), (3), and (4) as directed under the Liquid Chromatography according to the following conditions. The peak area of trihexyphenidyl related substance I obtained from the test solution is not larger than the area of the major peak from the standard solution (3) (NMT 0.5%), and the peak area of any other related substance is not larger than the area of the major peak from the standard solution (1) (NMT 0.1%). The total area of related substances is NMT 0.5%. Exclude any peak of which the area is less than 0.2 times the area of the major peak from the standard solution (1) (0.02%).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 5 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 45 °C.

Mobile phase: Mix 200 mL of water with 0.2 mL of triethylamine and adjust the pH of the solution to 4.0 with phosphoric acid. To this solution, add 800 mL of acetonitrile.

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution (4) according to the above operating conditions and perform the test; the resolution of the peaks of trihexyphenidyl and trihexyphenidyl related substance I is NLT 4.0.

Time span of measurement: About 3 times the retention time of trihexyphenidyl.

Loss on drying NMT 0.5% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Trihexyphenidyl Hydrochloride, previously dried, dissolve in 50 mL of ethanol and 5.0 mL of 0.01 mol/L hydrochloric acid TS, and titrate with 0.1 mol/L sodium hydroxide VS from 1st equivalent point and 2nd equivalent point (potentiometric titration under the Titrimetry).

Each mL of 0.1 mol/L sodium hydroxide VS
= 33.793 mg of $C_{20}H_{31}NO \cdot HCl$

Packaging and storage Preserve in tight containers.

Trihexyphenidyl Hydrochloride Tablets
트리헥시페니딜염산염 정

Trihexyphenidyl Hydrochloride Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of trihexyphenidyl hydrochloride ($C_{20}H_{31}NO \cdot HCl$: 337.93).

Method of preparation Prepare as directed under Tablets, with Trihexyphenidyl Hydrochloride.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay., and the ultraviolet-visible absorption spectrum at 190 to 300 nm is the same.

Dissolution Take 1 tablet of Trihexyphenidyl Hydrochloride Tablets, add 900 mL of pH 6.8 phosphate buffer solution (1 in 2), previously diluted with the dissolution medium, and perform the test at 50 revolutions per minute according to Method 2. Take 30 mL of the dissolved solution 30 minutes after starting the test, and filter through a membrane filer with a pore size of NMT 0.8 μm. Discard the first 10 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 10 mg of trihexyphenidyl hydrochloride RS, previously dried at 105 ℃ for 3 hours, and dissolve in diluted pH 6.8 phosphate buffer solution (1 in 2) to make exactly 100 mL. Pipet 2 mL of this solution, add diluted pH 6.8 phosphate buffer solution (1 in 2) to make exactly 100 mL, and use this solution as the standard solution. Pipet 20 mL each of the test solution, the standard solution and the diluted phosphate buffer solution, pH 6.8 (1 in 2), add exactly 1 mL of diluted acetic acid (1 in 10) and then immediately 5 mL of bromocresol green-sodium hydroxide-acetic acid-sodium acetate TS, respectively, and shake to mix. Add exactly 10 mL of dichloromethane, shake well to mix, and centrifuge. Using the dichloromethane layer as the control solution, perform the test as directed under the Ultraviolet-visible Spectroscopy. Determine the absorbances, A_T, A_S and A_B, at the wavelength of 415 nm.
It meets the requirements when the dissolution rate of Trihexyphenidyl Hydrochloride Tablets for 30 minutes is NLT 70%.

Dissolution rate (%) of the labeled amount of trihexyphenidyl hydrochloride ($C_{20}H_{31}NO \cdot HCl$)

$$= W_S \times \frac{A_T - A_B}{A_S - A_B} \times \frac{1}{C} \times 18$$

W_S: Amount (mg) of RS
C: Amount (mg) of the labeled amount of trihexyphenidyl hydrochloride ($C_{20}H_{31}NO \cdot HCl$) contained in 1 tablet

Uniformity of dosage units It meets the requirements when the Procedure for content uniformity is performed according to the following method.
Take 1 tablet of Trihexyphenidyl Hydrochloride Tablets, add 2 mL of dilute hydrochloric acid and 60 mL of water, shake vigorously for 10 minutes to disintegrate, and warm on a steam bath for 10 minutes with occasional shaking. After cooling, add 2 mL of methanol, and add water to obtain exactly V mL of a solution containing about 20 μg of trihexyphenidyl hydrochloride ($C_{20}H_{31}NO \cdot HCl$) per mL. If necessary, centrifuge, and use the clear supernatant as the test solution. Separately, weigh accurately about 20 mg of trihexyphenidyl hydrochloride RS (previously dried at 105 ℃ for 3 hours), and dissolve in methanol to make exactly 20 mL. Pipet 2 mL of this solution, add 2 mL of dilute hydrochloric acid, add water to make exactly 100 mL, and use this solution as the standard solution. Pipet 10 mL each of the test solution and the standard solution, transfer to glass-stoppered centrifuge tube, add 10 mL of bromocresol purple-dibasic potassium phosphate-citric acid TS and 15 mL of chloroform and stopper. Shake well to mix, and centrifuge. Pipet 10 mL of the chloroform layer from each tube, add chloroform to make exactly 50 mL. Perform the test with these solutions as directed under the Ultraviolet-visible Spectroscopy and determine the absorbances, A_T and A_S, at the wavelength of 408 nm.

Amount (mg) of trihexyphenidyl hydrochloride ($C_{20}H_{31}NO \cdot HCl$)
= Amount (mg) of trihexyphenidyl hydrochloride RS, calculated on the dried basis $\times \frac{A_T}{A_S} \times \frac{V}{1000}$

Assay Take 20 tablets of Trihexyphenidyl Hydrochloride Tablets, transfer to 0.1 mol/L hydrochloric acid, the amount equivalent to 10% of the entire solution, and sonicate for 10 minutes for complete disintegration. To this, add the mobile phase, the amount equivalent to 40% of

the entire solution, shake for 10 minutes, and cool at the ordinary temperature. To this, add 50% of the entire solution, mix, and filter to obtain a solution containing 0.2 mg of trihexyphenidyl hydrochloride ($C_{20}H_{31}NO \cdot HCl$) per mL according to the labeled amount. Use this solution as the test solution. Separately, weigh accurately about 20 mg of trihexyphenidyl hydrochloride RS, dissolve in the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak areas, A_T and A_S, of trihexyphenidyl hydrochloride in each solution.

Amount (mg) of trihexyphenidyl hydrochloride ($C_{20}H_{31}NO \cdot HCl$)
= Amount (mg) of trihexyphenidyl hydrochloride RS $\times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm). However, use a photo-diode array detector (190 to 300 nm) when the Identification is performed.

Column: A stainless steel column about 4.6 mm in internal diameter and about 8 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Mobile phase: To a mixture of acetonitrile, water and triethylamine (920 : 80 : 0.2), add phosphoric acid to adjust the pH to 4.0.

Flow rate: 2.0 mL/min

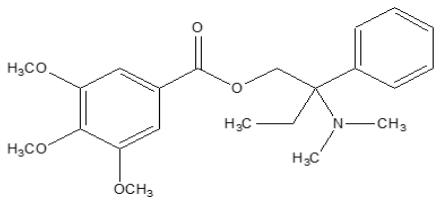
System suitability

System performance: Proceed with 10 μL of the standard solution according to the above conditions; the number of theoretical plate and the symmetry factor of the trihexyphenidyl hydrochloride peak is NLT 1300 and NMT 3.0, respectively.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of trihexyphenidyl hydrochloride is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Trimebutine
트리메부틴



$C_{22}H_{29}NO_5$: 387.48

2-(Dimethylamino)-2-phenylbutyl 3,4,5-trimethoxybenzoic acid ester, [*39133-31-8*]

Trimebutine contains NLT 98.5% and NMT 101.0% of trimebutine ($C_{22}H_{29}NO_5$: 387.48), calculated on the anhydrous basis.

Description Trimebutine occurs as a white, crystalline powder and is odorless.
It is very soluble in chloroform, freely soluble in ethanol, slightly soluble in hexane and practically insoluble in water.

Identification (1) Dissolve 2 mg of Trimebutine in 100 mL of 0.1 mol/L hydrochloric acid and determine the absorption spectrum of the solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at around 267 nm.

(2) Determine the infrared spectra of Trimebutine and trimebutine RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 78 and 84 ℃.

Purity ***Heavy metals***—Perform the test with 1.0 g of Trimebutine according to Method 1. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 20 ppm).

Water NMT 0.5% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.3 g of Trimebutine, dissolve in 50 mL of acetic acid(100) for non-aqueous titration, and titrate with 0.1 mol/L perchloric acid VS (indicator: methylrosaniline chloride TS). However, the endpoint is when the solution changes from violet to dark green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 38.748 mg of $C_{22}H_{29}NO_5$

Packaging and storage Preserve in tight containers.

Trimebutine Syrup
트리메부틴 시럽

Trimebutine syrup is a syrup to be dissolved before use, and contains NLT 95.0% and NMT 105.0% of the labeled amount of trimebutine ($C_{22}H_{29}NO_5$: 387.47).

Method of preparation Prepare as directed under Syrups, with Trimebutine.

Identification The retention time of the major peak of

the test solution corresponds to that of the standard solution, as obtained in the Assay.

Uniformity of dosage units (distribution) Meets the requirements.

pH Dissolve Trimebutine Syrup in water according to the directions for use; the pH of this solution is between 7.2 and 8.2.

Assay Pipet an amount of Trimebutine Syrup, equivalent to about 20 mg of trimebutine ($C_{22}H_{29}NO$), according to the labeled amount, add a mixture of 0.01 mol/L hydrochloric acid TS and acetonitrile (13 : 7) to make exactly 100 mL, filter, and use the filtrate as the test solution. Separately, weigh accurately about 20 mg of trimebutine RS, dissolve in a mixture of 0.01 mol/L hydrochloric acid TS and acetonitrile (13 : 7) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions, and determine the peak areas, A_T and A_S, of trimebutine, respectively.

$$\text{Amount (mg) of trimebutine } (C_{22}H_{29}NO) = \text{Amount (mg) of trimebutine RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 254 nm).

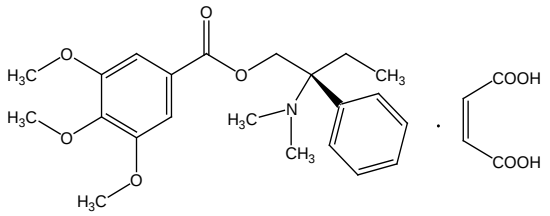
Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Dissolve 1 g of sodium 1-pentanesulfonate in 650 mL of a solution prepared by adjusting the pH of a dilute perchloric acid solution (17 in 20000) to 3.0 with an ammonium acetate solution (1 in 1000), filter with a membrane filter, and add 350 mL of acetonitrile to the filtrate.

Flow rate: 1.0 mL/min

Packaging and storage Preserve in tight containers.

Trimebutine Maleate
트리메부틴말레산염



and enantiomer

$C_{22}H_{29}NO_5 \cdot C_4H_4O_4$:503.54

(*Z*)-but-2-Enedioicacid;[2-(Dimethylamino)-2-phenylbutyl]3,4,5-trimethoxybenzoate [*34140-59-5*]

Trimebutine Maleate, when dried, contains NLT 98.5% and NMT 101.0% of Trimebutine Maleate ($C_{22}H_{29}NO_5 \cdot C_4H_4O_4$).

Description Trimebutine Maleate occurs as white crystals or a crystalline powder.

It is freely soluble in *N*,*N*-dimethylformamide or acetic acid(100), soluble in acetonitrile and slightly soluble in water or ethanol(99.5).

It dissolves in 0.01 mol/L hydrochloric acid TS.

A solution of Trimebutine Maleate in *N*,*N*-dimethylformamide (1 in 20) exhibits no optical rotation.

Identification (1) Determine the absorption spectra of solutions of Trimebutine Maleate and trimebutine maleate RS in 0.01 mol/L hydrochloric acid TS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Trimebutine Maleate and trimebutine maleate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 131 and 135 ℃.

Purity (1) ***Heavy metals*—**Proceed with 2.0 g of Trimebutine Maleate according to Method 2 under the Heavy Metals and perform the test. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 10 ppm).

(2) ***Arsenic*—**Proceed with 2.0 g of Trimebutine Maleate according to Method 3 and perform the test (NMT 1 ppm).

(3) ***Related substances***—Dissolve 0.10 g of Trimebutine Maleate in 100 mL of a mixture of hydrochloric acid TS and acetonitrile (13 : 7), and use this solution as the test solution. Pipet 1.0 mL of this solution, add a mixture of 0.01 mol/L hydrochloric acid TS and acetonitrile (13 : 7) to make exactly 250 mL, and use this solution as the standard solution. Perform the test with each 20 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas of each solution

by the automatic integration method; the area of each peak other than trimebutine and maleic acid from the test solution is not larger than 0.5 times the peak area of trimebutine from the standard solution. The total area of the peaks other than trimebutine and maleic acid from the test solution is not larger than the peak area of trimebutine from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Add ammonium acetate solution (1 in 1000) to diluted perchloric acid (17 in 20000) and adjust the pH to 3.0. Dissolve 650 mL of this solution in 1 g of sodium 1-pentanesulfonate. To 650 mL of this solution, add 350 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of trimebutine is about 9 minutes.

System suitability

Test for required detectability: Pipet 5 mL of the standard solution, add a mixture of 0.01 mol/L Hydrochloric acid TS and acetonitrile (13 : 7) to make 20 mL. Confirm that the peak area of trimebutine obtained from 20 μL of this solution is equivalent to between 20 and 30% of that of trimebutine from the standard solution.

System performance: Dissolve 40 mg of Trimebutine Maleate and 20 mg of Imipramine Hydrochloride in 100 mL of a mixture of 0.01 mol/L hydrochloric acid TS and acetonitrile (13 : 7). Proceed with 20 μL of this solution according to the above operating conditions; trimebutine and imipramine are eluted in this order with the resolution being NLT 2.5.

System repeatability: Perform the test 6 times with each 20 μL of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of trimebutine is NMT 5.0%.

Time span of measurement: About 2 times the retention time of trimebutine after the maleic acid peak.

Loss on drying NMT 0.5% (1 g, 105 °C, 3 hours).

Residue on Ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.8 g of Trimebutine Maleate, previously dried, dissolve in 70 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 3 drops of methylrosaniline chloride TS). The endpoint of the titration is when the color of the solution changes from violet through blue to bluish green. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 50.35 mg of $C_{22}H_{29}NO_5 \cdot C_4H_4O_4$

Packaging and storage Preserve in well-closed containers.

Trimebutine Maleate Tablets
트리메부틴말레산염 정

Trimebutine Maleate Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of trimebutine maleate ($C_{22}H_{29}NO_5\,C_4H_4O_4$: 503.55).

Method of preparation Prepare as directed under Tablets, with Trimebutine Maleate.

Identification The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Purity ***Related substances*—**Weigh accurately the mass of NLT 20 tablets of Trimebutine Maleate Tablets and powder them. Weigh accurately an amount, equivalent to about 0.1 g of trimebutine maleate ($C_{22}H_{29}NO_5 \cdot C_4H_4O_4$), add 60 mL of 0.01 mol/L hydrochloric acid TS, warm on a steam bath for 5 minutes, and shake for 15 minutes to mix. After cooling, add 35 mL of acetonitrile and then 0.01 mol/L hydrochloric acid TS to make exactly 100 mL, and centrifuge. Filter the clear supernatant, discard the first 20 mL of the filtrate, pipet 10 mL of the subsequent filtrate, and add 5 mL of acetonitrile and then water to make exactly 25 mL. Use the resulting solution as the test solution. Separately, weigh accurately 0.1 g of trimebutine maleate RS, add 60 mL of 0.01 mol/L hydrochloric acid TS, and warm on a steam bath to dissolve. After cooling, add 0.01 mol/L hydrochloric acid TS to make exactly 100 mL. Pipet 1 mL of this solution, add 35 mL of acetonitrile, add 0.01 mol/L hydrochloric acid TS to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas in each solution according to the automatic integration method; the sum of peak areas other than trimebutine from the test solution is not larger than the peak area of trimebutine from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase, flow rate and selection of column, proceed as directed under the operating conditions in the Assay.

Detection sensitivity: Adjust the sensitivity so that the peak height of trimebutine obtained from 20 μL of the standard solution is 3 to 10 mm.

Time span of area measurement: About twice the retention time of trimebutine after the peak of maleic acid.

Dissolution Perform the test with 1 tablet of Theophyl-

line Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of Solution 1 in the Dissolution as the dissolution medium. Take the dissolved solution 45 minutes after starting the test and filter it. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, and add Solution 1 under the Dissolution to obtain exactly *V′* mL of a solution containing 100 μg of trimebutine maleate per mL according to the labeled amount. Separately, weigh accurately about 100 mg of trimebutine maleate RS and dissolve in Solution 1 in the Dissolution to make exactly 100 mL. Pipet 10 mL of this solution, add Solution 1 in the Dissolution to make 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and measure the peak areas, A_T and A_S, of trimebutine maleate ($C_{22}H_{29}NO_5 \cdot C_4H_4O_4$) in each solution. The dissolution rate of Trimebutine Maleate Tablets is NLT 75% in 45 minutes.

Dissolution rate (%) of the labeled amount of trimebutine maleate ($C_{22}H_{29}NO_5 \cdot C_4H_4O_4$)

$$= W_S \times \frac{V'}{V} \times \frac{A_T}{A_S} \times \frac{1}{C}$$

*W*s: Amount (mg) of trimebutine maleate RS

C: Labeled amount (mg) of trimebutine maleate ($C_{22}H_{29}NO_5 \cdot C_4H_4O_4$) contained in 1 tablet

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 269 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 ℃.

Mobile phase: A mixture of Solution A and acetonitrile (65 : 35).

Flow rate: 1.0 mL/min

Solution A—A solution obtained by dissolving 1 g of sodium 1-pentanesulfonate in 650 mL of a solution of dilute perchloric acid (17 in 20,000) adjusted the pH to 3.0 with the ammonium acetate solution.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 tablets of Trimebutine Maleate Tablets and powder them. Weigh accurately an amount, equivalent to about 100 mg of trimebutine maleate ($C_{22}H_{29}NO_5 \cdot C_4H_4O_4$), and dissolve in 50% methanol to make exactly 100 mL. Filter this solution, take 10 mL of the filtrate, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately 100 mg of trimebutine maleate RS and dissolve in 50% methanol to make exactly 100 mL. Pipet 10 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and measure the peak areas, A_T and A_S, in each solution.

Amount (mg) of trimebutine maleate ($C_{22}H_{29}NO_5 \cdot C_4H_4O_4$)

$$= \text{Amount (mg) of trimebutine maleate RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption spectrophotometer (wavelength: 269 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 ℃.

Mobile phase: A mixture of Solution A and acetonitrile (65 : 35).

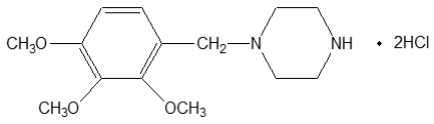
Flow rate: 1.0 mL/min

System suitability

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of trimebutine maleate is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Trimetazidine Hydrochloride
트리메타지딘염산염



$C_{14}H_{22}N_2O_3 \cdot 2HCl$: 339.26

1-[(2,3,4-Trimethoxyphenyl)methyl]piperazine dihydrochloride [*13171-25-0*]

Trimetazidine Hydrochloride contains NLT 98.0% and NMT 101.0% of trimetazidine hydrochloride ($C_{14}H_{22}N_2O_3 \cdot 2HCl$), calculated on the anhydrous basis.

Description Trimetazidine Hydrochloride occurs as a white crystalline powder.

It is very soluble in water or formic acid, soluble in methanol, and practically insoluble in ether.

Dissolve 1.0 g of Trimetazidine Hydrochloride in 20 mL of water; the pH of the solution is between 2.3 and 3.3.

Melting point—About 227 °C (with decomposition).

Identification (1) Determine the absorption spectra of solutions of Trimetazidine Hydrochloride and trimetazidine hydrochloride RS in 0.1 mol/L hydrochloric acid TS (1 in 6250) as directed under the Ultraviolet-visible

Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Trimetazidine Hydrochloride and trimetazidine hydrochloride RS as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Trimetazidine Hydrochloride (1 in 50) responds to the Qualitative Analysis for chloride.

Purity (1) ***Heavy metals***—Proceed with about 2.0 g of Trimetazidine Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Dissolve 0.2 g of Trimetazidine Hydrochloride in 50 mL of water and use this solution as the test solution. Pipet 2 mL of the test solution and add water to make exactly 20 mL. Pipet 2 mL of the resulting solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with each 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas of the test solution and standard solution by the automatic integration method; the area of any peak other than trimetazidine from the test solution is not larger than 1.5 times the peak area of Trimetazidine from the standard solution. The total area of the peaks other than trimetazidine from the test solution is not larger than 2.5 times the peak area of trimetazidine from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Control the mixing ratio of mobile phase A and mobile phase B stepwise or via the gradient elution as follows.

Mobile phase A: A mixture prepared by dissolving 2.87 g of sodium 1-heptanesulfonate in water to make 1000 mL and adjusting the pH to 3.0 with diluted phosphoric acid (1 in 10) and methanol (3 : 2).

Mobile phase B: Methanol

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 50	95 → 75	5 → 25

Flow rate: Adjust the flow rate so that the retention time of trimetazidine is about 25 minutes.

Time span of measurement: About 2 times the retention time of trimetazidine after the solvent peak.

System suitability

Test for required detectability: Pipet 5 mL of the standard solution and add water to make exactly 20 mL. Confirm that the peak area of trimetazidine obtained with 10 μL of this solution is equivalent to 18 to 32% of the peak area of trimetazidine obtained with 10 μL of the standard solution.

System performance: Proceed with 10 μL of the standard solution according to the above operating conditions; the number of theoretical plates and symmetry factor of the trimetazidine peak are NLT 15000 and NMT 1.5, respectively.

System repeatability: Perform the test 6 times with 10 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of trimetazidine is NMT 2.0%.

Water NMT 1.5% (2 g, volumetric titration, direct titration).

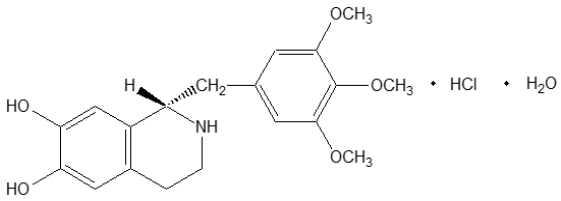
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.12 g of Trimetazidine Hydrochloride, dissolve in 5 mL of formic acid, add exactly 15 mL of 0.1 mol/L perchloric acid, and heat at 90 to 100℃ for 30 minutes. After cooling, add 45 mL of acetic acid(100) and titrate the excess perchloric acid with 0.1 mol/L sodium acetate VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner.

Each mL of 0.1 mol/L perchloric acid VS
= 16.963 mg of $C_{14}H_{22}N_2O_3 \cdot 2HCl$

Packaging and storage Preserve in tight containers.

Trimetoquinol Hydrochloride Hydrate
트리메토퀴놀염산염수화물



Trimetoquinol Hydrochloride

$C_{19}H_{23}NO_5 \cdot HCl \cdot H_2O$: 399.87

1-(3,4,5-Trimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-isoquinolinediol hydrate hydrochloride [*8559-59-6,* anhydride]

Trimetoquinol Hydrochloride Hydrate contains NLT 98.0% and NMT 101.0% of Trimetoquinol Hydrochloride ($C_{19}H_{23}NO_5 \cdot HCl$: 381.85), calculated on the anhydrous basis.

Description Trimetoquinol Hydrochloride Hydrate occurs as white crystals or a crystalline powder and is odorless.

It is freely soluble in methanol or water and sparingly soluble in ethanol(99.5).

Melting point—About 151 ℃ (with decomposition, in vacuum, dried for 4 hours at 105 ℃).

Identification (1) Determine the absorption spectra of solutions of Trimetoquinol Hydrochloride Hydrate and trimetoquinol hydrochloride hydrate RS in 0.01 mol/L hydrochloric acid TS (1 in 20000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Trimetoquinol Hydrochloride Hydrate and trimetoquinol hydrochloride hydrate RS as directed in the potassium chloride disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Trimetoquinol Hydrochloride Hydrate (1 in 50) responds to the Qualitative Analysis (1) for chloride.

Optical rotation $[\alpha]_D^{20}$: Between -16° and -19° (0.25 g calculated on the anhydrous basis, water, warming, after cooling, 25 mL, 100 mm).

pH Dissolve about 1.0 g of Trimetoquinol Hydrochloride Hydrate in 100 mL of water by warming; the pH of the solution is between 4.5 and 5.5.

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Trimetoquinol Hydrochloride Hydrate in 10 mL of water by warming; the solution is colorless and clear.

(2) ***Sulfate***—Weigh 0.5 g of Trimetoquinol Hydrochloride Hydrate and perform the test. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid (NMT 0.038%).

(3) ***Heavy metals***—Proceed with 1.0 g of Trimetoquinol Hydrochloride Hydrate according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Related substances***—Dissolve about 50 mg of Trimetoquinol Hydrochloride Hydrate in 50 mL of the mobile phase and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with each 20 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each peak from the test solution and the standard solution by the automatic integration method; the total area of the peaks other than trimetoquinol from the test solution is not larger than the peak area of trimetoquinol from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 283 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase: Dissolve 2 g of potassium dihydrogen phosphate and 2 g of sodium 1-pentanesulfonate in 1000 mL of water. Adjust the pH of the solution to 2.8 to 3.2 with phosphoric acid and filter with a membrane filter (0.4 μm in pore size). Take 800 mL of the filtrate and add 200 mL of acetonitile.

Flow rate: Adjust the flow rate so that the retention time of trimetoquinol is about 7 minutes.

System suitability

Test for required detectability: Pipet 2 mL of the standard solution and add the mobile phase to make exactly 20 mL. Confirm that the peak area of trimetoquinol obtained from 20 μL of this solution is equivalent to 7 to 13% of that of trimetoquinol from the standard solution.

System performance: Dissolve 5 mg of Trimetoquinol Hydrochloride Hydrate and 1 mg of Procaine Hydrochloride in 50 mL of the mobile phase. Proceed with 20 μL of this solution according to the above operating conditions; procaine and trimetoquinol are eluted in this order with the resolution being NLT 4.

System repeatability: Perform the test 6 times with 20 μL each of the standard solution according to the above operating conditions; the relative standard deviation of the peak area of trimetoquinol is NMT 2.0%.

Time span of measurement: About 2 times the retention time of the trimetoquinol after the solvent peak.

Water Between 3.5% and 5.5% (0.3 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Trimetoquinol Hydrochloride Hydrate, add 2 mL of 0.1 mol/L hydrochloric acid and 70 mL of ethanol(99.5), dissolve by stirring well to mix, and titrate with 0.1 mol/L potassium hydroxide-ethanol VS (potentiometric titration under the Titrimetry). Determine the amount of 0.1 mol/L potassium hydroxide-ethanol VS between the first inflection point and the second inflection point.

Each mL of 0.1 mol/L potassium hydroxide-ethanol VS
= 38.185 mg of $C_{19}H_{23}NO_5 \cdot HCl$

Packaging and storage Preserve in light-resistant, well-closed containers.

Tripotassium Bismuth Dicitrate
비스무트시트르산염칼륨

Tripotassium Bismuth Dicitrate, when dried, contains NLT 39.0% and NMT 42.0% of bismuth oxide (Bi_2O_3 : 465.96) and NLT 10.8% and NMT 13.2% of potassium (K : 39.10).

Description Tripotassium Bismuth Dicitrate occurs as a white to milky white powder and has an ammonia-like odor.

Identification Weigh about 1 g of Tripotassium Bismuth Dicitrate and dissolve in 10 mL of water; the resulting solution responds to the Qualitative Analysis for potassium salt, citrate and bismuth salt.

pH Between 6.0 and 8.0 (10% aqueous solution).

Purity (1) ***Clarity and color of solution***—Dissolve 0.10 g of Tripotassium Bismuth Dicitrate in 10 mL of water; the resulting solution is not more intense than the following control solution.

Control solution—Weigh 46.0 g of ferric chloride and dissolve in 25 mL of hydrochloric acid and water to make 1000 mL. To 1.25 mL of this solution, add 8.75 mL of water, and use this solution as the control solution.

(2) ***Chloride***—Weigh about 1.0 g of Tripotassium Bismuth Dicitrate and dissolve in water to make 100.0 mL. With 25.0 mL of this solution, perform the test as directed under the Chloride. Prepare the control solution with 0.13 mL of 0.01 mol/L hydrochloric acid (NMT 0.018%).

Loss on drying NMT 5.0% (1 g, 105 ℃, 3 hours).

Assay (1) ***Bismuth oxide***—Weigh accurately about 1.0 g of Tripotassium Bismuth Dicitrate, previously dried, dissolve in 20 mL of diluted nitric acid (2 in 5), add water to make exactly 100 mL, and filter. Pipet 50 mL of this solution, add 100 mL of water, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 5 drops of xylenol orange TS). The endpoint of the titration is when the reddish purple color of the solution changes to yellow.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 11.65 mg of Bi_2O_3

(2) ***Potassium***—Weigh accurately about 0.17 g of Tripotassium Bismuth Dicitrate [an amount equivalent to about 20 mg of potassium (K)], previously dried, and dissolve in water to make 100 mL. Pipet 1.0 mL of this solution, add 5.0 mL of 2% sodium chloride and water to make 100 mL, and use this solution as the test solution (about 2 μg/mL of potassium). Separately, weigh accurately about 190 mg of potassium chloride standard reagent, previously dried at 105 °C for 2 hours, and add water to make 1000 mL (about 100 μg/mL of potassium). Pipet a certain amount of this solution, add 5.0 mL each of 2% sodium chloride, add water to prepare a solution containing a range of 0 μg/mL - 25 μg/mL of potassium, and use this solution as the standard solution for calibration curve. Perform the test with the test solution and the standard solution as directed under the Atomic Absorption Spectroscopy according to the following conditions. Determine the potassium (K) content in the test solution based on the calibration curve obtained from the absorbance of the standard solution.

Gas: Air–acetylen
Lamp: Potassium hollow cathode lamp
Wavelength: 766 nm

Packaging and storage Preserve in well-closed containers.

Tripotassium Bismuth Dicitrate Tablets
비스무트시트르산염칼륨 정

Tripotassium Bismuth Dicitrate Tablets contain bixmuth oxide (Bi_2O_3: 465.96) equivalent to NLT 38.5% and NMT 42.5% and potassium equivalent to NLT 10.8% and NMT 13.2% of the labeled amount of tripotassium bismuth dicitrate.

Method of preparation Prepare as directed under Tablets, with Tripotassium Bismuth Dicitrate.

Identification Weight an amount equivalent to about 0.5 g of tripotassium bismuth dicitrate according to the labeled amount of Tripotassium Bismuth Dicitrate Tablets and add 20 mL of water to dissolve; the solution responds to the Qualitative Analysis for citrate, bismuth salt and potassium salt.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Bismuth oxide***—Weigh accurately the mass of NLT 20 Tripotassium Bismuth Dicitrate Tablets, and powder the tablets. Weigh accurately an amount equivalent to about 1 g of tripotassium bismuth dicitrate, dissolve in 20 mL of diluted nitric acid (2 in 5), add water to make 100.0 mL and filter. Take 50.0 mL of the filtrate, add 100 mL of water and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 5 drops of xylenol orange TS). The endpoint of the titration is when the reddish purple color of the solution changes to yellow.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 11.650 mg of Bi_2O_3

(2) ***Potassium***—Weigh accurately the mass of NLT 20 Tripotassium Bismuth Dicitrate Tablets, and powder the tablets. Weigh accurately an amount equivalent to about 0.17 g of tripotassium bismuth dicitrate, dissove in water to make 100.0 mL, and filter. Discard the first 10 mL of the filtrate, take 1.0 mL of the subsequent filtrate, add 5.0 mL of 2% sodium chloride solution and water to

make 100 mL, and use this solution as the test solution (potassium about 2 μg/mL). Separately, dry potassium chloride for 2 hours at 105 ℃, weigh accurately about 190 mg of potassium chloride, and add water to make 1000 mL (potassium about 100 μg/mL). Pipet a certain amount of this solution, add 5.0 mL of 2% sodium chloride solution and water to prepare a solution with potassium concentration in range between 0 and 25 μg/mL, and use this solution as the standard solution for calibration curve. Perform the test with the test solution and the standard solution as directed under the Atomic Absorption Spectroscopy according to the following conditions. Determine potassium (K) content in the test solution with the calibration curve obtained from the absorbance of the standard solution.

Gas: Air–acetylene
Lamp: Potassium hollow cathode lamp
Wavelength: 766 nm

Packaging and storage Preserve in well-closed containers.

Tripotassium Bismuth Dicitrate, Sucralfate and Ranitidine Hydrochloride Tablets
비스무트시트르산염칼륨·수크랄페이트·라니티딘염산염 정

Tripotassium Bismuth Dicitrate, Sucralfate and Ranitidine Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of bismuth oxide (Bi_2O_3 : 465.96) and potassium (K : 39.10) in tripotassium bismuth dicitrate, aluminum (Al : 26.98) and sucrose octasulfate ester ($C_{12}H_{22}O_{35}S_8$: 982.81) in sucralfate hydrate, and ranitidine ($C_{13}H_{22}N_4O_3S$: 314.40).

Method of preparation Prepare as directed Tablets, with Tripotassium Bismuth Dicitrate, Sucralfate Hydrate, and Ranitidine Hydrochloride.

Identification (1) ***Tripotassium Bismuth Dicitrate***—Weigh about 0.5 g of tripotassium bismuth dicitrate according to the labeled amount of Tripotassium Bismuth Dicitrate, Sucralfate and Ranitidine Hydrochloride Tablets, and dissolve in 20 mL of water; the resulting solution responds to the Qualitative Analysis for citrate, bismuth salt, and potassium salt.

(2) ***Sucralfate Hydrate***—(i) Dissolve 0.5 g of Sucralfate Hydrate in 10 mL of dilute hydrochloric acid; the solution responds to the Qualitative Analysis for aluminum salt.

(ii) Transfer 50 mg of Sucralfate Hydrate to a small test tube, add 50 mg of freshly cut pieces of sodium metal, and melt by careful heating. Immerse the test tube immediately in 100 mL of water, break the test tube, shake well to mix, and filter. To 5 mL of the filtrate, add 1 drop of sodium pentacyanonitrosylferrate(III) TS; the solution exhibits a reddish purple color.

(iii) Dissolve 40 mg of Sucralfate Hydrate in 2 mL of dilute sulfuric acid, and add gently 2 mL of anthrone TS to form 2 layers; the boundary layer exhibits a blue color, and gradually changes to bluish green.

(3) ***Ranitidine Hydrochloride***—(i) Weigh 0.22 g each of Tripotassium Bismuth Dicitrate, Sucralfate and Ranitidine Hydrochloride Tablets and ranitidine hydrochloride RS, dissolve in 100 mL of methanol, and use these solutions as the test solution and the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Separately, drop the test solution, and on top of the test solution, drop a solution prepared by dissolving 5-[[(2-aminoethyl)thio]methyl]-*N*,*N*-dimethyl-2-furan-methanamine in methanol so that the solution contains 1.27 mg per mL, and air-dry the plate. Develop the plate with a mixture of ethyl acetate, 2-propanol, ammonia water(28) and water (25 : 15 : 5 : 1) as a developing solvent so that the end of the developing solvent moves to a distance of about 15 cm from the starting line, and air-dry the plate. Then, expose the plate to iodine vapor until the chromatogram fully appears in a closed developing chamber. The R_f values and color of the spots from the test solution and the standard solution are the same.

(ii) The retention times of the major peaks obtained from the test solution and the standard solution in the Assay are the same.

(iii) Take a portion of the powdered Ranitidine Hydrochloride, weigh an amount, equivalent to about 100 mg of ranitidine, dissolve in 2 mL of water, and filter; the solution responds to the Qualitative Analysis for chloride.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Tripotassium Bismuth Dicitrate***—(i) Bismuth oxide: Weigh accurately the mass of NLT 20 Tripotassium Bismuth Dicitrate, Sucralfate and Ranitidine Hydrochloride Tablets, and powder them. Weigh accurately an amount, equivalent to about 1.0 g of tripotassium bismuth dicitrate, dissolve in 20 mL of diluted nitric acid (2 in 5), add water to make 100.0 mL, and filter. Take 50.0 mL of the filtrate, add 100 mL of water, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS. (5 drops of xylenol orange TS). The endpoint of the titration is when the reddish purple color of the solution changes to yellow. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 11.649 mg of Bi2O3

(ii) Potassium*:* Weigh accurately the mass of NLT 20 Tripotassium Bismuth Dicitrate, Sucralfate and

Ranitidine Hydrochloride Tablets, and powder the tablets. Weigh accurately an amount equivalent to about 0.17 g of tripotassium bismuth dicitrate, dissolve in water to make 100.0 mL, and filter. Discard the first 10 mL of the filtrate, take 1.0 mL of the subsequent filtrate, add 5.0 mL of 2% sodium chloride solution and water to make 100 mL, and use this solution as the test solution (potassium about 2 μg/mL). Separately, weigh accurately about 190 mg of potassium chloride, previously dried at 105 °C for 2 hours, and add water to make 1000 mL (about 100 μg/mL of potassium). Pipet a suitable amount of this solution, add 5.0 mL each of 2% sodium chloride solution, add water to prepare a solution containing potassium in the concentration range of 0 μg/mL - 25 μg/mL, and use this solution as the standard solution for calibration curve. Perform the test with the test solution and the standard solution as directed under the Atomic Absorption Spectroscopy according to the following conditions. Determine potassium (K) content in the test solution with the calibration curve obtained from the absorbance of the standard solution.

Gas: Air–acetylene
Lamp: Potassium hollow cathode lamp
Wavelength: 766 nm

(2) ***Sucralfate hydrate***—(i) Aluminum: Weigh accurately the mass of NLT 20 Sucralfate Hydrate Tablets, and powder the tablets. Weigh accurately an amount equivalent to about 1.0 g of sucralfate hydrate, add 10 mL of dilute hydrochloric acid and dissolve by warming. Cool, and add water to make 250.0 mL. Pipet 25.0 mL of this solution, add 25.0 mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt solution and 20 mL of acetic acid-ammonium acetate buffer solution, pH 4.5, and boil for 5 minutes. After cooling, add 50 mL of ethanol, and titrate the excess ethylenediaminetetraacetic acid disodium salt solution with 0.05 mol/L zinc acetate VS (indicator: 3 mL of dithizone TS). The endpoint of the titration is when the color of this solution changes from greenish purple through violet to red. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 1.3491 mg of Al

(ii) Sucrose octasulfate ester*:* Weigh accurately the mass of NLT 20 Sucralfate Hydrate Tablets, and powder them. Weigh accurately an amount, equivalent to about 0.5 g of sucralfate, add 10.0 mL of sulfuric acid-sodium hydroxide TS, and shake vigorously to mix. Sonicate the mixture for 5 minutes to dissolve while maintaining the temperature below 30 ℃. Add 0.1 mol/L sodium hydroxide solution to make 25.0 mL, and use this solution as the test solution. Separately, weigh accurately about 0.25 g of sucrose octasulfate ester RS, add the mobile phase to make 25.0 mL, and use this solution as the standard solution. Prepare rapidly the test solution and the standard solution, and perform the test immediately. Take exactly 50 μL each of the test solution and the standard solution, perform the test as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas A_T and A_S of sucrose octasulfate ester of each solution.

Amount (mg) of sucrose octasulfate ester ($C_{12}H_{22}O_{35}S_8$)
= Amount (mg) of sucrose octasulfate ester RS (calculated on the dried basis)$\times \frac{A_T}{A_S} \times 0.7633$

Operating conditions

Detector: A differential refractometer

Column: A stainless steel column about 4 mm in internal diameter and 30 cm in length, packed with aminopropylsilyl silica gel for liquid chromatography (about 8 μm in particle diameter).

Mobile phase: Dissolve an appropriate amount (26 g to 132 g) of ammonium sulfate in 1000 mL of water, and adjust the pH to 3.5 with phosphoric acid. Allow a solution of sucrose octasulfate ester RS in dilute hydrochloric acid (1 in 100) to stand at 60 °C for 10 minutes, cool, and perform the test immediately. Determine the amount of ammonium sulfate so that the peak of related substances with the relative retention time to that of sucrose octasulfate ester being about 0.7 is almost close to the base line, and the peak of sucrose octasulfate ester is eluted most rapidly.

Flow rate: Adjust the flow rate so that the retention time of sucrose octasulfate ester is between 6 and 11 minutes.

System suitability

System performance: Allow a solution of sucrose octasulfate ester RS in dilute hydrochloric acid (1 in 100) to stand at 60 °C for 10 minutes, cool, and proceed immediately with 50 μL of this solution according to the above operating conditions; the resolution of the peaks of the related substances with relative retention time to sucrose octasulfate ester being about 0.7 is NLT 1.5.

System repeatability: Repeat the test 6 times with 50 μL of the standard solution under the above conditions; the relative standard deviation of the peak area of sucrose octasulfate ester is NMT 2.0%.

(3) ***Ranitidine hydrochloride***—Add 10 tablets of Tripotassium Bismuth Dicitrate, Sucralfate and Ranitidine Hydrochloride Tablets in NLT 250 mL of the mobile phase, shake to completely disintegrate, and filter. Dilute the concentration according to the concentration of the standard solution, and use this solution as the test solution. Separately, weigh accurately ranitidine hydrochloride RS, dissolve in the mobile phase to obtain a concentration of 0.112 mg/mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of ranitidine.

Amount (mg) of ranitidine
= Concentration (mg/mL) of standard ranitidine hydro-

$$\text{chloride solution} \times \frac{A_T}{A_S} \times \frac{314.40}{350.86}$$
$$\times \text{dilution factor of the test solution}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 322 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and between 10 and 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm to 10 μm in particle diameter).

Mobile phase: A mixture of methanol and 0.1 mol/L ammonium acetate (85 : 15).

Flow rate: 2 mL/min

System suitability

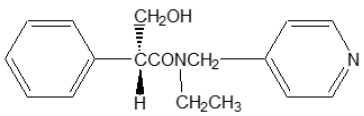
System performance: Proceed with 10 μL of the standard solution under the above operating conditions; the symmetry factor of ranitidine hydrochloride peak is NMT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation is NMT 2.0%.

Packaging and storage Preserve in well-closed containers.

Label Indicate bismuth oxide and potassium from tripotassium bismuth dicitrate, and aluminum and sucrose octasulfate ester from sucralfate hydrate.

Tropicamide
트로픽아미드



and enantiomer

$C_{17}H_{20}N_2O_2$: 284.35

N-Ethyl-3-hydroxy-2-phenyl-*N*-(pyridin-4-ylmethyl)propanamide [*1508-75-4*]

Tropicamide, when dried, contains NLT 98.5% and NMT 101.0% of tropicamide ($C_{17}H_{20}N_2O_2$).

Description Tropicamide occurs as a white crystalline powder. It is odorless and has a bitter taste.
It is freely soluble in ethanol(95) or chloroform, slightly soluble in water or ether and practically insoluble in petroleum ether.
It dissolves in dilute hydrochloric acid.
Dissolve 1.0 g of Tropicamide in 500 mL of water; the pH of the solution is between 6.5 and 8.0.

Identification (1) To 5 mg of Tropicamide, add 0.5 mL of ammonium vanadate in sulfuric acid solution (1 in 200) and heat; the resulting solution exhibits a bluish purple color.

(2) Dissolve 5 mg of Tropicamide in 1 mL of ethanol(95) and 1 mL of water, add 0.1 g of 1-chloro-2,4-dinitrobenzene, and heat on a steam bath for 5 minutes. After cooling, add 2 to 3 drops of sodium hydroxide solution (1 in 10) and 3 mL of ethanol(95); the resulting solution exhibits a purple color.

Melting point Between 96 and 99 ºC.

Absorbance $E_{1cm}^{1\%}$ (255 nm): Between 166 and 180 (5 mg after drying, 2 mol/L hydrochloric acid TS, 200 mL).

Purify (1) ***Chloride***—Dissolve 1.0 g of Tropicamide in 30 mL of ethanol(95) and add 6 mL of dilute nitric acid and water to make 50 mL. Use this solution as the test solution and perform the test. To 0.45 mL of 0.01 mol/L hydrochloric acid, add 30 mL of ethanol(95), 6 mL of dilute nitric acid and water to make 50 mL and use this solution as the control solution (NMT 0.016%).

(2) ***Heavy metals***—Dissolve 1.0 g of Tropicamide in 30 mL of ethanol(95) and add 2 mL of dilute acetic acid and water to make 50 mL. Use this solution as the test solution to perform the test. Prepare the control solution by adding 30 mL of ethanol(95), 2 mL of dilute acetic acid and water to 2.0 mL of the lead standard solution to make 50 mL (NMT 20 ppm).

(3) ***N-Ethyl-γ-picolylamine***—Add 5 mL of water to 0.10 g of Tropicamide, heat to dissolve, add 1 mL of acetaldehyde solution (1 in 20), and shake well to mix. Add 1 to 2 drops of sodium pentacyanonitrosylferrate(III) TS and 1 to 2 drops of sodium bicarbonate TS and shake to mix; the resulting solution does not exhibit a blue color.

(4) ***Tropic acid***—To 10 mg of Tropicamide, add 5 mg of sodium borate and 7 drops of 4-dimethylaminobenzaldehyde TS and heat on a steam bath for 3 minutes. Cool in iced water and add 5 mL of acetic anhydride; the resulting solution does not exhibit a purple color.

Loss on drying NMT 0.3% (1 g, in vacuum, silica gel, 24 hours).

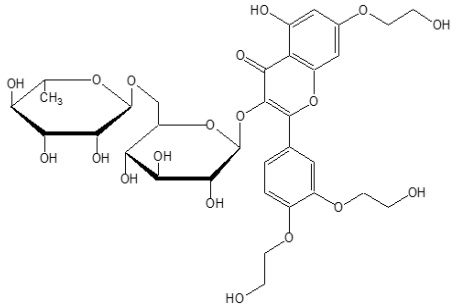
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Tropicamide, previously dried, dissolve in 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (indicator: 3 drops of methylrosaniline chloride TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 28.435 mg of $C_{17}H_{20}N_2O_2$

Packaging and storage Preserve in light-resistant, tight containers.

Troxerutin
트록세루틴



$C_{33}H_{42}O_{19}$: 742.68

2-[3,4-Bis(2-hydroxyethoxy)phenyl]-3-[[6-*O*-(6-deoxy-α-L-mannopyranosyl)-β-*D*-glucopyranosyl]oxy]-5-hydroxy-7-(2-hydroxyethoxy)-4*H*-1-benzopyran-4-one[tris(hydroxyethyl)rutin], [*7085-55-4*]

Troxerutin contains NLT 98.0% and NMT 101.0% of troxerutin ($C_{33}H_{42}O_{19}$), calculated on the dried basis.

Description Troxerutin occurs as a yellow to orange powder and is odorless.
It is freely soluble in water, very slightly soluble in ethanol or methanol and practically insoluble in chloroform.
The pH of a 10% aqueous solution of Troxerutin is between 6.0 and 7.0.

Identification Dissolve about 0.1 g of Teicoplanin in water to make 100 mL and use this solution as the test solution. Dissolve about 0.1 g of troxerutin in water to make 100 mL and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, n-propanol, acetic acid(100) and water (30 : 40 : 1: 30) as the developing solvent, and air-dry. Examine the plate under ultraviolet rays (main wavelength: 254 nm) or spray the plate with a solution of diphenylboric acid aminoethylester in methanol; the R_f values of the spots obtained from the test solution and the standard solution are the same.

(2) Determine the infrared spectra of Troxerutin and troxerutin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Determine the absorption spectrum of an aqueous solution of Troxerutin (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima at 254 nm and 348 nm.

Melting point Between 155 and 160 °C.

Purity (1) ***Clarity and color of solution***—A 5% aqueous solution of Troxerutin is yellow and almost clear.

(2) ***Heavy metals***—Proceed with 1.0 g of Troxerutin according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 0.2 g of Troxerutin according to Method 1 and perform the test (NMT 10 ppm).

Loss on drying NMT 5.0% (1 g, 4 hours).

Residue on ignition NMT 0.3% (0.5 g).

Assay Weigh accurately about 0.2 g of Troxerutin and dissolve in water to make 100.0 mL. Take 5.0 mL of the solution and add ethanol to make 100 mL. Take 5.0 mL of this solution and add 12.5 mL of a mixture of 0.1 mol/L sodium hydroxide, 0.05 mol/L sodium bicarbonate and methanol (1 : 1: 1), and ethanol to make 25.0 mL. Separately, weigh accurately 0.2 g of troxerutin RS and proceed in the same manner as in the test solution. Use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at 248 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (mg) of troxerutin } (C_{33}H_{42}O_{19}) = \text{Amount (mg) of troxerutin RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers.

Crystallized Trypsin and Bromelain Tablets
결정트립신·브로멜라인 정

Crystallized Trypsin and Bromelain Tablets contain NLT 90.0% and NMT 130.0% of the labeled amount of crystallized trypsin and bromelain.

Method of preparation Prepare as directed under Tablets, with Crystallized Trypsin and Bromelain.

Identification (1) ***Crystallized trypsin***—When tested as directed under the Assay of Crystallized Trypsin and Bromelain Tablets, the result is positive.

(2) ***Bromelain***—To a quantity of powdered Crystallized Trypsin and Bromelain Tablets, equivalent to about 10 mg of bromelain, add a 20% solution (pH 5.5) of skim milk powder, and warm to 37 ℃; the resulting solution solidifies (Rennet reaction).

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Crystallized trypsin***—Add 200 μL of 1 mmol/L hydrochloric acid to 3 mL of the substrate solution, and test this solution as directed under the Ultraviolet-visible Spectroscopy to ensure that the absorbance at a wavelength of 253 nm is 0.050. Pipet 200 μL of the crystallized trypsin solution containing between 10 and 12

units of trypsin RS, add 3 mL of the substrate solution, and immediately measure the absorbance at 30-second intervals for 5 minutes. Draw an absorbance curve with respect to time, and use the values of the straight line in which the rate of change remains constant for NLT 3 minutes as the activity value of crystallized trypsin. If necessary, lower concentrations may be used. Under the conditions of this Assay, the activity of 1 unit of trypsin RS shows a rate of change of absorbance of 0.003 per minute. Trypsin units per mg are obtained by the following formula.

$$\frac{A_1 - A_2}{0.003\mathrm{TW}}$$

A_1: Final activity value of the straight line
A_2: First activity value of the straight line
T: Elapsed time from the first time to the last time (minutes)
W: Weight (mg) of crystallized trypsin used for absorbance measurement

Substrate solution—Dissolve 85.7 mg of hydrochloric acid *N*-benzoyl-L-arginine-ethyl ester in water to make 100.0 mL. Take 10 mL of this solution and add 0.067 mol/L phosphate buffer to make 100 mL. Maintain this solution at 25 ± 0.1 ℃ in a 1 cm cell, use water as a control solution, and measure the absorbance at a wavelength of 253 nm as directed under the Ultraviolet-visible Spectroscopy. The absorbance before and after dilution with phosphate buffer should be between 0.575 and 0.585.

Crystallized trypsin solution—Weigh accurately a suitable amount of crystallized trypsin and dissolve it in 0.001 mol/L hydrochloric acid to make a crystallized trypsin solution with about 50 - 60 units/mL.

(2) ***Bromelain***—Weigh accurately the mass of NLT 20 Crystallized Trypsin and Bromelain Tablets, and powder. Weigh accurately an amount equivalent to about 50,000 units of bromelain, and add the enzyme diluent to make A mL. Dilute this solution by B times again to obtain a solution containing about between 40 and 50 units in 1 mL, and use it as the test solution. Put 1 mL of the test solution into a test tube, allow to stand in a thermostat at 37 ± 0.2 ℃ for 5 minutes, and quickly add 5 mL of 0.6% casein substrate solution preheated to 37 ℃ to the above test solution. At the same time, use a stopwatch to stop the reaction by adding 5 mL of precipitation TS after exactly 10 minutes have passed. Filter the contents of the test tube kept at 37 ℃ for 40 minutes through filter paper. Test this filtrate within 2 hours as directed under the Ultraviolet-visible Spectroscopy using water as a control solution, and measure the absorbance A_T at a wavelength of 275 nm.
Separately, add the precipitation TS and casein substrate solution to 1 mL of the test solution in the order, and measure the absorbance A_0 by treating with the test solution. Also, weigh accurately tyrosine RS and dissolve it in 0.1 mol/L hydrochloric acid to make a solution containing 50 μg of tyrosine per mL. Measure Absorbance A_S as directed under the Ultraviolet-visible Spectroscopy using water as a control solution.

$$\text{Potency of bromelain (unit/mg)} = \frac{A_T - A_0}{A_S} \times 50 \times \frac{11}{10} \times \frac{\mathrm{A} \times \mathrm{B}}{\text{Amount of sample taken (mg)}}$$

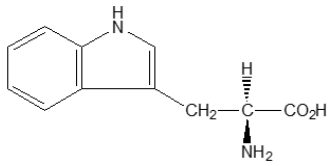
Enzyme dilute solution—Prepare a solution containing 0.03 mol/L cysteine hydrochloride and 0.006 mol/L ethylenediaminetetraacetic acid disodium salt as a final concentration. Adjust pH to 4.5 with 0.1 mol/L sodium hydroxide or 0.1 mol/L hydrochloric acid (prepare before use).

Casein substrate solution—Dissolve 0.6 g of casein by the Hammersteim method in 80 mL of 0.05 mol/L potassium monohydrogen phosphate, adjust the pH to 7.0 with 1 mol/L hydrochloric acid, and add water to make 100 mL (prepare before use).

Precipitation TS—Prepare a solution containing 0.11 mol/L trichloroacetic acid, 0.22 mol/L sodium acetate and 0.33 mol/L acetic acid.

Packaging and storage Preserve in tight containers.

L-Tryptophan
L-트리프토판



$C_{11}H_{12}N_2O_2$: 204.23
(2*S*)-2-Amino-3-(1*H*-indol-3-yl)propanoic acid [*73-22-3*]
L-Tryptophan, when dried, contains NLT 98.5% and NMT 101.0% of L-tryptophan ($C_{11}H_{12}N_2O_2$).

Description L-Tryptophan occurs as white to yellowish white crystals or a crystalline powder. It is odorless and has a slightly bitter taste.
It is freely soluble in formic acid, slightly soluble in water, very slightly soluble in ethanol(95), and practically insoluble in ether.
It dissolves in dilute hydrochloric acid.

Identification (1) Determine the infrared spectra of L-Tryptophan and L-tryptophan RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between -30.0° and -33.0°. Weigh accurately about 0.25 g of L-Tryptophan, previ-

ously dried, and dissolve in 20 mL of water by warming. After cooling, add water to make exactly 25 mL and determine the optical rotation with the layer length of 100 mm.

pH Dissolve 1.0 g of L-Tryptophan in 100 mL of water by warming; the pH of the cooled solution is between 5.4 and 6.4.

Purity (1) ***Clarity and color of solution***—Dissolve 0.20 g of L-Tryptophan in 10 mL of 2.0 mol/L hydrochloric acid TS; the resulting solution is clear.

(2) ***Chloride***—Dissolve 0.5 g of L-Tryptophan in 6 mL of dilute nitric acid and add water to make 50 mL. Use this solution as the test solution to perform the test. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.021%).

(3) ***Sulfate***—Dissolve 0.6 g of L-Tryptophan in 40 of water and 1 mL of dilute hydrochloric acid and add water to make 50 mL. Use this solution as the test solution to perform the test. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid (NMT 0.028%).

(4) ***Ammonium***—Perform the test with 0.25 g of L-Tryptophan. Prepare the control solution with 5.0 mL of ammonium standard solution (NMT 0.02%).

(5) ***Heavy metals***—Proceed with 1.0g of L-Tryptophan according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of the lead standard solution (NMT 20 ppm).

(6) ***Iron***—Dissolve 0.333 g of L-Tryptophan in water to make 45 mL, add 2 mL of hydrochloric acid, and use this solution as the test solution. Add water to 1.0 mL of the iron standard solution to make 45 mL, add 2 mL of hydrochloric acid, and use this solution as the standard solution. Add 50 mg of ammonium peroxydisulfate and 3 mL of 30% ammonium thiocyanate to the test solution and the standard solution and mix; the color of the test solution is not darker than that from the standard solution (NMT 30 ppm).

(7) ***Arsenic***—Dissolve 1.0 g of L-Tryptophan in 3 mL of 1 mol/L hydrochloric acid TS and 2 mL of water by heating and perform the test (NMT 2 ppm).

(8) ***Related substances***—Dissolve 0.30 g of L-Tryptophan in 1 mL of hydrochloric acid TS, add water to make 50 mL, and use this solution as the test solution. Pipet 1 mL of this solution and add water to make exactly 50 mL. Pipet 5 mL of this solution, add water to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each 5 μL of the test solution and the standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of 1-butanol, water, and acetic acid(100) (3 : 1 : 1) to a distance of about 10 cm and air-dry at 80 °C for 30 minutes. Spray a solution of ninhydrin in acetone (1 in 50) evenly on the plate and heat at 80 °C for 5 minutes; the spots other than the principal spot from the test solution are not darker than the spots from the standard solution.

Loss on drying NMT 0.3% (1 g, 105 ℃, 3 hours)

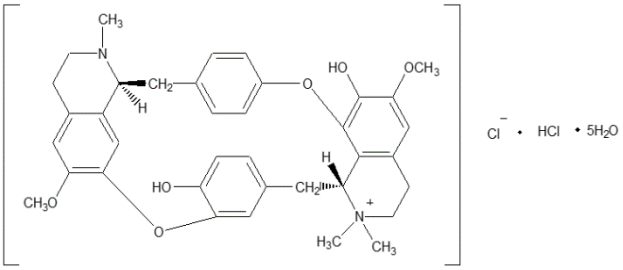
Residue on ignition NMT 0.1% (1 g)

Assay Weigh accurately about 0.2 g of L-Tryptophan, previously dried, dissolve in 3 mL of formic acid, add 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 20.423 mg of $C_{11}H_{12}N_2O_2$

Packaging and storage Preserve in light-resistant, tight containers.

Tubocurarine Chloride Hydrochloride Hydrate
투보쿠라린염화물염산염수화물



Tubocurarine Chloride

$C_{37}H_{41}ClN_2O_6 \cdot HCl \cdot 5H_2O$: 771.72

(1*S*,16*R*)-9,21-Dihydroxy-10,25-dimethoxy-15,15,30-trimethyl-7,23-dioxa-15,30-diazaheptacyclo[22.6.2.2^{3,6}.1^{8,12}.1^{18,22}.0^{27,31}.0^{16,34}]hexatriaconta-3,5,8,10,12(34),18(33),19,21,24(32),25,27(31),35-dodecaen-15-ium chloride, hydrochloride, pentahydrate [*6989-98-6*]

Tubocurarine Chloride Hydrochloride Hydrate contains NLT 98.0% and NMT 101.0% of tubocurarine chloride hydrochloride ($C_{37}H_{41}ClN_2O_6 \cdot HCl$: 681.65), calculated on the dried basis.

Description Tubocurarine Chloride Hydrochloride Hydrate occurs as white crystals or a crystalline powder and is odorless.

It is sparingly soluble in water or ethanol(95), slightly soluble in acetic acid(100), and practically insoluble in ether or chloroform.

Dissolve 1.0 g of Tubocurarine Chloride Hydrochloride Hydrate in 100 mL of water; the pH of the solution is between 4.0 and 6.0.

Melting point—About 270 °C (with decomposition).

Identification (1) To 20 mL of the aqueous solution of Tubocurarine Chloride Hydrochloride Hydrate (1 in

2000), add 0.2 mL of sulfuric acid and 2 mL of potassium iodate solution(1 in 100), shake to mix, and heat on a steam bath for 30 minutes; the solution exhibits a yellow color.

(2) Take 1 mL of an aqueous solution of Tubocurarine Chloride Hydrochloride Hydrate (1 in 100), and add 1 mL of Reinecke salt monohydrate TS (1 in 100); a red precipitate is formed.

(3) Determine the absorption spectra of aqueous solutions of Tubocurarine Chloride Hydrochloride Hydrate and tubocurarine chloride hydrochloride hydrate RS (3 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) An aqueous solution of Tubocurarine Chloride Hydrochloride Hydrate (1 in 50) responds to the Qualitative Analysis (2) for chloride.

Optical rotation $[\alpha]_D^{20}$: Between +210° and +220° (0.1 g, calculated on the dried basis, water, 10 mL, after allowing to stand for 3 hours, 100 mm)

Purity (1) ***Clarity and color of solution***—Dissolve about 0.1 g of Tubocurarine Chloride Hydrochloride Hydrate in 10 mL of ethanol(95); the resulting solution is colorless and clear.

(2) ***Chloroform solubles***—Weigh accurately 0.2 g of Tubocurarine Chloride Hydrochloride Hydrate, calculated on the dried basis, add 200 mL of water and 1 mL of the saturated sodium bicarbonate, and extract three times with 20 mL of chloroform. Combine all the chloroform extracts, and rinse with 10 mL of water. Filter through a absorbent cotton into a tared beaker, wash the cotton twice with each 5 mL of chloroform, combine the filtrate and the washings, evaporate chloroform on a steam bath, and dry the residue at 105 ° C for 1 hour; the amount is NMT 2.0%. The residue does not dissolve on the addition of 10 mL of water, but dissolves when stirring with 1 mL of hydrochloric acid added.

(3) ***Related substances***—Weigh accurately about 30 mg of Tubocurarine Chloride Hydrochloride Hydrate, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Perform the test with 10 μL of the test solution as directed under the Liquid Chromatography according to the following conditions and determine each peak area A_i and the total area A_S for all peaks other than the major peak from the test solution; the total amount of related substances is NMT 5.0%.

$$\text{Content (\%) of each related substance} = 100 \times \frac{A_i}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (between 1.5 μm and 10 μm in particle diameter).

Mobile phase: Mix 270 mL of a mixture of acetonitrile and methanol (3 : 2) and 20 mL of 25% tetramethylammonium hydroxide-methanol TS, add water to make 1000 mL, and adjust the pH to 4.0 with phosphoric acid.

Flow rate: 1 mL/min

System suitability

System performance: Weigh accurately 30 mg of tubocurarine chloride hydrochloride RS and 50 mg of phenol, dissolve in 100 mL of the mobile phase to prepare the solution containing 0.3 mg and 0.5 mg per mL, respectively, and use these solutions as the system suitability solution. Proceed with 10 μL of these solutions according to the under above conditions; the relative retention time of tubocurarine chloride with respect to phenol is about 0.50 with the resolution being NLT 2.0, and the symmetry factor of the peak of tubocurarine chloride is NMT 2.0.

System repeatability: Weigh accurately 30 mg of tubocurarine chloride hydrochloride RS, dissolve in 100 mL of the mobile phase to prepare a solution containing 0.3 mg per mL, and repeat the test 5 times with each 10 μL of this solution according to the above conditions; the relative standard deviation of the peak area of tubocurarine chloride is NMT 2.0%.

Loss on drying Between 9% and 12% (0.5 g, in vacuum, phosphorus pentoxide, 105 ℃, 4 hours).

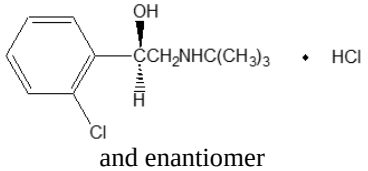
Residue on ignition NMT 0.2% (0.5 g).

Assay Weigh accurately about 0.5 g of Tubocurarine Chloride Hydrochloride Hydrate, add 20 mL of acetic acid(100), dissolve by heating on a steam bath, cool, add 60 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 34.082 mg of $C_{37}H_{41}ClN_2O_6 \cdot HCl$

Packaging and storage Preserve in light-resistant, tight containers.

Tulobuterol Hydrochloride
툴로부테롤염산염



and enantiomer

$C_{12}H_{18}ClNO \cdot HCl$: 264.19

1-(2-Chlorophenyl)-2-[(2-methyl-2-propanyl)amino]ethanol hydrochloride [*56776-01-3*]

Tulobuterol Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of tulobuterol hydrochloride ($C_{12}H_{18}ClNO \cdot HCl$).

Description Tulobuterol Hydrochloride occurs as white crystals or a crystalline powder.
It is very soluble in methanol, freely soluble in water, ethanol(95) or acetic acid(100), soluble in acetic anhydride, and very slightly soluble in ether.
An aqueous solution of Tulobuterol Hydrochloride (1 in 20) shows no optical rotation.

Melting point—About 163 °C.

Identification (1) Determine the absorption spectra of solutions of Tulobuterol Hydrochloride and tulobuterol hydrochloride RS (1 in 2500) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectrum of Tulobuterol Hydrochloride and tulobuterol hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Tulobuterol Hydrochloride (1 in 20) responds to the Qualitative Analysis for chloride.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Tulobuterol Hydrochloride in 10 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 2.0 g of Tulobuterol Hydrochloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 0.30 g of Tulobuterol Hydrochloride in 5 mL of methanol and use this solution as the test solution. Pipet 1 mL of this solution, add methanol to make exactly 50 mL, and use it as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Prepare a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography, develop the plate with the upper layer of a mixture of ethyl acetate and ammonia water(28) (200 : 9) to the upper part in advance, and air-dry the plate. Spot 5 μL each of the test solution and the standard solution on the plate. Develop the plate with the upper layer of a mixture of ethyl acetate and ammonia water(28) (200 : 9) (as the developing solvent) to a distance about 10 cm, and air-dry the plate. Expose the plate under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot and the origin spot from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.5% (0.5 g, in vacuum, 60 ℃, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately 0.5 g of Tulobuterol Hydrochloride, previously dried, dissolve in 80 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 26.419 mg of $C_{12}H_{18}ClNO \cdot HCl$

Packaging and storage Preserve in tight containers.

Tyrothricin
티로트리신

Tyrothricin consists principally of Gramicidin and tyrocidine and contains NLT 900 μg and NMT 1400 μg (potency) of tyrothricin per mg.

Description Tyrothricin occurs as a white to brownish powder, is odorless or almost odorless and is almost tasteless.
It is soluble in ethanol(95), freely soluble in acetic acid(100), slightly soluble in acetone and practically insoluble in water, chloroform or ether.

Identification To 5 mg (potency) of Tyrothricin, add 5 mL of 4-dimethylaminobenzaldehyde-iron(III) chloride TS, shake well to mix for 2 minutes, and add 2 drops of 0.1 mol/L sodium nitrite and 5 mL of water; the solution appears blue.

Purity Fat—Weigh accurately about 1.0 g of Tyrothricin, previously dried at 105 °C for 3 hours, mix with 2 g of asbestos, previously ignited and washed with hexane, transfer into a thimble filter for extraction inside a Soxhlet extractor, and extract with hexane for 18 hours using an 85 to 100 mL extraction flask, previously weighed. Remove the extraction flask, evaporate the solvent on a steam bath, and dry at 105 °C for 2 hours. Cool and weigh the extraction flask; the fat content is determined by the weight difference before and after the procedure (NMT 6.0%).

Loss on drying NMT 5.0% (0.1 g, 0.7 kPa, 60 ℃, 3 hours).

Residue on ignition NMT 3.5% (1 g).

Assay (1) ***Medium***—(i) Agar medium for transferring test organism

Peptone	5.0 g
Potassium dihydrogen phosphate	2.0 g
Yeast extract	20.0 g
Polysorbate 80	0.1 g
Glucose	100 g
Agar	15.0 - 20.0 g

Weigh the above, mix, add purified water to make 1000

mL, and sterilize. Adjust the pH of the solution so that it is 6.7 to 6.8 after sterilization.

(ii) Liquid medium for suspension of the test organism

Peptone	5.0 g
Glucose	1.0 g
Yeast extract	1.5 g
Dibasic potassium phosphate	3.68 g
Meat extract	1.5 g
Potassium dihydrogen phosphate	1.32 g
Sodium chloride	3.5 g

Weigh the above, mix, add purified water to make 1000 mL, and sterilize. Adjust the pH of the solution so that it is 6.95 to 7.05 after sterilization.

(2) ***Test organism and the suspension of test organism***—Use *Streptococcus faecium* ATCC 10541 as the test organism. Inoculate the test organism onto the stab agar medium for transferring the test organism, subculture NLT 3 times at 37 °C for 20 to 24 hours, and keep below 5 °C. Transfer the test organism to 8 to 10 mL of the liquid medium for suspension of test organism, incubate at 37 °C for 20 to 24 hours, and use as the suspension culture of the test organism. Before use, take 1.0 mL of the suspension culture, add to 100 mL of the liquid medium for suspension of test organism, and use it as the test culture.

(3) Weigh accurately a suitable amount of Tyrothricin and dissolve in ethanol(95) to obtain a solution with an appropriate concentration. Dilute with ethanol so that each mL contains 0.200 μg (potency), and use this solution as the test solution. Separately, weigh accurately an appropriate amount of gramicidin RS, dissolve in ethanol(95) so that each mL contains 1 mg (potency), and use this solution as the standard stock solution. Keep the standard stock solution below 5 °C and use it within 30 days. Pipet an appropriate amount of the standard stock solution, dilute with ethanol so that each mL contains 0.028, 0.034, 0.040, 0.048, and 0.057 μg (potency), and use these solutions as the standard solutions. Transfer each 1.0 mL of the standard solutions and the test solution to separate test tubes. Measure the average absorbance of the test solution, calculate the concentration of gramicidin from the calibration curve, and multiply the value by 5 to determine the amount (μg) of tyrothricin in the sample.

Packaging and storage Preserve in tight containers.

Tyrothricin Gel
티로트리신 겔

Tyrothricin Gel contains NLT 90.0% and NMT 120.0% of the labeled amount of tyrothricin.

Method of preparation Prepare as directed under gels, with Tyrothricin.

Identification Weigh 5 mg (potency) of Tyrothricin Gel, add 10 mL of ethyl acetate, shake well to mix, and filter. Add 10 mL of ethyl acetate to the residue, repeat the above operation 3 times, and then filter. Evaporate the filtrate to dryness on a steam bath, add 5 mL of 4-dimethylaminobenzaldehyde and iron(III) chloride TS to about 5 mg (potency) of the solution, shake well to mix for 2 minutes, and add 2 drops of 0.1 mol/L sodium nitrite solution and 5 mL of water; the resulting solution exhibits a blue color.

pH Dissolve Tyrothricin Gel in water to make 0.1 mg (potency) per mL; the pH of the solution is between 6.5 and 8.5.

Assay ***Turbidmetry***—(1) ***Medium*** (i) Agar medium for transferring test organisms

Peptone	5.0 g
Glucose	10.0 g
Yeast extract	20.0 g
Potassium dihydrogen phosphate	2.0 g
Agar	15.0 to 20.0 g
Polysorbate 80	0.1 g

Weigh the above, add purified water to make 1000 mL, sterilize, and adjust the pH to between 6.7 and 6.8.

(ii) Liquid media for suspending test organisms

Peptone	5.0 g
Glucose	1.0 g
Yeast extract	1.5 g
Dipotassium hydrogen phosphate	3.68 g
Meat extract	1.5 g
Potassium dihydrogen phosphate	1.32 g
Sodium chloride	3.5 g

Weigh the above, add purified water to make 1000 mL, sterilize, and adjust the pH to between 6.95 and 7.05.

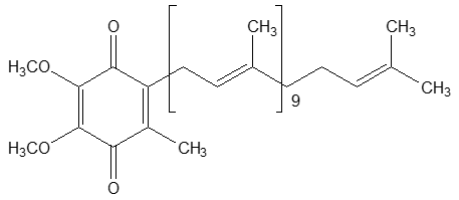
(2) ***Test organism and test organism suspension***—Use *Enterococcus hirae* ATCC 10541 as the test organism. Inoculate the test organism on the agar medium for transferring test organisms, and incubate at 37 ± 0.5 °C for 20 to 24 hours. Subculture at least 3 times at 37 ± 0.5 °C with agar medium for transferring test organisms or liquid media for suspending test organisms. Transparent the organism of the last passage into 8 to 10 mL of liquid media for suspending test organisms, and culture at 37 ± 0.5 °C for 20 to 24 hours, and use this solution as the bacterial solution. When using, add about 1.0 mL of the test suspension to 100 mL of the liquid media for suspending test organisms, and use this solution as the test organism solution. However, instead of the agar medium for transferring test organisms, a nutrient agar medium suitable for the characteristics of the strain can be used.

(3) Weigh accurately an appropriate amount of Tyrothricin Gel, and dissolve in ethanol to obtain a solution with appropriate concentration. Take an appropriate amount of this solution, dilute with ethanol to contain 0.2 μg (potency) per mL, and use this solution as the test solution. Separately, weigh an appropriate amount of gramicidin RS, and dissolve in methanol to obtain a solution containing 1 mg per mL. Store the standard stock solution at below 5 °C, and use it within 30 days. Pipet an appropriate amount of the standard stock solution, and dilute

with ethanol to obtain solutions containing 0.028, 0.034, 0.040, 0.048 and 0.057 μg (potency) of gramicidin per mL, respectively, and use these solutions as the standard solutions. Assign 3 test tubes to Group 1. For each concentration of the standard solution, assign it to Group 1, and also use Group 1 for the test solution. Transfer 100 μL each of the standard solution and the test solution with each concentration into each group's test tube, add 10 mL each of the stock suspension of test organisms, close the stopper, and incubate at 37°C for 3 to 4 hours. Separately, culture the test tube containing 100 μL of ethanol and 10 mL of liquid media for suspending test organisms, and use this solution as the control solution. After incubation, add 0.5 mL each of formaldehyde solution (1 in 3) to each group's test tube and the control solution, and measure the average absorbance at a wavelength of 530 nm using a spectrophotometer. Calculate the average absorbance of the test solution to obtain the concentration of gramicidin from the standard curve of gramicidin, and multiply this value by 5 to obtain the amount (μg) of tyrotricin in the sample.

Packaging and storage Preserve in tight containers.

Ubidecarenone
유비데카레논



$C_{59}H_{90}O_4$: 863.34

2-[(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,30*E*,34*E*)-3,7,11,15,19,23,27,31,35,39-Decamethyltetraconta-2,6,10,14,18,22,26,30,34,38-decaenyl]-5,6-dimethoxy-3-methylcyclohexa-2,5-diene-1,4-dione [*303-98-0*]

Ubidecarenone contains NLT 98.0% and NMT 101.0% of ubidecarenone ($C_{59}H_{90}O_4$), calculated on the anhydrous basis.

Description Ubidecarenone occurs as a yellow to orange crystalline powder, and is odorless and tasteless.
It is freely soluble in ether, very slightly soluble in ethanol(99.5), and practically insoluble in water.
It is gradually decomposed and strongly colored by light.

Melting point—About 48 °C.

Identification (1) Dissolve 50 mg of Ubidecarenone in 1 mL of ether and add 10 mL of ethanol(99.5). To 2 mL of this solution, add 3 mL of ethanol(99.5) and 2 mL of dimethylmalonic acid, then add dropwise 1 mL of potassium hydroxide solution (1 in 5) and shake to mix; the solution exhibits a blue color.

(2) Determine the infrared spectra of Ubidecarenone and ubidecarenone RS according to the potassium bromide disk method as directed under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wave numbers.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Ubidecarenone and perform the test according to Method 4. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substance***—Add 50 mL of ethanol(99.5) to 50 mg of Ubidecarenone, dissolve by heating for 2 minutes at about 50 ℃, cool, and use this solution as the test solution. Pipet 1 mL of this solution, add ethanol(99.5) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area obtained from each solution according to the automatic integration method; the sum of peak areas other than the major peak for the test solution is not larger than the major peak area for the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase, flow rate and selection of column, proceed as directed under the operating conditions in the Assay.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of ubidecarenone obtained from 5 μL of the standard solution is 20 mm to 40 mm.

Time span of measurement: About 2 times of the retention time of ubidecarenone after the solvent peak.

Water NMT 0.2% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg each of Ubidecarenone and ubidecarenone RS (measure moisture content beforehand), add 40 mL of ethanol(99.5) to each, dissolve by heating for 2 minutes at about 50 ℃, cool, add ethanol(99.5) to make exactly 50 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of ubidecarenone, A_T and A_S, in each solution.

$$\text{Amount (mg) of ubidecarenone } (C_{59}H_{90}O_4) = \text{Amount (mg) of ubidecarenone RS, as calculated on the anhydrous basis} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 275 nm).

Column: A stainless steel column about 5 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: A mixture of methanol and ethanol(99.5) (13 : 7).

Flow rate: Adjust the flow rate so that the retention time of ubidecarenone is about 10 minutes.

System suitability

System performance: Weigh 10 mg each of Ubidecarenone and ubiquinone-9, add 20 mL of ethanol(99.5), dissolve by heating for 2 minutes at about 50 ℃, and cool. Proceed with 5 μL of this solution under the above conditions; uniquinone-9 and ubidecarenone are eluted in this order with the resolution being NLT 4.

System repeatability: Repeat the test 6 times with 5 μL of the standard solution according to the above conditions; the relative standard deviation of the peak area for ubidecarenone is NMT 0.8%.

Packaging and storage Preserve in light-resistant, tight containers.

Undecylenic Acid
운데실렌산

$CH_2=CHCH_2(CH_2)_6CH_2CO_2H$

$C_{11}H_{20}O_2$: 184.28

Undec-10-enoic acid [*112-38-9*]

Undecylenic Acid contains NLT 97.0% and NMT 100.5% of undecylenic acid ($C_{11}H_{20}O_2$).

Description Undecylenic Acid occurs as a clear, colorless to pale yellow liquid and has a characteristic odor.
It is miscible with ethanol(95), ether, chloroform, benzene or non-volatile and volatile oil.
It is practically insoluble in water.

Identification (1) Add 1 mL of potassium permanganate TS to 1 mL of Undecylenic Acid; the color of the potassium permanganate solution disappears.

(2) To 3 mL of Undecylenic Acid, add 3 mL of newly distilled aniline, and heat for 10 minutes under a reflux condenser. After cooling, add 10 mL of ethanol(95) and 10 mL of ether, and transfer to a separatory funnel. Wash the ether solution 4 times with 20 mL of water each time; discard the washings. Heat on a steam bath until the odor of ether is no longer detectable, add a small amount of activated charcoal, shake vigorously to mix and filter. Evaporate the filtrate to dryness, then recrystallize the residue with 70% ethanol; the melting point is between 66.0 and 67.5 ℃.

Refractive index n_D^{25}: Between 1.447 and 1.448.

Specific gravity d_{25}^{25}: Between 0.910 and 0.913.

Iodine value Between 131 and 138.

Congealing temperature NLT 21 ℃.

Purity (1) ***Water-soluble acid***—Add 5 mL of water to 5 mL of Undecylenic Acid, shake to mix, and filter the water layer using filter paper pre-soaked in water. To the filtrate, add 1 drop of methyl orange TS and titrate with 0.01 mol/L sodium hydroxide solution; NMT 1.0 mL of 0.01 mol/L sodium hydroxide is required to match the color produced by 1 drop of methyl orange in 5 mL of water.

(2) ***Heavy metals***—Proceed with 1.0 g of Undecylenic Acid as directed under Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

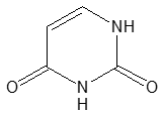
Residue on ignition NMT 0.15% (3 g).

Assay Weigh accurately about 0.75 g of Undecylenic Acid, dissolve in 50 mL of ethanol(95), and titrate with 0.1 mol/L sodium hydroxide VS (indicator: 3 drops of phenolphthalein TS). The endpoint is when a light red color appears and persists for 30 seconds. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 18.428 mg of $C_{11}H_{20}O_2$

Packaging and storage Preserve in light-resistant, tight containers.

Uracil
우라실



$C_4H_4N_2O_2$: 112.09

2,4-(1*H*,3*H*)-Pyrimidinedione, [*66-22-8*]

Uracil, when dried, contains NLT 98.0% and NMT 101.0% of uracil ($C_4H_4N_2O_2$).

Description Uracil occurs as a white, crystalline, odorless powder.
It dissolves in hot water or dilute alkaline solution, and is slightly soluble in water.

Melting point—About 335 ℃.

Identification (1) Determine the absorption spectrum of a phosphate buffer solution (pH 7.0) (0.6 in 100000) of Uracil as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 259 nm and 261 nm.

(2) Determine the infrared spectra of Uracil and uracil RS as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of Uracil in 10 mL of a sodium hydroxide solution (1 in 10); the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Uracil as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(3) ***Arsenic***—Proceed with 2.0 g of Uracil as directed under Method 3 and perform the test (NMT 1 ppm).

(4) ***Related substances***—Weigh 0.1 g of Uracil and dissolve in sodium hydroxide solution (1 in 10) to make 100 mL; perform the test with this solution as directed under the Thin Layer Chromatography. Spot 50 μL of this solution on the thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, acetic acid(31) and water (4 : 2 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Examine the plate under ultraviolet light (main wavelength: 254 nm); any spot other than the principal spot does not appear.

Loss on drying NMT 0.3% (1 g, 105 ℃, 3 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 60 mg of Uracil, previously dried, and dissolve in phosphate buffer solution (pH 7.0) to make exactly 100 mL. Pipet 2 mL of this solution, add phosphate buffer solution (pH 7.0) to make exactly 200 mL, and use this solution as the test solution. Separately, weigh accurately about 60 mg of uracil RS, proceed in the same manner as in the test solution, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the wavelength of 260 nm as directed under the Ultraviolet-visible Spectroscopy.

Amount (mg) of uracil ($C_4H_4N_2O_2$)
= Amount (mg) of uracil RS × (A_T / A_S)

Packaging and storage Preserve in well-closed containers.

Urea Ointment
요소 연고

Urea Ointment contains NLT 90.0% and NMT 110.0% of the labeled amount of urea (CH_4N_2O: 60.06).

Method of preparation Prepare as directed under Ointments, with Urea.

Identification (1) Weigh an amount of Urea Ointment equivalent to 50 mg of urea according to the labeled amount, add 1 mL of water, warm, then cool. Dissolve this solution in 4 mL of acetone, centrifuge, and use the clear supernatant as the test solution. Separately, weigh 50 mg of urea RS and proceed in the same manner as the test solution. Use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of 2,2,4-trimethylpenthane or ethanol and 13.5 mol/L ammonia (99 : 1) as the developing solvent, and air-dry the plate. Spray evenly 0.5% 4-dimethylaminobenzaldehyde solution and 0.5% ethanol sulfate solution; the R_f value and color of the spots obtained from the test solution and the standard solution are the same.

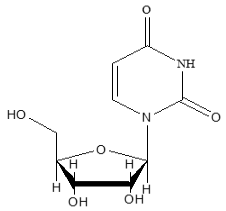
(2) Weigh an amount of Urea Ointment equivalent to 0.1 g of urea according to the labeled amount, add 50 mL of water and heat until dispersed. Chill on ice and filter with a glass filter. If the filtrate is not transparent, adjust pH to 6 to 7 using 0.1 mol/L hydrochloric acid TS or 0.1 mol/L sodium hydroxide TS. To 5 mL of this solution, add 5 mL of 0.1% urease active meal, allow to stand for 30 minutes at 37 ℃, then heat on a steam bath. The gas produced turns red litmus paper blue.

Assay Weigh accurately an amount of Urea Ointment equivalent to about 40 mg of urea (CH_4N_2O) according to the labeled amount, mix for 20 minutes in 150 mL of hot water and cool. Add water to make 500 mL, filter using glass filter paper (Whatman GF/C). Place 0.1 mL of the filtrate and 2.0 mL of 0.1% urease active meal in a stoppered flask, and allow to stand for 15 minutes at 37 ℃. Immediately add to this solution 25 mL of a solution prepared by adding water to 12 g of sodium salicylate and 0.24 g of sodium nitroprusside to make 200 mL, and then add 25 mL of a solution prepared by adding 0.2 mol/L of sodium hydroxide TS to a sodium hypochlorite solution containing an equivalent of 0.66 g of chlorine. Allow to stand for 5 minutes at 37 ℃, then add water to make 100 mL, and use this solution as the test solution. Separately, weigh accurately about 40 mg of urea RS, proceed in the same manner as in the test solution, and use this solution as the standard solution. Perform the test with the test solution and the standard solution as directed under Ultraviolet-visible Spectroscopy and determine the absorbances, A_T and A_S, respectively, at the wavelength of 665 nm.

Amount (mg) of urea (CH_4N_2O)
$= \text{Amount (mg) of urea RS} \times \frac{A_T}{A_S}$

Packaging and storage Preserve in tight containers.

Uridine
우리딘



$C_9H_{12}N_2O_6$: 244.20

1-β-*D*-Ribofuranosyluracil, [*58-96-8*]

Uridine contains NLT 99.0% and NMT 101.0% of uridine ($C_9H_{12}N_2O_6$), calculated on the anhydrous basis.

Description Uridine occurs as a white, crystalline, odorless powder.
It is freely soluble in water and sparingly soluble in ethanol.
The pH of 1% aqueous solution of Uridine is between 4.5 and 5.5.

Identification (1) To 5 mL of 0.1% aqueous solution of Uridine, add 0.1% iron(III) chloride TS and 5 mL of hydrochloric acid solution containing 0.1% orcin and warm on a steam bath; the solution turns green after 15 minutes.

(2) Prepare 0.1% aqueous solutions of Uridine and uridine RS, and use these solutions as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on thin-layer chromatographic plate made of cellulose for thin-layer chromatography (with fluorescence agent). Next, develop the plate with 1 mol/L sodium bicarbonate solution as the developing solvent, and air-dry the plate. Examine under ultraviolet light; the spots from the test solution and the standard solution have the same R_f values and colors.

(3) Determine the absorption spectra of a solution of Uridine in 0.05 mol/L phophate buffer solution (pH 7.0) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum at the wavelength of 262 nm. Comparing absorbances at 250 nm, 260 nm, and 280 nm, 250 nm / 260 nm = 0.74 ± 0.02, and 280 nm / 260 nm = 0.36 ± 0.02.

Melting point Between 164 and 169 ℃.

Purity ***Heavy metals***—Proceed with 2.0 g of Uridine as directed under Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

Water NMT 1.0% (1.0 g, volumetric titration, direct titration).

Residue on ignition 0.1% (1.0 g).

Assay Weigh accurately about 0.1 g of Uridine and dissolve in 0.2 mol/L phosphate buffer solution (pH 7.0) to make 100 mL. Pipet 2.0 mL of this solution, add 0.2 mol/L phosphate buffer solution (pH 7.0) to make 200 mL, and use this solution as the test solution. Separately, weigh accurately about 50 mg of uridine RS and dissolve in 0.2 mol/L phosphate buffer solution (pH 7.0) to make exactly 100 mL. Pipet 2 mL of this solution and add 0.2 mol/L phosphate buffer solution (pH 7.0) to make exactly 100 mL. Use this solution as the standard solution. Perform the test with the test solution and the standard solution using 0.2 mol/L phosphate buffer solution (pH 7.0) as the control solution as directed under the Ultraviolet-visible Spectroscopy, and measure the absorption A_T and A_S at the absorbance maximum wavelength of around 260 nm to 262 nm.

$$\text{Amount (mg) of uridine } (C_9H_{12}N_2O_6) = \text{Amount (mg) of uridine RS} \times \frac{A_T}{A_S} \times 2$$

Packaging and storage Preserve in tight containers.

Urokinase
유로키나제

[*62229-50-9*]

Urokinase is an enzyme obtained from human urine, having a molecular weight of about 54000 and having plasminogen-activating activity. Urokinase is a solution having an appropriate buffer solution as the solvent.

Urokinase contains NLT 60000 units of urokinase per mL, and NLT 120000 units of urokinase of protein per mg.

Description Urokinase occurs as a clear, colorless liquid.
The pH of Urokinase is between 5.5 and 7.5.

Identification (1) Dissolve 70 mg of fibrinogen in 10 mL of phosphate buffer solution (pH 7.4). To this solution, add and mix 1 mL of thrombin dissolved in isotonic sodium chloride injection to a concentration of 10 units per mL, then transfer to a petri dish about 90 mm in internal diameter and allow to stand level until the solution coagulates. To the surface, add 10 μL of a solution of gelatin-tris buffer solution added to Urokinase to a concentration of 100 units per mL dropwise and leave overnight; lysis circle is appeared.

(2) Dissolve 1.0 g of agar powder in 100 mL of a boric acid and sodium hydroxide buffer solution (pH 8.4) at by warming, then transfer to a petri dish to a depth of about 2 mm. After cooling, make 2 holes of diameter 2.5 mm, 6 mm apart. Into each of the holes, inject 10 μL of a solution of Urokinase in isotonic sodium chloride injection containing 30000 units per mL and 10 μL of anti-urokinase serum, then leave overnight; a clear precipitation line is formed.

Purity (1) ***Heavy Metals***—Proceed with 2.0 mL of Urokinase as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Blood group substance***—Add isotonic sodium chloride injection to Urokinase to obtain a solution containing 12000 units per mL, and use this solution as the test solution. Add isotonic sodium chloride injection to anti-A blood typing antibody and dilute by factors of 32, 64, 128, 256, 512 and 1024, and transfer 25 μL of each in the first six wells of the first and second column of a v-shaped 96-well micro plate. Next, put 25 μL of the test solution into each of the 6 wells of the first column, and put 25 μL of isotonic sodium chloride injection into each of the 6 wells of the second column. Shake to mix and allow to stand for 30 minutes. Put 50 μL of red blood cell suspension for type A into each well, shake to mix, and allow to stand for 2 hours. Compare the hemagglutination of red blood cells of the two sides; the anti-A antibody dilution factors of the wells where hemagglutination is observed are the same. Repeat the test, using anti-B blood typing antibody and red blood cell suspension for type B.

Abnormal toxicity Add isotonic sodium chloride injection to Urokinase to obtain a solution containing 12000 units per mL, and use this solution as the test solution. Use at least 2 healthy and well-fed guinea pigs of body weight about 350 g and at least 2 healthy and well-fed mice of about 5 weeks old. Inject 5.0 mL of the test solution into the abdominal cavity of each guinea pig, and inject 0.5 mL of the test solution into the abdominal cavity of each mouse, then observe for NLT 7 days; none of the animals exhibit abnormal symptoms.

High molecular weight urokinase Add gelatin and phosphate buffer solution to Urokinase to obtain a solution containing 10000 units per mL, and use this solution as the test solution. Take 100 μL of the test solution and perform the test as directed under the Liquid Chromatography according to the following conditions. Of the two peaks that appear at a retention time of near 35 minutes, measure the peak area *A*a whose retention time is shorter, and the peak area *A*b whose retention time is longer, using the automatic area integration method; *A*a/(*A*a+*A*b) is NLT 0.85.

Operating conditions

Device: Use a mobile phase transfer pump, sample injection port, column, reaction TS transfer pump, reaction coil, reaction vessel, fluorometer and data collection device; connect a 3-way tube to the mobile phase exit of the column, connect to the reaction TS transfer pump and reaction coil, then connect the reaction coil exit to the fluorometer.

Detector: A fluorometer (excitation wavelength: 365 nm, measurement wavelength: 460 nm).

Column: A stainless steel column about 7.5 mm in internal diameter and about 60 cm in length, packed with porous silica gel for liquid chromatography (10 to 12 μm in particle diameter).

Column temperature: A constant temperature of about 20 ℃.

Reaction coil: Stainless steel column about 0.25 mm in internal diameter and about 150 cm in length.

Reaction coil temperature: 37 ℃

Mobile phase: Gelatin and phosphate buffer solution

Flow rate: 0.5 mL/min

Reaction reagent: 7-(glutarylglycil-L-alginylamino)-4-methylcoumarine TS

Reaction reagent flow rate: 0.75 mL/min

Selection of column: Add sodium hydroxide TS to Urokinase and adjust pH to 7.5, then allow to stand for at least 24 hours at 37 ℃. Add gelatin and phosphate buffer solution to this solution to a concentration of 20000 units per mL. Proceed with 100 μL each of this solution according to the above conditions; high molecular weight urokinase of molecular weight 54000 and low molecular weight urokinase of molecular weight 33000 are eluted in this order, with a resolution of NLT 1.0.

Assay (1) ***Urokinase***—Pipet 1 mL of Urokinase and add gelatin and phosphate buffer solution, then dilute precisely to a concentration of about 30 units per mL, and use this solution as the test solution. Dissolve 1 ampoule of high molecular weight urokinase RS in 2 mL of gelatin and phosphate buffer solution, pipet 1mL of this solution, and add gelatin and phosphate buffer solution to dilute precisely to a concentration of about 30 units per mL. Use this solution as the standard solution. Add 1.0 mL of L-pyrroglutamilglycyl-L-alginine-*P*-nitroanilide TS to each of two silicone-coated test tubes of internal diameter 10 mm, warm for 5 minutes on a steam bath at 35 ± 0.2 ℃, add 0.50 mL each of the test solution and the standard solution, warm for precisely 30 minutes at 35 ± 0.2 ℃, then add 0.50 mL of diluted acetic acid(100) (2 in 5) to each. With these solutions, and using water as the blank, measure the absorbances A_T and A_S at 405 nm as directed under the Ultraviolet-visible Spectroscopy. Separately, add 1.0 mL of L-pyrroglutamilglycyl-L-alginine-*P*-nitroanilide to each of 2 test tubes, add 0.50 mL of diluted acetic acid(100) (2 in 5) to each, then add 0.50 mL of the test solution and the standard solution respectively. With these solutions, and using water as the blank, measure the absorbances A_{TO} and A_{SO} at 405 nm as directed under the Ultraviolet-visible Spectroscopy.

$$\text{Amount (units) of urokinase} = \frac{A_T - A_{T0}}{A_S - A_{S0}} \times a \times b$$

a: Amount (units) of urokinase in 1 mL of the standard solution

b: Total volume (mL) when the test solution was prepared

(2) ***Protein***—Pipet an amount of Urokinase equivalent to about 15 mg of protein and perform the test as directed under the Nitrogen Determination.

Each mL of 0.005 mol/L sulfuric acid

= 0.87544 mg of protein

Packaging and storage Preserve in tight containers and store at NMT -20 ℃.

Purified Urokinase Solution
정제유로키나제 액

Purified Urokinase Solution is a purified solution of crude urokinase, and contains NLT 8000 IU per mL of urokinase when tested in the potency assay. Purified Urokinase Solution is a drug substance.

Description Purified Urokinase Solution occurs as a clear liquid.

Identification Perform the test with Purified Urokinase Solution as directed under the Potency assay; the result is positive.

Pyrogen It meets the requirements when used in the manufacturing of sterile preparations. Weigh a suitable amount of Purified Urokinase Solution, dissolve in water to prepare a solution containing 100 IU per mL and use this solution as the test solution. Dose of injection is 3 mL per kg of rabbit weight.

Potency assay Pipet the amount of Purified Urokinase Solution equivalent to 300 IU, dissolve in distilled water for injection or isotonic sodium chloride injection, dilute to 200, 160, 140, 120, 100, and 80 IU/mL with phosphate buffer solution (pH 7.2), and use this solution as the test solution. Add 0.5 mL each of the test solution into a test tube of about 10 mm in internal diameter and about 10 mm in length, add 0.2 mL each of thrombin solution, and mix well taking care to avoid forming air bubbles. Then, add 1.0 mL of fibrinogen solution, mix well while tilting the test tube for about 15 seconds. Immediately, place the test tube on a thermostat at 37 °C and start the timer. After exactly 1 minute, gently drop a nylon ball (about 8.0 mm in diameter, about 297 mg in weight) into the test tube. Measure the time until the nylon ball reaches the bottom of the test tube, and use this time as the time to dissolve. Measure the time 3 times for each diluent, calculate the mean value of each measured time to dissolve, read the concentration according to the standard calibration curve, and calculate the total potency using the following formula.

$$\text{Potency (IU) of urokinase} = U \times V_1 \times V_2$$

U: Concentration (IU/mL) calculated from the standard calibration curve

V_1: Amount (mL) of distilled water for injection or isotonic sodium chloride injection with Purified Urokinase Solution dissolved

V_2: Dilution factor for preparation of each test solution with 0.1 mol/L phosphate buffer solution

Setting of the standard calibration curve

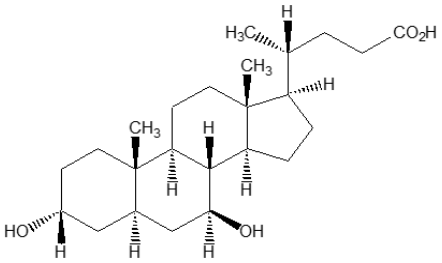
Preparation of standard urokinase solution: Dilute urokinase RS (with unit indicated) with 0.1 mol/L phosphate buffer solution (pH 7.2) and prepare 6 to 7 standard solutions with different concentrations (50 IU/mL to 300 IU/mL).

Measurement of the time to dissolve: Use thrombin solution, fibrinogen solution, and standard urokinase solution, and determine the time to dissolve of each standard urokinase solution.

Preparation of the standard calibration curve: Draw a calibration curve with the time to dissolve (second) on the vertical axis and concentration of standard urokinase solution on the horizontal axis of a logarithmic graph paper.

Packaging and storage Preserve in hermetic containers.

Ursodeoxycholic Acid
우르소데옥시콜산



$C_{24}H_{40}O_4$: 392.57

(4R)-4-[(1*S*,2*S*,5*R*,7*S*,9*S*,10*R*,11*S*,14*R*,15*R*)-5,9-Dihydroxy-2,15-dimethyltetracyclo[8.7.0.0^{2,7}.0^{11,15}]heptadecan-14-yl]pentanoic acid [*128-13-2*]

Ursodeoxycholic Acid, when dried, contains NLT 98.5% and NMT 101.0% of ursodeoxycholic acid ($C_{24}H_{40}O_4$).

Description Ursodeoxycholic Acid occurs as white crystals or a powder and has a bitter taste.
It is freely soluble in methanol, ethanol(99.5) or acetic acid(100), and practically insoluble in water.

Identification (1) Dissolve 10 mg of Ursodeoxycholid Acid in 1 mL of sulfuric acid and 1 drop of formaldehyde solution, and allow to stand for 5 minutes. Add 5 mL of water to this solution; a bluish green floating matter is formed.

(2) Determine the infrared spectra of Ursodeoxycholic Acid and ursodeoxycholic acid RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[\alpha]_D^{20}$: Between +59.0° and +62.0° (1.0 g, previously dried, ethanol(99.5), 25 mL, 100 mm).

Melting point Between 200 and 204 ℃.

Purity (1) ***Odor***—To 2.0 g of Ursodeoxycholic Acid, add 100 mL of water and boil for 2 minutes; the solution is odorless.

(2) ***Chloride***—Add 20 mL of acetic acid(100) to 2.0 g of Ursodeoxycholic Acid, shake to mix and dissolve. Add water to make 200 mL, shake to mix, and allow to stand for 10 minutes. Filter this solution, discard the first 10 mL of the filtrate, and collect the subsequent filtrate. To 40 mL of this solution, add 6 mL of dilute nitric acid and water to make 50 mL, and perform the test using this solution as the test solution. Prepare the control solution by adding, to 0.25 mL of 0.01 mol/L hydrochloric acid, 4 mL of acetic acid(100), 6 mL of dilute nitric acid and water to make 50 mL (NMT 0.022%).

(3) ***Sulfate***—Take 40 mL of the test solution obtained in (2), add 1 mL of dilute hydrochloric acid and water to make 50 mL and perform the test using this solution as the test solution. Prepare the control solution by adding, to 0.40 mL of 0.005 mol/L sulfuric acid, 4 mL of acetic acid(100), 1 mL of dilute hydrochloric acid and water to make 50 mL (NMT 0.048%).

(4) ***Heavy metals***—Proceed with 1.0 g of Ursodeoxycholic Acid as directed under Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(5) ***Barium***—To the solution obtained in (1), add 2 mL of hydrochloric acid and boil for 2 minutes. After cooling, filter and wash with water until 100 mL of the filtrate is obtained. To 10 mL of this solution, add 1 mL of dilute sulfuric acid; no turbidity is produced.

(6) ***Arsenic***—Proceed with 1.0 g of Ursodeoxycholic Acid as directed under Method 3 and perform the test (NMT 2 ppm).

(7) ***Related substances***—Weigh 0.20 g of Ursodeoxycholic Acid, dissolve in 1 mL of methanol, add acetone to make exactly 10 mL, and use this solution as the test solution. Take 1 mL of this solution and add acetone to make exactly 100 mL. Take 1 mL and 2 mL each of this solution, add acetone to make exactly 20 mL, and use these solutions as the standard solution (1) and the standard solution (2), respectively. Separately, weigh 50 mg of chenodeoxycholic acid RS, dissolve in 5 mL of methanol and add acetone to make exactly 50 mL. Take 2 mL of this solution, add acetone to make exactly 10 mL and use this solution as the standard solution (3). Weigh 25 mg of lithocholic acid RS, dissolve in 5 mL of methanol, and add acetone to make exactly 50 mL. Take 2 mL of this solution, add acetone to make exactly 50 mL and use this solution as the standard solution (4). With these solutions, perform the test as directed under the Thin Layer Chromatography. Apply 10 μL each of the test solution and the standard solutions (1), (2), (3) and (4), on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of isooctane, ethanol(95), ethyl acetate and acetic acid(100) (10 : 2 : 7 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Dry at 120 ℃ for 30 minutes, then immediately spray evenly with a solution prepared by adding ethanol(99.5) to 5 g of phosphomolybdic acid hydrate to make 50 mL, dropping 5 mL of sulfuric acid to this solution, then adding ethanol(99.5) to make 100 mL, and heat for 3 to 5 minutes at 120 ℃; the spots of the test solution are not more intense than the spots of the standard solutions (3) and (4), and the principal spot of the test solution and spots other than the above spots are not more intense than the spots obtained from the standard solution (2). Further, the total of the principal spot of the test solution and the spots other than the above spots is NMT 0.25% when compared to the spots obtained from the standard solutions (1) and (2).

Loss on drying NMT 1.0% (1 g, 105 ℃, 2 hours)

Residue on ignition NMT 0.2% (1 g)

Assay Weigh accurately about 0.5 g of Ursodeoxycholic Acid, previously dried, and dissolve by adding 40 mL of ethanol(95) and 20 mL of water. Titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 39.26 mg of $C_{24}H_{40}O_4$

Packaging and storage Preserve in well-closed containers.

Ursodeoxycholic Acid Capsules
우르소데옥시콜산 캡슐

Ursodeoxycholic Acid Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of ursodeoxycholic acid ($C_{24}H_{40}O_4$: 392.57).

Method of preparation Prepare as directed under Capsules, with Ursodeoxycholic Acid.

Identification Put the content of NLT 10 capsules of Ursodeoxycholic Acid Capsules into a Soxhlet extractor, extract with chloroform for 1 hour, evaporate the chloroform, dissolve the residue with 2 mL to 3 mL of acetic anhydride, and use this solution as the test solution. Separately, prepare a 0.1% acetic anhydride solution of ursodeoxycholic acid RS, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution to the thin-layer chromatographic plate made of silica gel for thin-layer chromatography, develop the plate with a mixture of isoamyl alcohol, acetic acid(31) and water (10 : 5 : 2) as the developing solvent, and air-dry the plate. Spray evenly sulfuric acid on the plate; the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Ursodeoxycholic Acid Capsules. Weigh accurately an amount of the content, equivalent to about 1 g of ursodeoxycholic acid ($C_{24}H_{40}O_4$), add the acetone, shake vigorously to mix, and make 100 mL. Centrifuge, take 50.0 mL of the clear supernatant, evaporate in vacuum, add 40 mL of neutralized ethanol to the residue, and shake for 5 minutes. Then, add 20 mL of water, and titrate with 0.1 mol/L sodium hydroxide VS using phenolphthalein as an indicator. Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 39.26 mg of $C_{24}H_{40}O_4$

Packaging and storage Preserve in well-closed containers.

Ursodeoxycholic Acid, Thiamine Hydrochloride and Riboflavin Capsules
우르소데옥시콜산·티아민염산염·리보플라빈 캡슐

Ursodeoxycholic Acid, Thiamine Hydrochloride and Riboflavin Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of ursodeoxycholic acid ($C_{24}H_{40}O_4$: 392.57) and NLT 90.0% and NMT 150.0% of the labeled amount of thiamine hydrochloride ($C_{12}H_{17}ClN_4OS{\cdot}HCl$: 337.27) and riboflavin ($C_{17}H_{20}N_4O_6$: 376.36).

Method of preparation Prepare as directed under Capsules, with Ursodeoxycholic Acid, Thiamine Hydrochloride and Riboflavin.

Identification (1) ***Ursodeoxycholic Acid***—Put the content of NLT 10 capsules of Ursodeoxycholic Acid, Thiamine Hydrochloride and Riboflavin Capsules into a Soxhlet extractor, extract with ethyl acetate for 1 hour, evaporate the ethyl acetate, dissolve the residue with 2 mL to 3 mL of acetic anhydride, and use this solution as the test solution. Separately, prepare a 0.1% acetic anhydride solution of ursodeoxycholic acid RS, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of toluene, acetone and acetic acid (60 : 30: : 1), and air-dry the plate. Spray evenly sulfuric acid on the plate; the colors and R_f values of the spots obtained from the test solution and the standard solution are the same.

(2) ***Thiamine hydrochloride and riboflavin***—Perform the test with the content of Ursodeoxycholic Acid, Thiamine Hydrochloride and Riboflavin Capsules as directed under the Analysis for Vitamins.

Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay (1) ***Ursodeoxycholic acid***—Weigh accurately the mass of about 20 capsules of Ursodeoxycholic Acid, Thiamine Hydrochloride and Riboflavin Capsules. Weigh accurately an amount of the content, equivalent to about 50 mg of ursodeoxycholic acid ($C_{24}H_{40}O_4$), add 40 mL of methanol, shake for 30 minutes to dissolve, then add 5.0 mL of the internal standard solution and methanol to make 50 mL, filter, and use this filtrate as the test solution. Separately, weigh accurately about 50 mg of ursodeoxycholic acid RS, dissolve in 40 mL of methanol, and add 5.0 mL of the internal standard solution and methanol to make 50 mL, use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the ratios, Q_T and Q_S, of peak area of the ursodeoxycholic acid to that of the internal standard.

Amount (mg) of ursodeoxycholic acid ($C_{24}H_{40}O_4$)
= Amount (mg) of ursodeoxycholic acid RS× $\frac{Q_T}{Q_S}$

Internal standard solution—Weigh 0.5 g of cholic acid, and add methanol to make 50 mL.

Operating conditions

Detector: A differential refractometer

Column: A stainless steel column about 4 mm in internal diameter and about 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

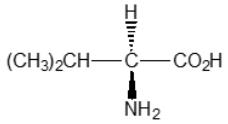
Mobile phase: To 500 mL of a mixture of methanol and water (70 : 50), add 0.1 mol/L phosphoric acid to adjust its pH to 3.5.

Flow rate: 1.0 mL/min

(2) ***Thiamine hydrochloride and riboflavin***—Weigh accurately the mass of the content of NLT 20 capsules of Ursodeoxycholic Acid, Thiamine Hydrochloride and Riboflavin Capsules, and perform the test as directed under the Analysis for Vitamins.

Packaging and storage Preserve in well-closed containers.

L-Valine
L-발린



$C_5H_{11}NO_2$: 117.15

(2*S*)-2-Amino-3-methylbutanoic acid [*72-18-4*]

L-Valine, when dried, contains NLT 98.5% and NMT 101.0% of L-valine ($C_5H_{11}NO_2$).

Description L-Valine occurs as white crystals or a crystalline powder. It is odorless or has a slightly characteristic odor. It has a sweet taste, but the aftertaste is bitter.
It is freely soluble in formic acid, soluble in water, and practically insoluble in ethanol(95) and ether.
It is soluble in dilute hydrochloric acid.

Identification Determine the infrared spectra of L-Valine and L-valine RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Optical rotation $[a]_D^{20}$: Between +26.5° and +29.0° (2 g, previously dried, 6 mol/L hydrochloric acid TS, 25 mL, 100 mm).

pH Dissolve 0.5 g of L-Valine in 20 mL of water; the pH of this solution is between 5.5 and 6.5.

Purity (1) ***Clarity and color of solution***—Dissolve 0.5 g of L-Valine in 20 mL of water; the resulting solution is clear and colorless.

(2) ***Chloride***—Perform the test with 0.5 g of L-Valine. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.021%).

(3) ***Sulfate***—Perform the test with 0.6 g of L-Valine. Prepare the control solution with 0.35 mL of 0.005 mol/L sulfuric acid (NMT 0.028%).

(4) ***Ammonium***—Perform the test with 0.25 g of L-Valine. Prepare the control solution with 5.0 mL of ammonium standard solution (NMT 0.02%).

(5) ***Heavy metals***—Proceed with 2.0 g of L-Valine according to Method 1 under the Heavy Metals and perform the test. Prepare the control solution with 3.0 mL of lead standard solution (NMT 15 ppm).

(6) ***Iron***—Dissolve about 0.333 g of L-Valine in water to make 45 mL, add 2 mL of hydrochloric acid, and use this solution as the test solution. Add water to 1.0 mL of iron standard solution to make 45 mL, add 2 mL of hydrochloric acid, and use this solution as the standard solution. Add 50 mg of ammonium peroxydisulfate and 3 mL of 30% ammonium thiocyanate solution in the test solution and the standard solution and mix; the color obtained from the test solution is not more intense than that from the standard solution (NMT 30 ppm).

(7) ***Arsenic***—Prepare the test solution with 1.0 g of L-Valine according to Method 2 and perform the test (NMT 2 ppm).

(8) ***Related substances***—Dissolve 0.10 g of L-Valine in 25 mL of water, and use this solution as the test solution. Pipet 1 mL of this solution and add water to make exactly 50 mL. Pipet 5 mL of this solution, add water to make exactly 20 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution and the standard solution on a plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of 1-butanol, water and acetic acid(100) (3 : 1 : 1) (as the developing solvent) to a distance of about 10 cm, and air-dry the plate. Spray evenly a solution of ninhydrin in acetone (1 in 50) on the plate and heat at 80 ℃ for 5 minutes; the spots other than the principal spot obtained from the test solution are not more intense than the spots from the standard solution.

Loss on drying NMT 0.3% (1 g, 105 ℃, 3 hours).

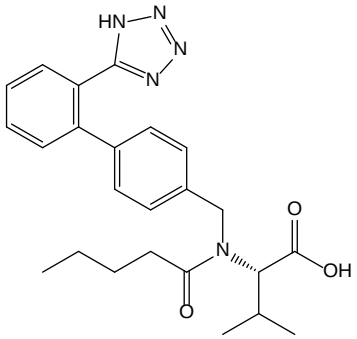
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.12 g of L-Valine, previously dried, and dissolve in 3 mL of formic acid, add 50 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 11.715 mg of $C_5H_{11}NO_2$

Packaging and storage Preserve in tight containers.

Valsartan
발사르탄



$C_{24}H_{29}N_5O_3$: 435.52

(*S*)-3-Methyl-2-[pentanoyl-[[4-[2-(2*H*-tetrazol-5-yl)phenyl]phenyl]methyl]amino]butanoic acid [*137862-53-4*]

Valsartan contains NLT 98.0% and NMT 102.0% of valsartan ($C_{24}H_{29}N_5O_3$: 435.52), calculated on the anhydrous basis.

Description Valsartan occurs as a white powder.
It is freely soluble in ethanol(95), sparingly soluble in

dichloromethane, and practically insoluble in water.
It is hygroscopic.

Identification (1) Determine the infrared spectra of Valsartan and valsartan RS, as directed in the paste method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Valsartan in 20 mL of methanol and perform the test as directed under the Ultraviolet-visible Spectroscopy; the absorbance at a wavelength of 420 nm divided by the layer length is NMT 0.02.

(2) ***Heavy metals***—Proceed with 1.0 g of Valsartan according to Method 2 and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***— (i) Valsartan related substance I: Weigh accurately about 50 mg of Valsartan, add 40 mL of the mobile phase, dissolve with sonication for 5 minutes, add the mobile phase to make exactly 50 mL, and use this solution as the test solution. Separately, weigh an appropriate amount of valsartan related substance I {*R*-*N*-valeryl-*N*-([2'-(1*H*-tetrazol-5-yl)biphen-4-yl]methyl)valine} RS, add the mobile phase to make a solution containing 0.01 mg in 1 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution as directed in the automatic integration method and calculate the amount of valsartan related substance I; it is NMT 1.0%.

$$\text{Content (\%) of valsartan related substance I} = 100 \times \frac{C_S}{C_T} \times \frac{A_T}{A_S}$$

C_T: Concentration (mg/mL) of Valsartan in the test solution

C_S: Concentration (mg/mL) of valsartan related substance I in the standard solution

A_T: Peak area of valsartan related substance I obtained from the test solution

A_S: Peak area of valsartan related substance I obtained from the standard solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with cellulose tris-(3,5-dimethylcarbamate)-coated porous silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of hexane, 2-propanol and trifluoroacetic acid (85 : 15 : 0.1).

Flow rate: 0.8 mL/min

System suitability

System performance: Proceed with 10 μL of the system suitability solution according to the above conditions; the resolution between the peak of valsartan and the peak of valsartan related substance I is NLT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the system suitability solution according to the above conditions; the relative standard deviation of the peak area of valsartan related substance I is NMT 5.0%

System suitability solution: Weigh accurately an appropriate amount of valsartan RS and valsartan related substance I RS, dissolve in the mobile phase so that each solution contains 0.04 mg per mL.

(ii) Vaslartan related substance II, valsartan related substance III and other related substances: Weigh accurately about 50 mg of Valsartan, add the mobile phase to make exactly 100 mL, and use this solution as the test solution. Separately, weigh accurately an appropriate amount of valsartan RS, valsartan related substance II {*S*-*N*-butyryl-*N*-(2'-(1*H*-tetrazol-5-yl)biphen-4-yl]methyl)-valine} RS and valsartan related substance III {*S*-*N*-valeryl-*N*-([2'-(1*H*-tetrazol-5-yl)biphen-4-yl]methyl)-valine benzyl ester} RS, add the mobile phase, make solutions containing 0.001 mg per mL, respectively, and use these solutions as the standard solutions. Perform the test with 10 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, determine the peak area of each solution as directed in the automatic integration method, and calculate the amount of related substances; the amount of valsartan related substance II is NMT 0.2%, the amount of valsartan related substance III is NMT 0.1%, the each amount of other related substances other than valsartan related substance I is NMT 0.1%, and the total amount of related substances other than valsartan related substance I is NMT 0.3%.

$$\text{Content (\%) of related substances} = 100 \times \frac{C_S}{C_T} \times \frac{A_i}{A_S}$$

C_T: Concentration (mg/mL) of Valsartan in the test solution

C_S: Concentration (mg/mL) of each valsartan related substance in the standard solution (concentration (mg/mL) of valsartan RS in the standard solution in the case of calculating other individual related substances)

A_i: Peak area of each valsartan related substance obtained from the test solution

A_S: Peak area of each valsartan related substance obtained from the standard solution (peak area of valsartan obtained from the standard solution in the case of calculating other individual related substances)

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

For the column, mobile phase and flow rate, comply

with the operating conditions in the Assay.

System suitability

System performance: Proceed with 10 μL each of the standard solution according to the above conditions; the resolution between valsartan peak and valsartan related substance II is NLT 1.8.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of valsartan related substance II is NMT 10.0% and the relative standard deviation of valsartan peak area is NMT 2.0%

Water NMT 2.0% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 50 mg of Valsartan and valsartan RS, respectively, dissolve in the mobile phase to make exactly 100 mL, and use these solutions as the test solution and the standard solution. Perform the test with 10 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of valsartan.

$$\text{Amount (mg) of valsartan } (C_{24}H_{29}N_5O_3) = \text{Amount (mg) of valsartan RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 273 nm).

Column: A stainless steel column about 3.0 mm in internal diameter and 125 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: Filter a mixture of water, acetonitrile and acetic acid(100) (500 : 500 : 1) and deaerate to use.

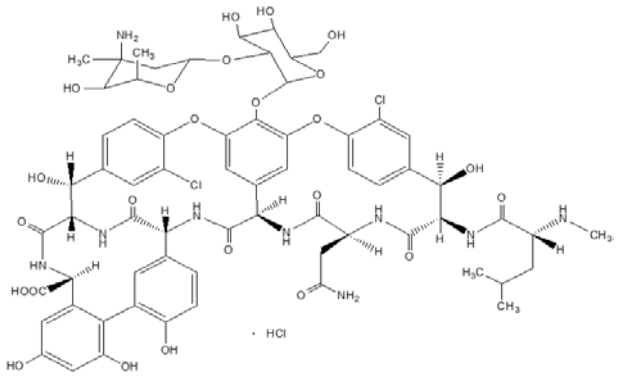
Flow rate: 0.4 mL/min

System suitability

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of valsartan is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Vancomycin Hydrochloride
반코마이신염산염



$C_{66}H_{75}Cl_2N_9O_{24}\cdot HCl$: 1485.71

(1*S*,2*R*,18*R*,19*R*,22*S*,25*R*,28*R*,40*S*)-50-[3-Amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*lyxo*-hexopyranosyl-(1→2)-β-D-glucopyranosyloxy]-22-carbamoylmethyl-5,15-dichloro-2,18,32,35,37-pentahydroxy-19-[(2*R*)-4-methyl-2-(methylamino)pentanoylamino]-20,23,26,42,44-pentaoxo-7,13-dioxa-21,24,27,41,43-pentaazaoctacyclo[26.14.2.2^{3,6}.2^{14,17}.1^{8,12}.1^{29,33}.0^{10,25}.0^{34,39}]pentaconta-3,5,8,10,12(50),14,16,29,31,33(49),34,36,38,45,47-pentadecaene-40-carboxylic acid monohydrochloride [*1404-93-9*]

Vancomycin Hydrochloride is the hydrochloride of a kind of glycopeptide substance having antibacterial activity produced by the growth of *Streptomyces orientalis*.

Vancomycin Hydrochloride contains NLT 1000 μg (potency) and NMT 1200 μg (potency) of vancomycin ($C_{66}H_{75}N_2O_{24}S$: 1000) per mg, calculated on the anhydrous basis.

Description Vancomycin Hydrochloride occurs as a white powder.

It is freely soluble in formamide, slightly soluble in methanol, very slightly soluble in ethanol(95), and practically insoluble in acetonitrile. It is hygroscopic.

Identification (1) Determine the absorption spectra of solutions of Vancomycin Hydrochloride and vancomycin hydrochloride RS (1 in 10000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared spectra of Vancomycin Hydrochloride and vancomycin hydrochloride RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) Dissolve 20 mg of Vancomycin Hydrochloride in 10 mL of water and add 1 drop of silver nitrate TS; the resulting solution is turbid.

Optical rotation $[\alpha]_D^{20}$: Between -30° and -40° (0.2 g, calculated on the anhydrous basis, water, 20 mL, 100 mm).

pH Dissolve 0.25 g of Vancomycin Hydrochloride in 5 mL of water; the pH of this solution is between 2.5 and

4.5.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Vancomycin Hydrochloride according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—Dissolve 0.1 g of Vancomycin Hydrochloride in 10 mL of the mobile phase A, and use this solution as the test solution. Pipet 1 mL of this solution, add the mobile phase A to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. If necessary, proceed with 20 μL of the mobile phase A in the same manner and make any necessary correction for the solvent peak and the baseline change. Determine peak areas of the test solution and the standard solution by the automatic integration method; each peak area other than the peak of vancomycin obtained from the test solution is not larger than the peak area of vancomycin from the standard solution. The total area of the peaks other than vancomycin from the test solution is not larger than 3 times the peak area of vancomycin from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: Use mobile phases A and B to control a step or gradient elution as follows.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 12	100	0
12 - 20	100 → 0	0 → 100
20 - 22	0	100

Mobile phase A: Add water to 4 mL of triethylamine to make 2000 mL. Adjust the pH to 3.2 with phosphoric acid. Take 920 mL of this solution, add 70 mL of acetonitrile, and add 10 mL of tetrahydrofuran. Adjust the amount of acetonitrile so that the retention time of vancomycin is 7.5 minutes - 10.5 minutes.

Mobile phase B: Add water to 4 mL of triethylamine to make 2000 mL. Adjust the pH to 3.2 with phosphoric acid. Take exactly 700 mL of this solution, add 290 mL of acetonitrile, and add 10 mL of tetrahydrofuran.

Flow rate: 1.5 mL/min

System suitability

Detection sensitivity: The peak area of vancomycin obtained from 20 μL of the standard solution is 3% - 5% of the peak area of vancomycin from 20 μL of the test solution.

System performance: Dissolve 5 mg of Vancomycin Hydrochloride in 10 mL of water, warm at 65 °C for 48 hours, and cool at the ordinary temperature. Proceed with 20 μL of this solution according to the above conditions; related substances I and related substances II are eluted in this order. The resolution between related substances I and vancomycin is NLT 3, the number of theoretical plate of vancomycin peak is NLT 1500, and related substances II is eluted between 15 and 18 minutes.

System repeatability: Repeat the test 5 times with 20 μL each of the standard solutions according to the above conditions; the relative standard deviation of peak areas of vancomycin is NMT 2.0%

Time span of measurement: About 2.5 times the retention time of vancomycin after the solvent peak.

Water NMT 5.0% (0.1 g, volumetric titration, direct titration). Use a mixture of formamide for water determination and methanol for water determination (3 : 1).

Residue on ignition NMT 1.0% (1.0 g).

Sterility It meets the requirements when used in sterile preparations. However, it is exempt from the requirements when there is a final sterilization process in the manufacturing processes of the sterile preparations.

Bacterial endotoxins It is NMT 0.25 EU per mg of vancomycin when used in sterile preparations

Assay ***Cylinder-plate method***—(1) Medium (i) Agar media for seed and base layers

Peptone	5.0 g
Meat extract	3.0 g
Agar	15.0 g

Weigh the above materials, add purified water to make 1000 mL, sterilize, and adjust the pH to between 6.2 and 6.4.

(2) Test organism-Use *Bacillus subtilis* ATCC 6633 as the test organism.

(3) Weigh accurately about 25 mg (potency) of Vancomycin Hydrochloride and dissolve in water to make exactly 25 mL. Take exactly an appropriate amount of this solution add 0.1 mol/L phosphate buffer solution. pH 4.5, to make solutions containing 100.0 μg (potency) and 25.0 μg (potency) per mL, and use these solutions as the high concentration test solution and low concentration test solution, respectively. Separately, weigh accurately about 25 mg of vancomycin hydrochloride RS, dissolve in water to make exactly 25 mL, and use this solution as the standard stock solution. Store the standard stock solution at below 5 °C and use it within 7 days. Take exactly an appropriate amount of the standard stock solution, add 0.1 mol/L phosphate buffer solution, pH 4.5, to make solutions containing 100.0 μg (potency) and 25.0 μg (potency) per mL, and use these solutions as the high concentration standard solution and low concentration stand-

ard solution, respectively. With these solutions, perform the test as directed under the Microbial Assays for Antibiotics (i) (8).

Packaging and storage Preserve in tight containers.

Vancomycin Hydrochloride Capsules
반코마이신염산염 캡슐

Vancomycin Hydrochloride Capsules are Vancomycin Hydrochloride separated in polyethylene glycol and contain NLT 90.0% and NMT 120.0% of the labeled amount of vancomycin hydrochloride ($C_{66}H_{75}Cl_2N_9O_{24}$: 1449.26).

Method of preparation Prepare as directed under Capsules, with Vancomycin Hydrochloride.

Identification Weigh an amount of the contents of Vancomycin Hydrochloride Capsules equivalent to 10 mg of vancomycin hydrochloride and dissolve in water to make 100 mL. Determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 279 nm and 284 nm.

Water NMT 8.0% (0.2 g, volumetric titration, direct titration).

Dissolution Perform the test with 1 capsule of Vancomycin Hydrochloride Capsules at 100 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the test solution. Take the dissolved solution 45 minutes from the start of the test and filter. Use the filtrate as the test solution and perform the test as directed under the Assay of Vancomycin Hydrochloride. Meets the requirements if the dissolution rate in 45 minutes is NLT 85%.

Uniformity of dosage units Meets the requirements.

Assay ***Cylinder plate method***—Proceed as directed under the Assay under Vancomycin Hydrochloride. Weigh accurately the contents of NLT 20 capsules of Vancomycin Hydrochloride Capsules. According to the labeled potency, weigh accurately an amount equivalent to about 25 mg (potency) of Vancomycin Hydrochloride and dissolve in water to make exactly 25 mL. Take exactly an appropriate amount of this solution, add 1 mL of 0.1 mol/L phosphate buffer solution (pH 4.5) to obtain solutions having known concentrations of 100 μg (potency) and 25 μg (potency) per mL, and use this solution as the high concentration test solution and low concentration test solution, respectively.

Packaging and storage Preserve in tight containers.

Vancomycin Hydrochloride for Injection
주사용 반코마이신염산염

Vancomycin Hydrochloride for Injection, dissolved before use, contains NLT 90.0% and NMT 115.0% of the labeled amount of vancomycin ($C_{66}H_{75}Cl_2N_9O_{24}$: 1449.25).

Method of preparation Prepare as directed under Injections, with Vancomycin Hydrochloride.

Description Vancomycin Hydrochloride for Injection occurs as a white mass or a powder.

Identification (1) Prepare 50 mL of a solution made by dissolving an amount equivalent to 5 mg (potency) of vancomycin hydrochloride, according to the labeled amount of Vancomycin Hydrochloride for Injection, in 50 mL of water, and determine the absorption spectrum of the solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum between 279 nm and 283 nm.

(2) Weigh an amount equivalent to 20 mg (potency) of vancomycin hydrochloride, according to the labeled amount of Vancomycin Hydrochloride for Injection, dissolve in 10 mL of water, and add 1 drop of silver nitrate TS; a white turbidity is produced.

pH Dissolve an amount equivalent to about 0.5 g (potency) of vancomycin hydrochloride, according to the labeled amount of Vancomycin Hydrochloride for Injection in 10 mL of water; the pH of the solution is between 2.5 and 4.5.

Purity (1) ***Clarity and color of solution***—Weigh an amount equivalent to about 0.5 g (potency) of vancomycin hydrochloride, according to the labeled amount of Vancomycin Hydrochloride for Injection, and dissolve in 10 mL of water; the color of the solution is colorless to pale yellow and clear. Perform the test with this solution as directed under the Ultraviolet-visible Spectroscopy; the absorbance at 465 nm is NMT 0.05.

(2) ***Heavy metals***—Weigh 0.66 g of Vancomycin Hydrochloride for Injection and perform the test as directed under Method 2. Prepare the control solution with 3.0 mL of lead standard solution (NMT 30 ppm).

(3) ***Related substances***—Weigh the amount equivalent to 0.1 g of vancomycin hydrochloride, according to the labeled amount of Vancomycin Hydrochloride for Injection, dissolve in 10 mL of the mobile phase A, and use this solution as the test solution. Perform the test as directed under Purity (2) of Vancomycin Hydrochloride.

Water NMT 5.0% (0.1 g, volume titration, direct titration). Use a mixture of formamide for water determination and methanol for water determination (3 : 1).

Sterility It meets the requirements when used in a sterile preparation.

Bacterial endotoxins It is less than 0.25 EU per mg (potency) of vancomycin when used in a sterile preparation.

Particulate contamination: Visible particles Meets the requirements.

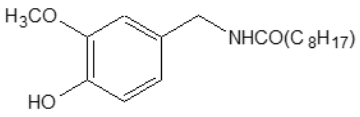
Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay ***Cylinder plate method***—Perform the test as directed under the Assay of Vancomycin Hydrochloride. However, weigh accurately the mass of the contents of NLT 10 Vancomycin Hydrochloride for Injections. Weigh accurately an amount equivalent to 25 mg (potency) of Vancomycin Hydrochloride, according to the labeled potency, and dissolve in water to make exactly 25 mL. Take exactly an appropriate amount of this solution, add 0.1 mol/L phosphate buffer solution, pH 4.5, to make solutions containing 100 μg (potency) and 25 μg (potency) per mL, and use these solutions as the high concentration test solution and the low concentration test solution, respectively.

Packaging and storage Preserve in hermetic containers.

Vanillyl Nonylamide
노닐산바닐릴아미드



$C_{17}H_{27}NO_3$: 293.41

N-(4-Hydroxy-3-methoxybenzyl) nonanamide, [*2444-46-4*]

Vanillyl Nonylamide, when dried, contains NLT 95.0% and NMT 101.0% of vanillyl nonylamide ($C_{17}H_{27}NO_3$).

Description Vanillyl Nonylamide occurs as a white to pale yellow crystalline powder, grain, or a mass.
It has a very spicy taste.
It is freely soluble in ethanol(95), chloroform, dimethylformamide or ether and practically insoluble in water.

Identification (1) Weigh about 0.1 g of Vanillyl Nonylamide, dissolve in 5 mL of 0.1 mol/L sodium hydroxide TS, add 1 mL of phosphomolybdic acid solution (3 in 100), and allow it to stand; the resulting solution exhibits a blue color.

(2) Weigh about 0.1 g of Vanillyl Nonylamide, dissolve in 5 mL of ethanol, add 1 to 4 drops of ferric chloride TS; the resulting solution exhibits a blue green color.

Melting point Between 48 and 51 ℃.

Acid value NMT 10.

Purity (1) ***Amine***—Weigh accurately about 0.1 g of Vanillyl Nonylamide, dissolve in 25 mL of methanol, add 0.1 mol/L of sodium dihydrogen phosphate TS, pH 3.0, to make exactly 100 mL. Filter and use the filtrate as the test solution. Separately, weigh accurately about 20 mg of vanillyl amine hydrochloride (4-hydroxy-3-methoxybenzylamine hydrochloride) RS, dissolve in 25 mL of methanol, and add 0.1 mol/L of sodium dihydrogen phosphate TS, pH 3.0, to make exactly 100 mL. Pipet 5 mL of this solution and add 0.1 mol/L of sodium dihydrogen phosphate TS, pH 3.0, to make exactly 50 mL. Use this solution as the standard solution. Perform the test with 20 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of vanillyl amine(NMT 1.53% as vanillyl amine).

$$\text{Content (\%) of vanillyl amine } (C_8H_{11}NO_2) = \frac{[\text{Amount (mg) of vanillyl amine hydrochloride RS}]}{\text{Amount (mg) of Vanillyl Nonylamide taken}} \times \frac{A_T}{A_S} \times \frac{153.18}{189.64} \times 10$$

153.18: Molecular weight of vanillyl amine
189.64: Molecular weight of vanillyl amine hydrochloride

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of 0.5% ammonium carbonate solution and methanol (95 : 5).

Flow rate: 1.0 mL/min

(2) ***Arsenic***—Proceed with1.0 g of Vanillyl Nonylamide according to Method 3 and perform the test (NMT 2 ppm).

Loss on drying NMT 0.5% (1 g, sulfuric acid, 5 hours).

Residue on ignition NMT 0.01% (1.0 g).

Assay Weigh accurately about 0.1 g of Vanillyl Nonylamide, previously dried, and dissolve in ethanol to make 100 mL. Take 5.0 mL of this solution, add methanol to make 100 mL, and use it as the test solution. Separately, proceed in the same manner as in the preparation of the test solution with about 0.1 g of vanillyl nonylamide RS, and use this solution as the standard solution. Determine the absorbance, A_T and A_S, of the test solution and the standard solution at 282 nm as directed under the Ultra-

violet-visible Spectroscopy.

$$\text{Amount (mg) of vanillyl nonylamide } (C_{17}H_{27}NO_3) = \text{Amount (mg) of vanillyl nonylamide RS} \times \frac{A_T}{A_S}$$

Packaging and storage Preserve in tight containers.

Vasopressin Injection
바소프레신 주사액

Vasopressin Injection is an aqueous solution for injection. Vasopressin Injection contains synthetic vasopressin or the pressor principle, vasopressin, obtained from the posterior lobe of the pituitary of healthy cattle and pigs, from which the majority of the oxytocic principle, oxytocin, has been removed.

Vasopressin Injection contains NLT 85.0% and NMT 120.0% of labeled Vasopressin units.

Method of preparation Prepare as directed under Injections, with vasopressin obtained from the posterior pituitary gland or synthetically produced vasopressin.

Description Vasopressin Injection occurs as a colorless and clear liquid, which is odorless or has a slightly characteristic odor.

pH—Between 3.0 and 4.0.

Purity ***Uterine contraction component***—Perform the test according to the following procedure; the amount of uterine contraction component is NMT 0.6 units of oxytocin per quantified 10 vasopressin units.

(1) ***Standard stock solution***—Dissolve 200 units of oxytocin RS according to the labeling unit in exact 10 mL of diluted acetic acid(100) (1 in 400). Pipet 1 mL of this solution, and add diluted acetic acid(100) (1 in 400) to make exactly 10 mL. Store this solution in a cold place, avoiding freezing, and use it within 6 months after preparation.

(2) ***Standard solution***—Add isotonic sodium chloride injection to the standard stock solution to dilute so that 1 mL of this solution contains 0.020 units of oxytocin.

(3) ***Test solution***—Assume oxytocin units are equivalent to 6/100 of the determined vasopressin units. Add isotonic sodium chloride injection to Vasopressin Injection to dilute so that 1 mL of this solution contains the assumed 0.020 units of oxytocin.

(4) ***Apparatus***—Use the apparatus for the uterus contraction test, equipped with a thermostatic bath. Maintain a temperature of the bath at 37 ℃ to 38 ℃ with a variation of NMT 0.1 ℃ during the course of the test. Also, use a 100-mL Magnus container to suspend the uterus vertically.

(5) ***Test animals***—Perform with healthy virgin guinea pigs weighing between 175 g and 350 g, in a non-estrus stage. Separate and raise them without exposure to males from a young age, and be prevented from sensing the scent of males.

(6) ***Procedure***—Immerse the Magnus container in a thermostat maintained at a constant temperature, add Locke-Ringer TS to the container, and ensure adequate oxygen flow. Sacrifice a guinea pig by means of a blow on the head, immediately remove the uterus from the body, suspend it vertically in the Magnus container, and connect one end of the uterine horn to the lever with a thread. If necessary, the lever is weighted and its mass is not changed throughout the Assay. Perform the test after 15 to 30 minutes when the uterus has sufficiently expanded. Place the same quantities of 0.1 to 0.5 mL, each of the standard solution and the test solution alternatively to the Magnus container twice at regular intervals of 10 to 20 minutes. Finally add a 25% increase in the amount of the standard solution separately to contract the uterus, and measure the height of every contraction.

The average height of the uterus contraction by the standard solution is equal or NLT that by the test solution. In addition, the height of contraction caused by the last increased standard solution is distinctly higher than those caused by the previous standard solution.

Sterility Meets the requirements.

Bacterial endotoxins Less than 15 EU per unit of vasopressin

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay (1) ***Test animals***—Perform with healthy male white rats weighing between 200 g and 300 g.

(2) ***Standard stock solution***—Dissolve about 2000 units of oxytocin RS according to the labeling unit in exact 100 mL of diluted acetic acid(100) (1 in 400). Pipet 1 mL of this solution, and add diluted acetic acid(100) (1 in 400) to make exactly 10 mL. Store this solution in a cold place, avoiding freezing, and use it within 6 months after preparation.

(3) ***Standard solution***—Dilute the standard stock solution with Isotonic Sodium Chloride Injection. Inject 0.2 mL of the obtained solution according to (6) to the test animals; it adjusts the blood pressure of the test animal to increase by 35 mmHg to 60 mmHg and use this solution as the high-dose standard solution (S_H). Then dilute this solution with Isotonic Sodium Chloride Injection to 1.5 to 2.0 times by volume and use this solution as the low-dose standard solution (S_L).

(4) ***Test solution***—Dilute an accurately measured volume of Vasopressin Injection with Isotonic Sodium Chloride Injection so that the obtained solution contains the same concentration in units as the high-dose standard solution based on the labeled units and use this solution

as the high-dose test solution (T_H). Then dilute this solution with Isotonic Sodium Chloride Injection to 1.5 to 2.0 times by volume and use this solution as the low-dose test solution (T_L). Make the concentration ratio of S_H to S_L equal to the ratio of T_H to T_L. When a change in reaction occurs, adjust the concentration of S_H and S_L at the beginning of the next test in set 1. In this case, set the concentration ratio between S_H and S_L and between T_H to T_L the same as the initial concentration ratio.

(5) ***Dose of injection***—Although 0.2 mL of each solution is usually injected, the dose of injection can be determined based from preliminary tests or experiences. Inject the same volume throughout set 1 of tests.

(6) ***Procedure***—Anesthetize the test animals by subcutaneous injection (s.c.) of 0.7 mL of ethyl carbamate solution (1 in 4) per 100 g of body weight, insert the cannula into the trachea for artificial respiration (respiratory rate: approximately 60 breaths per minute), remove a part of the second cervical vertebra to sever the spinal cord, and destroy the brainstem through the foramen magnum. Insert cannula filled with Isotonic Sodium Chloride Injection into the femoral vein. Through this cannula, inject the solution prepared by dissolving 200 heparin units of heparin sodium in 0.1 mL of Isotonic Sodium Chloride Injection per 100 g of body weight and then immediately inject 0.3 mL of Isotonic Sodium Chloride Injection. Insert a cannula into a carotid artery and connect the cannula to a manometer for blood pressure measurement with vinyl tube. The artery cannula and the vinyl tube have previously been filled with Isotonic Sodium Chloride Injection. Inject the standard and the test solutions at regular intervals of 10 to 15 minutes into the femoral vein through the cannula when the blood pressure increased caused by each solution returns to the original level. Measure the height of blood pressure increases within 1 mmHg on the kymogram. Maintain a constant temperature between 20 and 25 ℃ during the assay. In addition, make four pairs from S_H, S_L, T_H, T_L as follows. Randomize the order of injection for pairs, but keep the order of injection within pairs as indicated.

Pair 1 S_H, T_L, Pair 2 S_L, T_H,
Pair 3 T_H, S_L, Pair 4 T_L, S_H

Perform the test by creating four pairs for set 1 using the same test animal; however, it can also be conducted with set 2. If necessary, however, use the different animals for each set of tests.

(7) ***Calculation***—Set the differences in blood pressure caused by high and low doses in each of Pair 1, 2, 3 and 4 as y_1, y_2, y_3 and y_4, respectively. Add y_1, y_2, y_3 and y_4 for each set to obtain Y_1, Y_2, Y_3 and Y_4.

Number of units in each mL of Vasopressin Injection = anti log M × (Number of units in each mL of the high-dose standard solution)× $\frac{b}{a}$

$$M = \frac{IY_a}{Y_b}$$

$$I = \log \frac{S_H}{S_L} = \log \frac{T_H}{T_L}$$

$$Y_a = - Y_1 + Y_2 + Y_3 - Y_4$$
$$Y_b = Y_1 + Y_2 + Y_3 + Y_4$$

a: Volume (mL) of sample taken
b: Total volume (mL) when diluted with an isotonic sodium chloride injection to create a high-dose test solution from the volume of sample taken

However, when calculating L (p = 0.95) using the following equation, L is NMT 0.15. If this value is exceeded, increase the number of test sets until it falls below this value, or adjust the experimental conditions, and then repeat the test.

$$L = 2\sqrt{(C-1)(CM^2 + I^2)}$$
$$C = \frac{Y_b^2}{Y_b^2 - 4fs^2t^2}$$

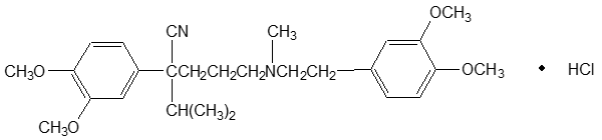
f = Number of the test set
$s^2 = \sum y^2 - \frac{Y}{f} - \frac{Y'}{4} + \frac{Y_b^2 4f}{n}$

$\sum y^2$: Sum of the squares of y_1, y_2, y_3, and y_4 for each set
$Y = Y_1^2 + Y_2^2 + Y_3^2 + Y_4^2$
Y': Square of the sum of y_1, y_2, y_3, and y_4 for set 1, summed across all sets.
$n = 3(f\text{-}1)$
t^2: Values in the table in the Assay under Insulin Injection for n when s^2 calculated.

Packaging and storage Preserve in hermetic containers in a cold place, avoiding freezing.

Expiration date 36 months after preparation.

Verapamil Hydrochloride
베라파밀염산염



Iproveratril Hydrochloride $C_{27}H_{38}N_2O_4 \cdot HCl$: 491.06
2-(3,4-Dimethoxyphenyl)-5-[2-(3,4-dimethoxyphenyl)ethyl-methylamino]-2-propan-2-yl-pentanenitrile hydrochloride [*152-11-4*]

Verapamil Hydrochloride, when dried, contains NLT 98.5% and NMT 101.0% of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$).

Description Verapamil Hydrochloride occurs as a white crystalline powder and it is odorless.
It is freely soluble in methanol, acetic acid(100) or chlo-

roform, soluble in ethanol(95) or acetic anhydride, sparingly soluble in water, and practically insoluble in ether.

Identification (1) Add 5 drops of Reinecke Salt TS to 2 mL of an aqueous solution of Verapamil Hydrochloride (1 in 50); a pale red precipitate is formed.

(2) Determine the absorption spectra of solutions of Verapamil Hydrochloride and verapamil hydrochloride RS in 0.01 mol/L hydrochloric acid TS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Verapamil Hydrochloride and verapamil hydrochloride RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(4) An aqueous solution of Verapamil Hydrochloride (1 in 50) responds to the Qualitative Analysis for chloride.

Melting point Between 141 and 145 ℃.

pH Weigh 1.0 g of Verapamil Hydrochloride and dissolve in 20 mL of freshly boiled and cooled water by warming, and allow to cool; the pH of this solution is between 4.5 and 6.5.

Purity (1) ***Clarity and color of solution***—Add 1.0 g of Verapamil Hydrochloride in 20 mL of water to dissolve by warming; the solution is clear and colorless.

(2) ***Heavy metals***—Proceed with 1.0 g of Verapamil Hydrochloride according to Method 2 under the Heavy Metals and perform the test. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Arsenic***—Proceed with 1.0 g of Verapamil Hydrochloride according to Method 3 and perform the test (NMT 2 ppm).

(4) ***Related substances***—Weigh 0.50 g of Verapamil Hydrochloride and dissolve in 10 mL of chloroform. Use this solution as the test solution. Pipet 1 mL of the test solution, and add chloroform to make exactly 100 mL. Use this solution as the standard stock solution. Pipet 5 mL of the standard stock solution, and add chloroform to make exactly 100 mL. Use this solution as the standard solution (1). Separately, pipet 5 mL of the standard stock solution, and add chloroform to make exactly 50 mL. Use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution, standard solution (1), and standard solution (2) on 2 plates of silica gel for thin-layer chromatography. Develop one of the 2 plates with a mixture of cyclohexane and diethylamine (17 : 3) (as the developing solvent) to a distance of about 15 cm, air-dry the plate, then dry at 110 ℃ for 1 hour, and allow to cool. Spray evenly iron(III) chloride-iodine TS on that plate and examine it immediately; the three intense spots, other than the principal spot and the spot of the origin spot from the test solution, are not more intense than the spots obtained from the standard solution (2). Additionally, other spots are not more intense than the spots from the standard solution (1). Perform the test with the remaining 1 plate in the same manner specified above, using a mixture of toluene, methanol, acetone and acetic acid(100) (14 : 4 : 1 : 1) (as the developing solvent).

Loss on drying NMT 1.0% (1 g, 105 ℃, 2 hours).

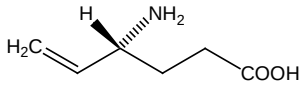
Residue on Ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.7 g of Verapamil Hydrochloride, previously dried, dissolve it in 50 mL of a mixture of acetic anhydride and acetic acid(100) (7 : 3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 49.11 mg of $C_{27}H_{38}N_2O_4 \cdot HCl$

Packaging and storage Preserve in light-resistant, well-closed containers.

Vigabatrin
비가바트린



and enantiomer

$C_6H_{11}NO_2$: 129.16

4-Aminohex-5-enoic acid [*68506-86-5*]

Vigabatrin contains NLT 98.0% and NMT 102.0% of vigabatrin ($C_6H_{11}NO_2$), calculated on the anhydrous basis.

Description Vigabatrin occurs as a white powder.
It is very soluble in water.

Identification (1) Determine the infrared spectra of Vigabatrin and vigabatrin RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay.

Optical rotation $[\alpha]_D^{20}$: Between -0.5° and +0.5° (2 g, water, 10 mL, 100 mm).

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Vigabatrin according to Method 2 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Ethanol***—Weigh accurately 0.5 g of Vigabatrin, transfer to a 5-mL head space vial, dissolve in 10 mL of 0.0025 w/v% toluene solution (internal standard solution), close tightly with a stopper, and heat at 60 ℃ for 30 minutes. Use this solution as the test solution. Separately, prepare a solution containing 0.025 w/v% ethanol and 0.0025 w/v% toluene in water, and use this solution as the standard solution. Use water as the blank test solution. Perform the test with 10 μL each of the blank test solution, the test solution, and the standard solution according to the following conditions using a headspace sample injector as directed under the Gas Chromatography and calculate ratios of the peak area of ethanol to the peak area of the internal standard from each solution, respectively; the amount of ethanol is NMT 0.6%.

Operating conditions

Detector: A flame ionization detector (FID)

Column: A glass column about 0.25 mm in internal diameter and about 30 m in length, packed with 5% phenylmethylsilicone polymer for gas chromatograph y (5 μm in particle diameter).

Carrier gas: Helium

Sample injection port temperature: 200 ℃

Detector temperature: 250 ℃

Column temperature: Maintain at 35 ℃ for the first 12 minutes and increase at a speed of 10 ℃ per min up to 175 ℃.

Split ratio: About 100 : 1.

(3) ***Related substances***—The total amount of related substances calculated form the two methods is NMT 0.5%.

(i) Dissolve 0.4 g of Vigabatrin in the mobile phase to make exactly 100 mL and use this solution as the test solution. Separately, dissolve 4.0 mg of 3-aminopent-4-en-1,1-dicarboxylic acid RS in the mobile phase to make exactly 100 mL, add the mobile phase to 5.0 mL of this solution to make exactly 50 mL, and use this solution as the standard solution (1). Dissolve 4.0 mg of 5-vinyl-2-pyrrolidinone RS in the mobile phase to make exactly 100 mL, add the mobile phase to 5.0 mL of this solution to make exactly 50 mL, and use this solution as the standard solution (2). Dissolve 4.0 mg of (*E*)-4-amino-2-ethylidene-butyrate RS in the mobile phase to make exactly 100 mL, add the mobile phase to 5.0 mL of this solution to make exactly 50 mL, and use this solution as the standard solution (3). Dissolve 2.0 mg of 5-vinyl-2-pyrrolidinone RS and 0.40 g of vigabatrin RS in the mobile phase to make exactly 100 mL and use this solution as the standard solution (4). Perform the test with 20 μL each of the test solution, the standard solution (1), the standard solution (2), and the standard solution (3) as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of each solution by the automatic integration method. The peak areas of 5-vinyl-2-pyrrolidinone and (*E*)-4-amino-2-ethylidene-butyrate obtained from the test solution are not greater than the peak area from each of the standard solution (2) and the standard solution (3) (each NMT 0.1%). The peak area of each of related substances is not greater than the peak area from the standard solution (1) (NMT 0.1%). Calculate the amount of 5-vinyl-2-pyrrolidinone and (*E*)-4-amino-2-ethylidene-butyrate of Vigabatrin from the peak areas of the major peak from the standard solution (2) and the standard solution (3), calculate the amount of related substances from 0.1% of the major peak area of the standard solution (1), and calculate the total amount of related substances.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: Use by connecting column 1 and column 2.

Column 1: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with hexyl silyl silica gel for liquid chromatography (5 μm in particle diameter).

Column 2: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with cation exchange resin for liquid chromatography (10 μm in particle diameter).

Mobile phase: A mixture of water, acetonitrile and phosphate buffer (950 : 25 : 25).

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 20 μL of the standard solution (4) according to the above conditions; 5-vinyl-2-pyrrolidinone and vigabatrin are eluted in this order with the resolution between these peaks being NLT 1.5.

Time span of measurement: About twice the retention time of the major peak obtained from the test solution.

Phosphate buffer—Dissolve 58.5 g of sodium dihydrogen phosphate monohydrate in water, add 23 mL of phosphoric acid, and add water to make 1000 mL.

(2) Dissolve 20.0 mg of Vigabatrin in water to make exactly 10 mL. To 1.0 mL of this solution, add 2 mL of a solution, prepared by dissolving 7.7 g of boric acid in water, adjusting the pH to 7.7 with 50% sodium hydroxide and adding water to make 250 mL, and mix. To this solution, add 3 mL of a solution of 0.16 w/v% 9-fluorenylmethyl chloroformate in acetone and 3 mL of ethyl acetate, shake strongly for a few seconds, and use the separated bottom layer as the test solution within 8 hours. Separately, dissolve 2.0 mg of 4-aminobutyric acid and 0.20 g of Vigabatrin in water to make 100 mL. Take 1.0 mL of this solution and proceed in the same manner as in the preparation of the above solution, and use this solution as the standard solution. Perform the test with 25 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area of 4-aminobutyric acid for each solution by the automatic integration method and calculate the amount of 4-aminobutyric acid; it is NMT 0.2%.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 263 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with phenyl silica gel for liquid chromatography (5 μm in particle diameter).

Mobile phase: A mixture of acetate buffer and acetonitrile (75 : 25).

Flow rate: 1.0 mL/min

System suitability

System performance: Proceed with 25 μL of the standard solution according to the above conditions; 9-fluorenylmethanol, 4-aminobutyric acid and vigabatrin are eluted in this order with the retention time of each being about 6 minutes, about 9 minutes, and about 14 minutes, respectively, and the resolution between the peak of each of the derivative from 4-aminobutyric acid and 9-fluorenylmethanol being NLT 2.0.

Acetate buffer—Dissolve 8.2 g of sodium acetate anhydride in water, adjust the pH to 4.2 with acetic acid(100), and add water to make 2000 mL.

Water NMT 0.5% (0.3 g, purified methanol, 50 mL, volumetric titration, direct titration).

Assay Weigh accurately about 0.2 g each of Vigabatrin and vigabatrin RS, dissolve in water to make 100 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with 20 μL of these solutions as directed under the Liquid Chromatography according to the following conditions and determine the peak areas of vigabatrin, A_T, and A_S, respectively, from each solution.

$$\text{Amount (mg) of vigabatrin } (C_6H_{11}NO_2) = \text{Amount (mg) of vigabatrin RS} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 25 cm in length, packed with cation exchange resin for liquid chromatography (10 μm in particle diameter).

Mobile phase: A mixture of phosphate buffer solution, methanol and acetonitrile (1000 : 40 : 4).

Flow rate: 1.5 mL/min

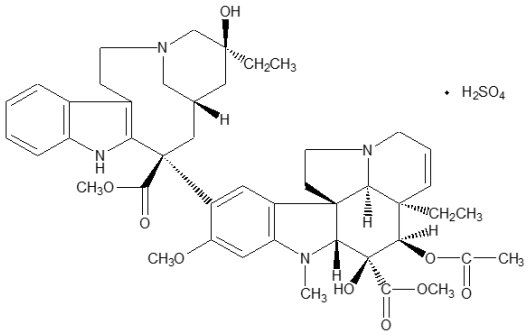
System suitability

System performance: dissolve 2.0 mg of 5-vinyl-2-pyrrolidinon RS and 0.2 g of vigabatrin RS in water to make 100 mL, proceed with 20 μL of this solution according to the above conditions; 5-vinyl-2-pyrrolidinon and vigabatrin are eluted in this order with the resolution between these peaks being NLT 1.5.

Phosphate buffer—Weigh 3.4 g of potassium dihydrogen phosphate, dissolve in water to make 1000 mL, and adjust the pH to 2.8 with phosphoric acid.

Packaging and storage Preserve in well-closed containers.

Vinblastine Sulfate
빈블라스틴황산염



$C_{46}H_{58}N_4O_9 \cdot H_2SO_4$: 909.05

Methyl (3a*R*,4*R*,5*S*,5a*R*,10b*R*,13a*R*)-4-acetyloxy-3a-ethyl-9-[(5*S*,7*S*,9*S*)-5-ethyl-5-hydroxy-9-methoxycarbonyl-1,4,5,6,7,8,9,10-octahydro-3,7-methano-3-azacycloundecino[5,4-*b*]indol-9-yl]-5-hydroxy-8-methoxy-6-methyl-3a,4,5,5a,6,11,12,13a-octahydro-1*H*-indolizino[8,1-*cd*]carbazole-5-carboxylate monosulfate [*143-67-9*]

Vinblastine Sulfate contains NLT 96.0% and NMT 102.0% of vinblastine sulfate ($C_{46}H_{58}N_4O_9 \cdot H_2SO_4$), calculated on the dried basis.

Description Vinblastine Sulfate occurs as a white to pale yellow powder.
It is soluble in water, sparingly soluble in methanol and practically insoluble in ethanol(95) or ether.
It is hygroscopic.

Identification (1) Determine the absorption spectra of the aqueous solutions of Vinblastine Sulfate and vinblastine sulfate RS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the absorption spectra of Vinblastine Sulfate and vinblastine sulfate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both exhibit similar intensities of absorption at the same wavenumbers.

(3) An aqueous solution of Vinblastine Sulfate (1 in 100) responds to the Qualitative Analysis for sulfate.

Optical rotation $[\alpha]_D^{20}$: Between -28° and -35° (20 mg calculated on the dried basis, methanol, 10 mL, 100 mm).

pH Dissolve 15 mg of Vinblastine Sulfate in 10 mL of water; the pH of this solution is between 3.5 and 5.0.

Purity (1) ***Clarity and color of solution***—Dissolve 50

mg of Vincristine Sulfate in 10 mL of water; the solution is clear and colorless.

(2) ***Related substances***—Dissolve 10 mg of Vinblastine Sulfate in 10 drug mL of water and use this solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 200 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area from each of the solutions according to the automatic integration method; the peak area of individual peaks other than the major peak from the test solution is not greater than 1/4 the peak area of vinblastine from the standard solution. The sum of areas of all peaks other than the major peak from the test solution is not greater than 3/ 4 of the peak area of vinblastine from the standard solution.

Operating conditions

For the detector, column, column temperature, mobile phase and flow rate, proceed as directed in the operating conditions under the Assay.

System suitability

System performance: Proceed as directed under the system suitability under the Assay.

Test for required detectability: Pipet 2.5 mL of the standard solution and add water to make exactly 100 mL. Proceed with 200 μL of this solution according to the conditions; the peak area of vinblastine is 1.7% to 3.3% of the peak area of vinblastine from the standard solution.

System repeatability: Repeat the test 6 times with 200 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of vinblastine is NMT 1.5%.

Time span of measurement: About 4 times the retention time of vinblastine after the solvent peak.

Loss on drying Perform the test according to the following conditions as directed according to Method 2 under the Thermal Analysis; it is NMT 15.0%.

Operating conditions

Heating rate: 5 ℃ per minute.

Measured temperature range: Room temperature to 200 ℃.

Atmosphere gas: Dried nitrogen

Flow rate of atmosphere gas: 40 mL per minute.

Sterility It meets the requirements when used in sterile preparations.

Bacterial endotoxins Less than 10.0 EU/mg per mg when used in a manufacturing of sterile preparations.

Assay Weigh accurately about 10 mg each of Vinblastine Sulfate and vinblastine sulfate RS (determine the loss on drying in the same manner as vincristine sulfate in advance), dissolve in water to make exactly 10 mL, and use these solutions as the test solution and the standard solution, respectively. Perform the test with exactly 20 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions and determine the peak areas, A_T and A_S, of vinblastine.

Amount (mg) of vinblastine sulfate ($C_{46}H_{58}N_4O_9 \cdot H_2SO_4$) = Amount (mg) of vinblastine sulfate RS, calculated on the dried basis $\times \frac{A_T}{A_S}$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 262 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: To 7 mL of diethylamine, add water to make 500 mL and adjust the pH to 7.5 by adding phosphoric acid. To 380 mL of this solution, add 620 mL of a mixture of methanol and acetonitrile (4 : 1).

Flow rate: Adjust the flow rate so that the retention time of vinblastine is about 8 minutes.

System suitability

System performance: Dissolve 10 mg each of Vinblastine Sulfate and vincristine sulfate in 25 mL of water. Proceed with 20 μL of this solution according to the above conditions; vincristine and vinblastine are eluted in this order with the resolution being NLT 4.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of vinblastine is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers at NMT -20 ℃.

Vinblastine Sulfate for Injection
주사용 빈블라스틴황산염

When dried, Vinblastine Sulfate for Injection contains NLT 90.0% and NMT 110.0% of the labeled amount of vinblastine sulfate (C46H58N4O9·H2SO4: 909.05).

Method of preparation Prepare as directed under Injections, with Vinblastine Sulfate.

Description Vinblastine Sulfate for Injection occurs as a white to pale yellow solid mass or a powder.
It is freely soluble in water.
The pH of its aqueous solution (1 in 1000) is 3.5 to 5.0.

Identification Perform the test as directed under the Identification (1) of Vinblastine Sulfate.

Purity ***Related substances***—Dissolve 4 mg of Vinblastine Sulfate for Injection in 10 mL of water, and use this

solution as the test solution. Pipet 1 mL of this solution, add water to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 200 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area from each of the solutions by the automatic integration method; the peak area of individual peaks other than the major peak from the test solution is not greater than 1/2 the peak area of vinblastine from the standard solution. And the total area of any peaks other than the major peak from the test solution is not larger than 2 times the peak area of vinblastine from the standard solution.

Operating conditions

Proceed as directed under the operating conditions under the Purity (2) of Vinblastine Sulfate.

System suitability

Proceed as directed under the system suitability under the Purity (2) of Vinblastine Sulfate.

Sterility Meets the requirements.

Bacterial endotoxins Less than 10 EU per mg of Vinblastine Sulfate for Injection

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Uniformity of dosage units It meets the requirements when the procedure for content uniformity is performed according to the following procedure.

Take 1 container of Vinblastine Sulfate for Injection, dissolve in water to make *V* mL of a solution containing about 0.4 mg of vinblastine sulfate ($C_{46}H_{58}N_4O_9 \cdot H_2SO_4$) according to the labeled amount per mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of Vinblastine Sulfate RS (previously determine the loss on drying in the same manner as Vinblastine Sulfate), dissolve in water to make exactly 25 mL, and use this solution as the standard solution. Proceed as directed under the Asay under Vinblastine Sulfate.

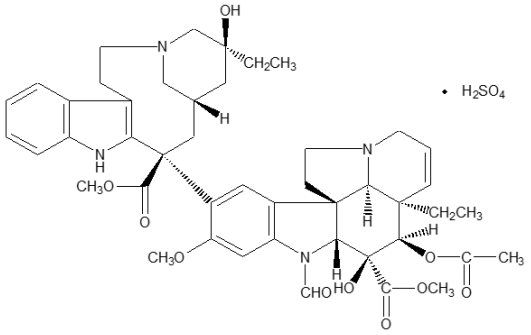
Amount (mg) of vinblasine sulfate ($C_{46}H_{58}N_4O_9 \cdot H_2SO_4$) = Amount (mg) of vinblastine sulfate RS, calculated on the dried basis $\times \frac{A_T}{A_S} \times \frac{25}{V}$

Assay Take a number of Vinblastine Sulfate for Injection, equivalent to 0.10 g of vinblastine sulfate ($C_{46}H_{58}N_4O_9 \cdot H_2SO_4$), dissolve each content in water, and transfer to a 100-mL volumetric flask. Wash each container with water, transfer the washings into the volumetric flask, and add water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately about 10 mg of Vinblastine Sulfate RS (previously determine the loss on drying in the same manner as Vinblastine Sulfate), dissolve in water to make exactly 25 mL, and use this solution as the standard solution. Proceed as directed under the Asay under Vinblastine Sulfate.

Amount (mg) of vinblastine sulfate ($C_{46}H_{58}N_4O_9 \cdot H_2SO_4$) = Amount (mg) of vinblastine sulfate RS, calculated on the dried basis $\times \frac{A_T}{A_S} \times 10$

Packaging and storage Preserve in light-resistant, hermetic containers in a cold place.

Vincristine Sulfate
빈크리스틴황산염



$C_{46}H_{56}N_4O_{10} \cdot H_2SO_4$: 923.04

Methyl (3a*R*,4*R*,5*S*,5a*R*,10b*R*,13a*R*)-4-acetyloxy-3a-ethyl-9-[(5*S*,7*S*,9*S*)-5-ethyl-5-hydroxy-9-methoxycarbonyl-1,4,5,6,7,8,9,10-octahydro-3,7-methano-3-azacycloundecino[5,4-*b*]indol-9-yl]-6-formyl-5-hydroxy-8-methoxy-3a,4,5,5a,6,11,12,13a-octahydro-1*H*-indolizino[8,1-*cd*]carbazole-5-carboxylate monosulfate [*2068-78-2*]

Vincristine Sulfate contains NLT 95.0% and NMT 105.0% of vincristine sulfate ($C_{46}H_{56}N_4O_{10} \cdot H_2SO_4$), calculated on the dried basis.

Description Vincristine Sulfate occurs as a white to pale yellowish white powder.

It is very soluble in water and practically insoluble in ethanol(95).

It is hygroscopic.

Optical rotation $[\alpha]_D^{20}$: Between +28.5° and +35.5° (0.2 g, calculated on the dried basis, water, 10 mL, 100 mm).

Identification (1) Determine the absorption spectra of aqueous solutions of Vincristine Sulfate and vincristine sulfate RS (1 in 50000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the absorption spectra of Vincristine Sulfate and vincristine sulfate RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of ab-

sorption at the same wavenumbers.

(3) An aqueous solution of Vincristine Sulfate (1 in 100) responds to the Qualitative Analysis for sulfate.

pH Dissolve 10 mg of Vincristine Sulfate in 10 mL of water; the pH of this solution is between 3.5 and 4.5.

Purity (1) ***Clarity and color of solution***—Dissolve 50 mg of Vincristine Sulfate in 10 mL of water; the solution is clear and colorless.

(2) ***Related substances***—Dissolve 10 mg of Vincristine Sulfate in 10 mL of water and use this solution as the test solution. Pipet 2 mL of this solution, add water to make exactly 50 mL, and use this solution as the standard solution. Perform the test with 200 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of these solutions each according to the automatic integration method; the peak area of desacetylvincristine with a relative retention time of about 0.9 to that of vincristine and the peak area of vinblastine with a relative retention time of about 1.6 from the test solution is not greater than 1/8 and 3/20 of vincristine peak area from the standard solution, respectively. The sum of peak areas other than vincristine, desacetylvincristine and vinblastine from the test solution is not greater than 1/4 of the peak area of vincristine from the standard solution. In addition, the sum of peak areas other than vincristine from the test solution is not greater than that of vincristine from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 297 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Mobile phase A: Methanol

Mobile phase B: To a mixture of water and diethylamine (197 : 3), add phosphoric acid to adjust the pH to 7.5.

Rosin of the mobile phase: Control the mixing ratio of mobile phase A and mobile phase B via the gradient elution as follows.

Time (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 - 12	62	38
12 - 27	62 → 92	38 → 8

Flow rate: Adjust the flow rate so that the retention time of vincristine is about 15 minutes.

System suitability

Test for required detectability: Pipet 5 mL of the standard solution and add water to make exactly 200 mL. Confirm that the peak area of vincristine obtained from 200 μL of this solution is equivalent to 1.75% to 3.25% of the peak area of vincristine from the standard solution.

System performance: Dissolve 15 mg each of Vincristine Sulfate and vinblastine sulfate in 100 mL of water. Proceed with 200 μL of this solution according to the above conditions; vincristine and vinblastine are eluted in this order with the resolution being NLT 4.

System repeatability: Repeat the test 6 times with 200 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of vincristine is NMT 1.5%.

Time span of measurement: About 1.7 times the retention time of vincristine after the solvent peak.

Loss on drying Perform the test with about 10 mg of Vincristine Sulfate as directed in Method 2 under the Thermal Analysis according to the following conditions; it is NMT 12.0%.

Operating conditions

Heating rate: 5 ℃ per minute.

Measured temperature range: Room temperature to 200 °C.

Atmosphere gas: Dried nitrogen

Flow rate of atmosphere gas: 40 mL per minute.

Assay Weigh accurately about 10 mg each of Vincristine Sulfate and vincristine sulfate RS (determine the loss on drying in the same manner as vincristine sulfate beforehand), dissolve each in water to make exactly 10 mL, and use these solutions as the test solution and the standard solution, respectively. Pipet 10 μL each of these solutions, perform the test as directed under the Liquid Chromatography according to the following conditions, and calculate the peak areas, A_T and A_S, of vincristine.

$$\text{Amount (mg) of vincristine sulfate } (C_{46}H_{56}N_4O_{10}\cdot H_2SO_4) = \text{Amount (mg) of vinblastine sulfate RS, calculated on the dried basis} \times \frac{A_T}{A_S}$$

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 297 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: To a mixture of water and diethylamine (59 : 1), add phosphoric acid to adjust the pH to 7.5. Add 700 mL of methanol to 300 mL of this solution.

Flow rate: Adjust the flow rate so that the retention time of vinblastine is about 7 minutes.

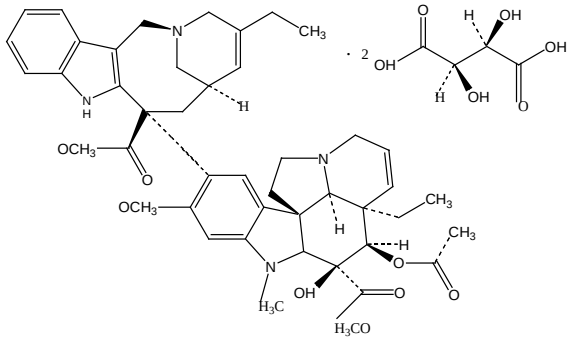
System suitability

System performance: Dissolve 5 mg each of Vincristine Sulfate and vinblastine sulfate in 5 mL of water. Proceed with 10 μL of this solution according to the above conditions; vincristine and vinblastine are eluted in this order with the resolution being NLT 4.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area of vincristine is NMT 1.0%.

Packaging and storage Preserve in light-resistant, tight containers at below -20 ℃.

Vinorelbine Tartrate
비노렐빈타르타르산염



$C_{45}H_{54}N_4O_8 \cdot 2C_4H_6O_6$: 1079.11

Methyl (1*R*,9*R*,10*R*,11*R*,12*R*,19*R*)-11-(acetyloxy)-12-ethyl-4-[(12S,14R)-16-ethyl-12-(methoxycarbonyl)-1,10-diazatetracyclo[12.3.1.03,11.04,9]octadeca-3(11),4,6,8,15-pentaen-12-yl]-10-hydroxy-5-methoxy-8-methyl-8,16-diazapentacyclo[10.6.1.0^{1,9}.02,7.016,19]nonadeca-2,4,6,13-tetraene-10-carboxylate bis[(2R,3R)-2,3-dihydroxybutanedioate] [*125317-39-7*]

Vinorelbine Tartrate contains NLT 98.0% and NMT 102.0% of vinorelbine tartrate ($C_{45}H_{54}N_4O_8 \cdot 2C_4H_6O_6$), calculated on the anhydrous basis.

Description Vinorelbine Tartrate occurs as a white to yellow or bright brown amorphous powder.
It is freely soluble in water.

Identification (1) Dissolve 50 mg of Vinorelbine Tartrate in 1 mL of water. To 0.1 mL of this solution, add 0.1 mL of 10 w/v% potassium bromide solution, 0.1 mL of 2 w/v% resorcinol solution, and 3 mL of sulfuric acid. Heat on a steam bath for 5 to 10 minutes until a deep blue color develops. Allow to cool and pour the solution into the water; the color of the solution changes to red.

(2) Dissolve 10 mg each of Vinorelbine Tartrate and vinorelbine tartrate RS in 5 mL of water, add 0.5 mL of 5 mol/L sodium hydroxide TS, and extract with 5 mL of methylene chloride. Filter the organic layer through anhydrous sodium sulfate and evaporate the filtrate to make about 0.5 mL. Use these solutions as the test solution and the standard solution. Determine the infrared spectra of these solutions as directed in the potassium bromide disk method under Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(3) The retention time of the major peak from the test solution for related substances under the Purity is identical to the retention time of the major peak from the standard solution (2).

pH Dissolve 0.5 g of Vinorelbine Tartrate in 50 mL of water; the pH of this solution is between 3.3 and 3.8.

Purity (1) ***Clarity and color of solution***—Dissolve 0.1 g of Vinorelbine Tartrate in 10 mL of water: the solution is clear. Determine the absorbance at the wavelength of 420 nm of this solution as directed under Ultraviolet-visible Spectroscopy using water as the control solution; its absorption is NMT 0.03.

(2) ***Related substances*** —Weigh exactly 35 mg of Vinorelbine Tartrate, dissolve it in a mobile phase to make exactly 25 mL, and use this solution as the test solution. Separately, weigh exactly 35 mg of Vinorelbine Tartrate, dissolve in the mobile phase to make exactly 25 mL, and use this solution as the standard solution (1). Add the mobile phase to 1.0 mL of the standard solution to make exactly 50 mL and then add the mobile phase to 1.0 mL of this mixture to make exactly 100 mL. Use this solution as the standard solution (2). Perform the test with 20 μL each of the test solution and standard solution under the following conditions as directed under the Liquid Chromatography, and determine the peak areas in each solution by the automatic integration method; The amount of photodegradation products obtained from the test solution is NMT 0.3%, and the amount of any of each individual related substance or co-eluted related substance is NMT 0.2%. Additionally, the total amount of related substances, excluding the photodegradation product, is NMT 0.7%. Exclude any peaks whose area is NMT 0.5 times the area of the peak of vinorelbine obtained from the standard solution (2).

$$\text{Content (\%) of each related substance} = 100 \times \frac{A_i}{A_S}$$

A_i: Area of each peak from the test solution
A_S: Sum of areas of all peaks from the test solution

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 267 nm).

Column: A stainless steel column about 3.9 mm in internal diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μ*m* in particle diameter).

Column temperature: A constant temperature of about 40 °C.

Flow rate: 1.0 mL/min

Mobile phase: Dissolve 1.22 g of sodium 1-decanesulfonate in 620 mL of methanol, and add 380 mL of phosphate buffer to mix.

System suitability

System performance: Dissolve an appropriate amount of vinorelbine tartrate RS and vinorelbine-related substance I (4-O-deacetylvinorelbine) RS in water to prepare solutions containing 1.4 mg and 0.01 mg per mL respectively. Expose this solution to an appropriate xenon

lamp capable of emitting a dose of 1600 KJ/m2 in the range of 310 nm to 800 nm with an intensity of 500 W/m² for 1 hour to obtain an additional photodegradation product (3',4',7,8-tetradehydro-3,4'-dideoxy3,6-epoxy-6,7-dihydro-C'-norvincaleukoblastine) with a relative retention time of approximately 0.8. Proceed with 20 μL of this solution under the above conditions; the retention time of vinorelbine is 13.5 minutes, the relative retention time of photodegradation product with respect to the retention time of vinorelbine is about 0.8, and the relative retention time of vinorelbine-related substance I is 1.2. Additionally, the resolution factor between vinorelbine tartrate and vinorelbine-related substance I is NLT 1.1.

Time span of measurement: About 3 times the retention time of vinorelbine.

Phosphate buffer—Dissolve 6.9 g of sodium dihydrogen phosphate monohydrate in 900 mL of water, adjust with phosphoric acid to a pH of 4.2, and add water to make 1000 mL.

Water NMT 4.0% (1 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Dissolve about 0.35 g of Vinorelbine Tartrate, accurately weighed, in 40 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration, Endpoint Detection Method in Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 53.96 mg of $C_{45}H_{54}N_4O_8 \cdot 2C_4H_6O$

Packaging and storage Preserve in light-resistant, tight containers. Store in a freezer.

Vitamin A Oil
비타민A유

Retinol Oil

Vitamin A Oil is synthetic vitamin A ester diluted in vegetable oil.

Each gram of Vitamin A Oil contains NLT 30000 unit of Vitamin A.

Vitamin A Oil may contain appropriate antioxidants.

Vitamin A Oil contains NLT 90.0% and NMT 120.0% of the labeled units of vitamin A.

Description Vitamin A Oil occurs as a clear, yellow to yellowish brown or slightly turbid latex. It is odorless or has a characteristic odor.
Decomposition of Vitamin A Oil is accelerated by air or light.

Identification Weigh an amount, equivalent to 15000 unit of Vitamin A Oil, retinol acetate RS, and retinol palmitate RS, respectively, dissolve in 5 mL of petroleum ether, and use these solutions as the test solution, the standard solution (1), and the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot each 5 μL each of the test solution, the standard solution (1), and the standard solution (2) on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of cyclohexane and ether (12 : 1) as the developing solvent to a distance of about 10 cm, and air-dry the plate. Spray evenly a solution of antimony(III) chloride TS; the color and the R_f value of the major peak obtained from the test solution is equal to the blue major peak from the standard solution (1) or (2).

Purity (1) ***Acidity***—To 1.2 g of Vitamin A Oil, add 30 mL of a mixture of neutralized ethanol and ether (1 : 1), attach the reflux condenser, boil with mild heat for 10 minutes, and dissolve. Cool it down, add 5 drops of phenolphthalein TS and 0.60 mL of 0.1 mol/L sodium hydroxide; the resulting solution exhibits a red color.

(2) ***Rancidity***—No unpleasant odor of rancid oil is perceptible when warming Vitamin A Oil.

(3) ***Related substances***—Vitamin A Oil meets the requirements for the conditions that can be determined according to Method 1 under the assay of Vitamin A. The *f* value is NLT 0.85 when quantified.

Assay Perform the test according the Assay of Vitamin A.

Packaging and storage Preserve in light-resistant, tight containers. The reservoir must be almost filled with vitamin A or under nitrogen gas.

Vitamin A Oil Capsules
비타민A유 캡슐

Vitamin A Capsules

Vitamin A Oil Capsules contain NLT 90.0% and NMT 130.0% of the labeled unit of vitamin A.

Method of preparation Prepare as directed under Capsules, with Vitamin A Oil.

Description Extract the contents of Vitamin A Oil Capsules and perform the test with the contents; it meets the requirements of the Description of Vitamin A Oil.

Identification Extract the contents of Vitamin A Oil Capsules and perform the test with the contents as directed under the Identification of Vitamin A Oil; it meets the requirements

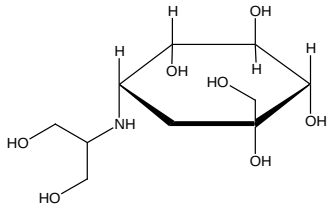
Disintegration Meets the requirements.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of about 20 capsules of Vitamin A Oil Capsules, cut the capsules, take oil contents, and mix well. Perform the test with this oil contents as directed under the Vitamin A Assay. Wash the capsules with a small amount of ether, allow to stand at room temperature to evaporate the ether and weigh accurately. Calculate the weight of Vitamin A Oil from the difference between the weights before and after the above-described procedure. Calculate the Vitamin A units per 1 capsule from the weight and the Vitamin A units of the oil.

Packaging and storage Preserve in light-resistant, well-closed containers.

Voglibose
보글리보스



$C_{10}H_{21}NO_7$: 267.28

(1*S*,2*S*,3*R*,4*S*,5*S*)-5-(1,3-dihydroxypropan-2-yl-amino)-1-(hydroxymethyl)cyclohexane-1,2,3,4-tetrol [*83480-29-9*]

Voglibose contains NLT 99.5% and NMT 101.0% of voglibose ($C_{10}H_{21}NO_7$), calculated on the anhydrous basis.

Description Voglibose occurs as white crystals or a crystalline powder.
It is very soluble in water, freely soluble in acetic acid(100), slightly soluble in methanol and very slightly soluble in ethanol(99.5).
It dissolves in 0.1 mol/L hydrochloric acid TS.

Identification (1) Determine the infrared spectra of Voglibose and voglibose RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Determine the ^1H spectrum of a solution of Voglibose in deuterium oxide for nuclear magnetic resonance spectroscopy (3 in 70) as directed under the Nuclear Magnetic Resonance Spectroscopy, using 3-(trimethyl)-propionic acid-d_4 sodium salt as an internal standard; it exhibits two double signal A at about δ 1.5 ppm, two double signal B at around δ 2.1 ppm, a multiple signal C at about δ 2.9 ppm and a multiple signal D at between δ 3.4 ppm and δ 3.9 ppm. The area intensity ratio of signals A : B : C : D is about 1 : 1 : 1 : 10.

Optical rotation $[\alpha]_D^{20}$: Between +45° and +48° (0.2 g, calculated on the anhydrous basis, 0.1 mol/L hydrochloric acid TS, 20 mL, 100 mm).

Melting point Between 163 and 168 ℃.

pH Dissolve 1.0 g of Voglibose in 10 mL of water; the pH of this solution is between 9.8 and 10.4.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Voglibose as directed under Method 1 and perform the test. Adjust pH of the test solution to between 3.0 and 3.5 with dilute hydrochloric acid instead of dilute acetic acid. Prepare the control solution with 1.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Related substances***—Dissolve 50 mg of Voglibose in 50 mL of the mobile phase, and use this solution as the test solution. Pipet 1.0 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine peak areas of each solution by the automatic integration method; each area of the peaks other than the peak of voglibose obtained from the test solution is not greater than 0.2 times the peak area of voglibose from the standard solution. For the calculation of the peak area for peaks having the retention times with respect to voglibose of about 1.7, 2.0 and 2.3, multiply them by the response factors, 2, 2 and 2.5, respectively.

Operating conditions

Apparatus: Use the pumping systems for transporting the mobile phase and the reaction reagent, sample injection port, column, reaction coil, cooling coil, detector and data collection device. Attach a 3-way tube to the outlet for the mobile phase of the column, connect it to the pumping system for transporting the reaction reagent and the reaction coil, and then connect the outlet of the reaction coil to the fluorometer.

Detector: A fluorometer (excitation wavelength: 350 nm, fluorescence measurement wavelength: 430 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 25 cm in length, packed with penta ethylenehexaaminated polyvinyl alcohol polymer for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Reaction coil: A polytetrafluoroethylene tube about 0.5 mm in internal diameter and about 20 m in length.

Cooling coil: A polytetrafluoroethylene tube about 0.3 mm in internal diameter and about 2 m in length.

Mobile phase: To 1.56 g of sodium dihydrogen phosphate hydrate, add water to make 500 mL. To this solution, add a solution prepared by dissolving 3.58 g of sodium dihydrogen phosphate dodecahydrate in water to make 500 mL, and adjust pH to 6.5. To 370 mL of this solution, add 630 mL of acetonitrile.

Reaction reagent: Dissolve 6.25 g of taurine and 2.56 g of sodium periodate in water to make 1000 mL.

Reaction coil temperature: A constant temperature of about 100 ℃.

Cooling coil temperature: A constant temperature of about 15 ℃.

Flow rate: Adjust the flow rate so that the retention time of voglibose is about 20 minutes.

Flow rate of the reaction reagent: The same as the flow rate of the mobile phase.

System suitability

Test for required detectability: Pipet 10 mL of the standard solution and add the mobile phase to make exactly 100 mL. The peak area obtained from 50 μL of this solution is 7% to 13% of the peak area of voglibose from the standard solution.

System performance: Proceed with 50 μL of the standard solution according to the above conditions; for the peak areas of voglibose, the number of theoretical plate is NLT 7000 and the symmetry factor is between 0.8 and 1.2.

System repeatability: Repeat the test 6 times with 50 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak areas of voglibose is NMT 3.0%.

Time span of measurement: About 2.5 times the retention time of voglibose.

Water NMT 0.2% (0.5 g, coulometric titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.4 g of Voglibose, dissolve in 80 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 26.73 mg of $C_{10}H_{21}NO_7$

Packaging and storage Preserve in tight containers.

Voglibose Tablets
보글리보스 정

Voglibose Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of voglibose ($C_{10}H_{21}NO_7$: 267.28).

Method of preparation Prepare as directed under Tablets, with Voglibose.

Identification Weigh an amount of Voglibose Tablets, previously powdered, equivalent to 5 mg of voglibose according to the labeled amount, add 40 mL of water, shake vigorously to mix, and then centrifuge. Inject the clear supernatant into a glass column about 8 mm in internal diameter and about 130 mm in length, packed with 1.0 mL of strongly acidic ion exchange resin for column chromatography (H type) (100 μm to 200 μm in particle diameter). Elute at the rate of about 5 mL per minute. Next, use 200 mL of water to wash the column, and use 10 mL of dilute ammonia TS (1 in 4) to elute at the rate of about 5 mL per minute. Filter this eluate 2 times through a membrane filter with a pore size of NMT 0.22 μm. Evaporate this filtrate to dryness in vacuum at 50 ℃, dissolve the residue in 0.5 mL of a mixture of water and methanol (1 : 1), and use this solution as the test solution. Separately, dissolve 20 mg of voglibose RS for assay in 2 mL of a mixture of water and methanol (1 : 1), and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 20 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Next, develop the plate with a mixture of acetone, ammonia water(28), and water (5 : 3 : 1) to a distance of about 12 cm, and air-dry the plate. Allow the plate to stand in a stream of iodine vapor; the spots obtained from the test solution and the standard solution exhibit a yellowish brown color and have the same R_f value.

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 20 Voglibose Tablets, add 80 mL of the mobile phase, and mix by shaking to completely collapse. Pipet an amount equivalent to about 4 mg of voglibose ($C_{10}H_{21}NO_7$) according to the labeled amount, add the mobile phase to make exactly 100 mL, and centrifuge. Filter the upper clear liquid through a membrane filter with a pore size of NMT 0.45 μm. Discard the first 1 mL of the filtrate and use the subsequent filtrate as the test solution. Separately, weigh accurately about 20 mg of voglibose RS (previously measure the water content), and dissolve in the mobile phase to make exactly 25 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 50 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak areas of voglibose, A_T and A_S, for the test solution and the standard solution, respectively.

$$\text{Amount (mg) of voglibose } (C_{10}H_{21}NO_7) = W_S \times \frac{A_T}{A_S} \times \frac{V}{500}$$

W_S: Amount (mg) of voglibose RS, calculated on the anhydrous basis.

Operating conditions

Apparatus: Use the pumping systems for transporting the mobile phase and the reaction reagent, sample injection port, column, reaction coil, cooling coil, detector, and data collection device. Attach a 3-way tube to the outlet for the mobile phase of the column, connect it to the pumping system for transporting the reaction reagent and the reaction coil, and then connect the outlet of the

reaction coil to the fluorometer.

Detector: A fluorometer (excitation wavelength: 350 nm, fluorescence measurement wavelength: 430 nm).

Column: A stainless steel column about 4.0 mm in internal diameter and 15 cm in length, packed with aminopropylsilyl silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 ℃.

Reaction coil: A polytetrafluoroethylene tube about 0.5 mm in internal diameter and about 20 m in length.

Cooling coil: A polytetrafluoroethylene tube about 0.3 mm in internal diameter and about 2 m in length.

Mobile phase: To 1.56 g of sodium dihydrogen phosphate hydrate, add water to make 500 mL. To this solution, add a solution prepared by dissolving 3.58 g of sodium hydrogen phosphate decahydrate in water to make 500 mL, and adjust the pH to 6.5. To 300 mL of this solution, add 600 mL of acetonitrile.

Reaction reagent: Dissolve 6.25 g of taurine and 2.56 g of sodium periodate in water to make 1000 mL.

Reaction coil temperature: A constant temperature of about 100 ℃.

Cooling coil temperature: A constant temperature of about 15 ℃.

Flow rate: Adjust the flow rate so that the retention time of voglibose is about 20 minutes.

Flow rate of the reaction reagent: The same as the flow rate of the mobile phase.

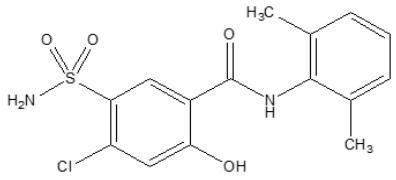
System suitability

System performance: Dissolve 2 mg of voglibose for assay and 0.2 g of lactose hydrate in 5 mL of water, and add the mobile phase to make 50 mL. Proceed with 50 μL of this solution according to the above conditions; lactose and voglibose are eluted in this order with the resolution being NLT 4.0.

System repeatability: Repeat the test 6 times with 50 μL each of the standard solutions according to the above conditions; the relative standard deviation of the peak areas of voglibose is NMT 2.0%.

Packaging and storage Preserve in tight containers.

Xipamide
지파미드



$C_{15}H_{15}ClN_2O_4S$: 354.80

5-(Aminosulfonyl)-4-chloro-*N*-(2,6-dimethylphenyl)-2-hydroxy-benzamide, [*14293-44-8*]

Xipamide contains NLT 98.0% and NMT 102.0% of xipamide ($C_{15}H_{15}ClN_2O_4S$), calculated on the dried basis.

Description Xipamide occurs as a white powder.
It is freely soluble in acetone, soluble in ethanol(95), slightly soluble in chloroform or ether, and practically insoluble in water.

Melting point—Between 259 and 261 ℃ (with decomposition).

Identification (1) Determine the absorption spectrum of a solution of Xipamide in 0.01 mol/L methanolic hydrochloric acid (1 in 200000) as directed under the Ultraviolet-visible Spectroscopy; it exhibits a maximum absorption at the wavelength of about 302 nm.

(2) Determine the infrared spectra of Xipamide and xipamide RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Purity (1) ***Clarity and color of solution***—To 0.5 g of Xipamide, dissolve in 10 mL of methanol; the solution is clear and colorless.

(2) ***Chloride***—Weigh 2.5 g of Xipamide, add 20 mL of water, shake for 10 minutes to mix, and filter using a glass filter. Perform the test with 2.0 mL of the filtrate as directed under the Chloride. Prepare the control solution with 0.14 mL of 0.01 mol/L hydrochloric acid (NMT 0.02%).

(3) ***Heavy metals***—Proceed with 1.0 g of Xipamide according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(4) ***Related substances***—Weigh 0.4 g of Xipamide, add methanol to make 100 mL, and use this solution as the test solution. Pipet 1.0 mL of the test solution and add methanol to make 100 mL. Pipet 10.0 mL of this solution, add methanol to make 100 mL, and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 10 μL each of the test solution and the standard solution on a thin-layer chromatographic plate made of silica gel with fluorescent indicator for thin-layer chromatography, develop the plate with a mixture of chloroform and methanol (4 : 1) as the developing solvent and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the spots other than the principal spot in the chromatogram obtained from the test solution are not more intense than the principal spot from the standard solution.

Loss on drying NMT 0.5% (1 g, 120 ℃, 1 hour).

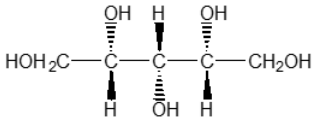
Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Xipamide, add 40 mL of methanol to dissolve, add 10 mL of water to mix, and titrate with potassium hydroxide-ethanol VS (potentiometric titration under the Titrimetry, electrode: combination glass electrode). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L potassium hydroxide-ethanol VS = 35.48 mg of $C_{15}H_{15}ClN_2O_4S$

Packaging and storage Preserve in tight containers.

Xylitol
자일리톨



Xylite

$C_5H_{12}O_5$: 152.15

(2*R*,4*S*)-Pentane-1,2,3,4,5-pentol [*87-99-0*]

Xylitol, when dried, contains NLT 98.0% and NMT 101.0% of xylitol ($C_5H_{12}O_5$).

Description Xylitol occurs as a white crystalline powder, is odorless and has a sweet taste.
It is very soluble in water and slightly soluble in ethanol(95).
It is hygroscopic.

Identification (1) To 1 mL of an aqueous solution of Xylitol (1 in 2), add 2 mL of iron(II) sulfate TS and 1 mL of a sodium hydroxide solution (1 in 5); the resulting solution exhibits a bluish green color with no turbidity.

(2) Determine the infrared spectra of Xylitol and Xylitol RS, previously dried, as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

pH Dissolve 5.0 g of Xylitol in 10 mL of freshly boiled and cooled water; the pH of this solution is between 5.0 and 7.0.

Melting point Between 93.0 and 95.0 °C.

Purity (1) ***Clarity and color of solution***—Dissolve 5 g of Xylitol in 10 mL of water; the solution is clear and colorless.

(2) ***Chloride***—Perform the test with 2.0 g of Xylitol. Prepare the control solution with 0.30 mL of 0.01 mol/L hydrochloric acid (NMT 0.005%).

(3) ***Sulfate***—Perform the test with 4.0 g of Xylitol. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid (NMT 0.006%).

(4) ***Heavy metals***—Proceed with 4.0 g of Ceftazidime Hydrate according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 5 ppm).

(5) ***Nickel***—Dissolve 0.5 g of Xylitol in 5 mL of water, add 3 drops of dimethylglyoxime TS and 3 drops of ammonia TS, and allow to stand for 5 minutes: the solution exhibits no red color.

(6) ***Arsenic***—Prepare the test solution with 1.5 g of Xylitol, according to Method 1 and perform the test (NMT 1.3 ppm).

(7) ***Sugars***—Dissolve 5.0 g of Xylitol in 15 mL of water, add 4.0 mL of dilute hydrochloric acid, and heat on a steam bath for 3 hours with a reflux condenser attached. After cooling, neutralize with sodium hydroxide TS (indicator: 2 drops of methyl orange TS) Then, add water to make 50 mL, transfer 10 mL of this solution to a flask, add 10 mL of water and 40 mL of Fehling's TS, boil gently for 3 minutes, and allow to stand to precipitate cuprous oxide. Filter the clear supernatant through a glass filter and wash the precipitate with warm water until the washing does not show alkalinity. Filter the washings through the glass filter mentioned above. Dissolve the precipitate in the flask in 20 mL of iron(III) sulfate TS, filter the solution through the glass filter mentioned above, wash with water, combine the washings with the filtrate, heat at 80 °C and titrate with 0.02 mol/L potassium permanganate VS; the consumed amount is NMT 1.0 mL.

(8) ***Related substances (other polyols)***—Weigh accurately 1.0 g of Xylitol, dissolve in water to make 100 mL, and use this solution as the test solution. Separately, weigh accurately 50 mg each of L-arabinitol RS, galactitol RS, D-mannitol RS, and sorbitol RS, dissolve in water to make 100 mL, and use this solution as the standard solution (1). Separately, weigh accurately 0.5 g of Xylitol RS, dissolve in water to make 25 mL, and use this solution as the standard solution (2). Pipet 1 mL of the standard solution (1) and 5 mL of the standard solution (2), add water to make 10 mL so that the solution contains about 0.05 mg each of L-arabinitol, galactitol, D-mannitol, and sorbitol and about 10 mg of Xylitol per mL, and use this solution as the standard solution. Pipet 1.0 mL each of the test solution and standard solution into a 10 mL round-bottom flask, add exactly 1.0 mL of the internal standard solution to each flask, and evaporate to dryness with a reflux condenser on a steam bath at 60 °C. Add 1 mL of ethanol(99.5), shake carefully, and evaporate to dryness under the same conditions as above. To each residue, add exactly 1 mL of pyridine and 1 mL of acetic acid(100), stopper the flask, mix for 30 seconds, and allow to stand in a dry oven at 70 °C for 30 minutes. Perform the test with 1 μL each of the test solution and standard solution as directed under the Gas Chromatography according to the following conditions; the total amount of related substances is NMT 2.0%.

$$\text{Content (\%) of related substances} = 100 \times \frac{C_S}{C_T} \times \frac{Q_T}{Q_S}$$

C_S: Concentration (mg/mL) of each related substance in the standard solution

C_T: Concentration (mg/mL) of Xylitol in the test solution

Q_T: Ratio of the peak area of each derivatized related substance to that of derivatized erythritol obtained from the test solution

Q_S: Ratio of the peak area of each derivatized related substance to that of derivatized erythritol obtained from the standard solution

Internal standard solution—A solution of erythritol (7 in 2000).

Operating conditions

Detector: A hydrogen flame ionization detector

Column: A column about 0.25 mm in internal diameter and about 30 m in length, coated with 0.25 μm-thick 14% cyanopropylphenol-86% methylpolysiloxane.

Column temperature: Maintain at 170 °C for 5 minutes, raise the temperature to 215 °C at the rate of 6 °C per minute, and maintain at 215 °C for 8 minutes. Then, raise the temperature to 270 °C at the rate of 10 °C per minute, and maintain at 270 °C for 14 minutes.

Carrier gas: Helium

Flow rate: 1 mL/min

Sample injection port temperature: 270 °C

Detector temperature: 280 °C

System suitability

System performance: Proceed with 1 μL of the standard solution under the above operating conditions; the relative retention times of derivatives of erythritol, L-arabinitol, xylitol, D-mannitol, and galactitol to the retention time of derivatized sorbitol are about 0.47, about 0.75, 0.81, 0.98 and 0.99, respectively.

System repeatability: Repeat the test 5 times with 1 μL each of the standard solution under the above operating conditions; the relative standard deviation of the ratios of the peak area of Xylitol to that of erythritol is NMT 1.5%.

Loss on drying NMT 1.0% (1 g, in vacuum, phosphorus pentoxide, 24 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.2 g of Xylitol, previously dried, dissolve in water to make exactly 100 mL. Pipet 10 mL of this solution into an iodine flask, add exactly 50 mL of potassium periodate TS, and heat for 15 minutes on a steam bath. After cooling, add 2.5 g of potassium iodide, stopper the flask immediately, shake well to mix, allow to stand for 5 minutes in a dark place, and titrate with 0.1 mol/L sodium thiosulfate VS (indicator: 3 mL of starch TS). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium thiosulfate VS
= 1.9018 mg of $C_5H_{12}O_5$

Packaging and storage Preserve in tight containers.

Xylitol Injection
자일리톨 주사액

Xylite Injection

Xylitol Injection is an aqueous solution for injection and contains NLT 95.0% and NMT 105.0% of the labeled amount of xylitol ($C_5H_{12}O_5$: 152.15).

Method of preparation Prepare as directed under Injections, with Xylitol.
No preservative is added.

Description Glucose Injection occurs as a clear, colorless liquid and has a sweet taste.

Identification Weigh an amount of Xylitol Injection, equivalent to 0.1 g of xylitol, according to the labeled amount, add water to make 10 mL, and use this solution as the test solution. Separately, dissolve 0.1 g of Xylitol RS in 10 mL of water and use this solution as the standard solution. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 2 μL each of the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethanol(95), ammonia water(28) and water (25 : 4 : 3) as the developing solvent to a distance of about 10 cm and air-dry the plate. Spray silver nitrate-ammonia TS evenly on the plate, and heat at 105 °C for 15 minutes; the spots obtained from the test solution and the standard solution exhibit blackish brown color and the R_f values of these solutions are the same.

pH Between 4.5 and 7.5.

Sterility Meets the requirements.

Bacterial endotoxins Less than 0.50 EU per mL of glucose injection.

Particulate contamination: Visible particles Meets the requirements.

Insoluble particulate matter in injections Meets the requirements.

Extractable volume of injections Meets the requirements.

Assay Pipet an amount of Xylitol Injection, equivalent to about 5 g of xylitol ($C_5H_{12}O_5$), add 5.0 mL of the internal standard solution and water to make exactly 25 mL, and use this solution as the test solution. Separately, weigh accurately about 0.5 g of xylitol RS, previously dried for 24 hours in a desiccator (in vacuum, phosphorus pentoxide), dissolve in 5.0 mL of the internal standard solution, add water to make exactly 25 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak area ratios, Q_T and Q_S, of xylitol to the peak area of the internal standard.

$$\text{Amount (g) of xylitol } (C_5H_{12}O_5) = \text{Amount (g) of xylitol RS} \times \frac{Q_T}{Q_S}$$

Internal standard solution—A solution of white sugar (5 in 50).

Operating conditions

Detector: A differential refractometer

Column: A stainless steel column, about 7.8 mm in internal diameter and about 15 to 30 cm in length, packed with strong acidic ion exchange resin (the calcium form of the sulfonated styrene divinylbenzene copolymer, 9 μm in particle diameter).

Column temperature: Ordinary temperature

Mobile phase: A mixture of acetonitrile and water (75 : 25).

Flow rate: Adjust the flow rate so that the retention time of xylitol is about 5 minutes.

System suitability

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, xylitol and the internal standard are eluted in this order with the resolution between their peaks being NLT 2.0.

System repeatability: Repeat the test 6 times with 10 μL each of the standard solution according to the above conditions; the relative standard deviation of the peak area ratio is NMT 2.0%.

Packaging and storage Preserve in hermetic containers.

Dried Yeast
건조효모

Dried Yeast is dried and powdered cells of yeast belonging to Saccharomyces.

Dried Yeast contains NLT 0.4 g of protein and NLT 100 μg of thiamine compounds [as thiamine hydrochloride ($C_{12}H_{17}ClN_4OS \cdot HCl$: 337.27)] per g.

Description Dried Yeast occurs as a pale yellow to brown powder and has a characteristic odor and taste.

Identification Dried Yeast is composed of single cells in round or oval shape with its length between 6 μm and 12 μm when examined under a microscope.

Purity (1) ***Rancidity***—Dried Yeast is free from any unpleasant or rancid odor or taste.

(2) ***Starch***—Add iodine TS to Dried Yeast and examine microscopically; no or only a few granules are tinted blackish purple.

Loss on drying NMT 8.0% (1 g, 100 °C, 8 hours).

Ash NMT 9.0% (1 g, perform the test as directed under the Ash under the Crude drugs test).

Assay (1) ***Protein***—Weigh accurately about 50 mg of Dried Yeast and perform the test as directed under the Nitrogen Determination.

$$\text{Amount of protein per g of Dried Yeast (mg)} = \text{Amount of nitrogen (N)} \times 6.25 \times \frac{1}{\text{Amount of sample (g)}}\ (\text{mg})$$

(2) ***Thiamine***—Weigh accurately about 1 g of Dried Yeast, add 1 mL of dilute hydrochloric acid and 80 mL of water, and heat in the water bath at 80 - 85 ℃ for 30 minutes with occasional shaking. After cooling, add water to make exactly 100 mL and centrifuge for 10 minutes. Pipet 4.0 mL of the clear supernatant, add exactly 5 mL of acetic acid-sodium acetate TS and 1 mL of enzyme TS, and allow to stand at 45 - 50 ℃ for 3 hours. Take exactly 2 mL of this solution, put it into a chromatographic column about 1 cm in internal diameter and about 17 cm in height, prepared by pouring 2.5 mL of a weakly acidic CM-bridged cellulose cation exchanger (H type) (40 - 110 μm in particle diameter), and elute at the flow of about 0.5 mL per minute. Next, wash the inner wall of the chromatographic column with a small amount of water, and wash the column again with 10 mL of water at the flow rate of about 1 mL per minute. Repeat this procedure twice. Elute the column with 2.5 mL of diluted phosphoric acid (1 in 50) twice at the flow rate of about 0.5 mL of per minute, and combine the eluate. Add exactly 1 mL of the internal standard solution and 10 mg of sodium 1-octanesulfonate to the eluate, dissolve, and use this solution as the test solution. Separately, weigh accurately about 15 mg of thiamine hydrochloride RS (determine in advance its water content in the same way as the Thiamine Hydrochloride), dissolve in 0.001 mol/L hydrochloric acid TS, and make exactly 100 mL. Pipet 1 mL of this solution and add the mobile phase to make exactly 100 mL. Pipet 1 mL of this solution, and add 1 mL of the internal standard solution and additional 3 mL of the mobile phase, and use this solution as the standard solution. Perform the test with 200 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Calculate the peak area ratios, Q_T and Q_S, of thiamine to that of the internal standard.

$$\text{Amount of thiamine per g of Dried Yeast (μg)} = \text{Amount of thiamine hydrochloride RS calculated on the anhydrous basis (mg)} \times \frac{Q_T}{Q_S} \times \frac{1}{\text{Amount of sample (g)}} \times 12.5$$

Internal standard solution—Dissolve 10 mg of phenacetin in acetonitrile to make 100 mL. To 1 mL of this solution, add diluted acetonitrile (1 in 5) to make 100 mL.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in

internal diameter and about 15 cm to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Column temperature: A constant temperature of about 40 °C.

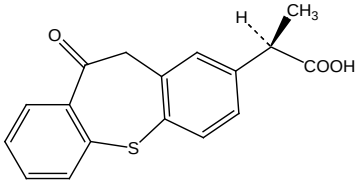
Mobile phase: Dissolve 2.7 g of potassium dihydrogen phosphate in 1000 mL of water and adjust pH to 3.5 with diluted phosphoric acid (1 in 10). Dissolve 1.6 g of sodium 1-octanesulfonate in 800 mL of dried Yeas and add 200 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of thiamine is about 8 minutes.

Selection of column: Proceed with 200 μL of the standard solution under the above conditions; thiamine and the internal standard are eluted in this order with the resolution being NLT 8.

Packaging and storage Preserve in tight containers.

Zaltoprofen
잘토프로펜



and enantiomer

$C_{17}H_{14}O_3S$: 298.36

2-(10-Oxo-10,11-dihydrodibenzo[b,f]thiepin-2-yl)propanoic acid [*74711-43-6*]

Zaltoprofen, when dried, contains NLT 99.0% and NMT 101.0% of zaltoprofen ($C_{17}H_{14}O_3S$).

Description Zaltoprofen occurs as white to light yellow crystals or a crystalline powder.
It is freely soluble in acetone, soluble in methanol or ethanol(99.5), and practically insoluble in water.
It is gradually decomposed by light.
A solution of Zaltoprofen in acetone (1 in 10) shows no optical rotation.

Identification (1) To 0.2 g of Zaltoprofen, add 0.5 g of sodium hydroxide, heat gradually, and carbonize. After cooling, add 5 mL of diluted hydrochloric acid (1 in 2); the gas produced darkens moist lead acetate paper.

(2) Determine the absorption spectra of solutions of Zaltoprofen and zaltoprofen RS in ethanol(99.5) (1 in 100000) as directed under the Ultraviolet-visible Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared spectra of Zaltoprofen and zaltoprofen RS as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy; both spectra exhibit similar intensities of absorption at the same wavenumbers.

Melting point Between 135 and 139 °C.

Purity (1) ***Heavy metals***—Proceed with 2.0 g of Zaltoprofen according to Method 4 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(2) ***Arsenic***—Prepare the test solution with 1.0 g of Zaltoprofen according to Method 3 and perform the test. Use a solution of magnesium nitrate hexahydrate in ethanol(95) (2 in 25) (NMT 2 ppm).

(3) ***Related substances***—Dissolve 50 mg of Zaltoprofen in 50 mL of the mobile phase, and use this solution as the test solution. Pipet 1 mL of the test solution and add the mobile phase to make exactly 20 mL. Pipet 1 mL of this solution, add the mobile phase to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine the peak area of each solution by the automatic integration method; the peak area other than the peaks of zaltoprofen from the test solution and peaks with relative retention time to zaltoprofen of about 0.7 is not greater than the peak area of zaltoprofen from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of acetonitrile, water and acetic acid(100) (300 : 200 : 1).

Flow rate: Adjust the flow rate so that the retention time of zaltoprofen is about 4 minutes.

System suitability

Test for required detectability: Pipet 2 mL of the standard solution and add the mobile phase to make exactly 20 mL. Confirm that the peak area obtained from 20 μL of this solution is equivalent to 8% to 12% of the peak area of zaltoprofen from the standard solution.

System performance: Dissolve 25 mg of zaltoprofen and 50 mg of isopropyl benzoate in 100 mL of ethanol(99.5). Pipet 1 mL of this solution and add the mobile phase to make exactly 50 mL. Proceed with 20 μL of this solution according to the above operating conditions; zaltoprofen and isopropyl benzoate are eluted in this order with the resolution being NLT 6.0.

System repeatability: Repeat the test 6 times with 20 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of zaltoprofen is NMT 2.0%.

Time span of measurement: About 15 times the retention time of zaltoprofen after the solvent peak.

Loss on drying NMT 0.5% (1 g, 105 °C, 4 hours).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.5 g of Zaltoprofen, dissolve in 50 mL of methanol, and titrate with 0.1 mol/L sodium hydroxide VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L sodium hydroxide VS
= 29.84 mg of $C_{17}H_{14}O_3S$

Packaging and storage Preserve in light-resistant, tight containers.

Zaltoprofen Tablets
잘토프로펜 정

Zaltoprofen Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of zaltoprofen ($C_{17}H_{14}O_3S$: 298.36).

Method of preparation Prepare as directed under Tablets, with Zaltoprofen.

Identification Powder Zaltoprofen Tablets, weigh an amount of this powder, equivalent to 80 mg of zaltoprofen according to the labeled amount, add 30 mL of ethanol(99.5), shake to mix well, and centrifuge. To 1 mL of the clear supernatant, add ethanol(99.5) to make 20 mL. To 2 mL of this solution, add ethanol(99.5) to make 25 mL, and determine the absorption spectrum of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits absorption maxima at wavelengths of between 227 to 231 nm and between 329 nm to 333 nm, and a shoulder between 241 nm to 245 nm.

Dissolution Perform the test with 1 tablet of Definition of Zaltoprofen Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of the solution 2 for the dissolution test as the dissolution medium. Take NLT 20 mL of the dissolved solution after 30 minutes from the start of the dissolution test, and filter through a membrane filter with a pore size of NMT 0.45 μm. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add the solution 3 for the dissolution test to make *V'* mL so that each mL contains about 44 μg of zaltoprofen ($C_{17}H_{14}O_3S$) per mL according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 22 mg of zaltoprofen RS, previously dried at 105 °C for 4 hours, and dissolve in 20 mL of ethanol(99.5), then add the solution 2 for the dissolution test to make exactly 100 mL. Pipet 4 mL of this solution, add the solution 2 for the dissolution test to make exactly 20 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, respectively, at the absorption maximum wavelength of about 340 nm as directed under the Ultraviolet-visible Spectroscopy, using the dissolution medium as the control solution. It meets the requirements if the dissolution rate of Zaltoprofen Tablets in 30 minutes is NLT 75%.

Dissolution rate (%) of the labeled amount of zaltoprofen ($C_{17}H_{14}O_3$)
= Amount (mg) of zaltoprofen RS (mg)
$$\times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times 180$$

C: Labeled amount (mg) of zaltoprofen ($C_{17}H_{14}O_3$) in 1 tablet

Uniformity of dosage units Meets the requirements.

Assay Weigh accurately the mass of NLT 10 tablets of Zaltoprofen Tablets, add 40 mL of water, and shake well to disintegrate. Next, add ethanol(95), shake well to mix, and add ethanol(95) to make exactly 200 mL. Centrifuge this solution, take exactly an amount of the clear supernatant, equivalent to about 8 mg of zaltoprofen ($C_{17}H_{14}O_3S$), add exactly 10 mL of internal standard solution, add ethanol(95) to make 50 mL, and use this solution as the test solution. Separately, weigh accurately about 80 mg of zaltoprofen RS, previously dried at 105 °C for 4 hours, add 4 mL of water, and add ethanol(95) to make exactly 20 mL. Take 2 mL of this solution, add exactly 10 mL of the internal standard solution, add ethanol(95) to make 50 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of zaltoprofen to that of internal standard, respectively.

Amount (mg) zaltoprofen ($C_{17}H_{14}O_3S$)
$$= \text{Amount (mg) of zaltoprofen RS} \times \frac{Q_T}{Q_S} \times \frac{1}{10}$$

Internal standard solution—A solution of benzyl benzoate in acetonitrile (1 in 1000).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of acetonitrile, water and acetic acid(100) (300 : 200 : 1).

Flow rate: Adjust the flow rate so that the retention time of zaltoprofen is about 4 minutes.

System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions;

zaltoprofen and the internal standard are eluted in this order with the resolution being NLT 10.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution according to the above conditions; the relative standard deviation of peak area of zaltoprofen to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in tight containers.

Zinc Chloride
염화아연

$ZnCl_2$: 136.32

Dichlorozinc [*7646-85-7*]

Zinc Chloride contains NLT 97.0% and NMT 101.0% of zinc chloride ($ZnCl_2$).

Description Zinc Chloride occurs as a white, crystalline powder, rod or a mass, and is odorless.
It is very soluble in water and freely soluble in ethanol(95); it may sometimes be slightly turbid. The solution becomes clear by addition a small amount of hydrochloric acid.
The pH of a solution of 1.0 g of Zinc Chloride in 2 mL of water is between 3.3 and 5.3.
It is deliquescent.

Identification An aqueous solution of Zinc Chloride (1 in 30) responds to the Qualitative Analysis for zinc salt and chloride.

Purity (1) ***Clarity and color of solution***—Dissolve 1.0 g of Zinc Chloride in 10 mL of water and 2 drops of hydrochloric acid: the solution is colorless and clear.

(2) ***Oxychloride***—Weigh 0.25 g of Zinc Chloride, add 5 mL of water and 5 mL of ethanol(95), shake thoroughly to mix well, and add 0.30 mL of 1 mol/L hydrochloric acid; the solution is clear.

(3) ***Sulfate***—Perform the test with 2.0 g of Zinc Chloride. Prepare the control solution with 0.40 mL of 0.005 mol/L sulfuric acid (NMT 0.010%).

(4) ***Ammonium***—Dissolve 0.5 g of Zinc Chloride in 5 mL of water, and warm with 10 mL of sodium hydroxide solution (1 in 6); the evolving gas does not change the moistened red litmus paper to blue.

(5) ***Heavy metals***—Dissolve 0.5 g of Zinc Chloride in 5 mL of water in a Nessler tube, shake thoroughly with 15 mL of potassium cyanide TS, add 1 drop of sodium sulfide TS, allow to stand for 5 minutes, and observe from the top downward against a white background; the color of the solution is not more intense than that of the following control solution.

Control solution—To 2.5 mL of lead standard solution, add 3 mL of water and 15 mL of potassium cyanide TS, shake thoroughly, and add 1 drop of sodium sulfide TS (NMT 50 ppm).

(6) ***Alkali earth metals and alkali metals***—Dissolve 2.0 g of Zinc Chloride in 120 mL of water, add ammonium sulfide TS to complete precipitation, add water to make 200 mL, shake thoroughly, and filter through dry filter paper. Discard the first 20 mL of the filtrate, take the following 100 mL of the filtrate, evaporate with 3 drops of sulfuric acid to dryness, and heat the residue strongly at 600 °C to a constant mass; the mass is NMT 10.0 mg.

(7) ***Arsenic***—Proceed with 0.40 g of Zinc Chloride according to Method 1 and perform the test (NMT 5 ppm).

Assay Weigh accurately about 0.3 g of Zinc Chloride, add 0.4 mL of dilute hydrochloric acid and water to make exactly 200 mL. Pipet 20 mL of the resulting solution, add 80 mL of water, 2 mL of ammonia-ammonium chloride buffer solution (pH 10.7) and titrate with 0.01 mol/L ethylenediaminetetraacetic acid disodium salt solution VS (indicator: 40 mg of Eriochrome black T-sodium chloride indicator).

Each mL of 0.01 mol/L Ethylenediaminetetraacetic acid disodium salt VS
= 1.3630 mg of $ZnCl_2$

Packaging and storage Preserve in tight containers.

Zinc Oxide
산화아연

ZnO : 81.41

[*1314-13-2*]

Zinc Oxide, when ignited, contains NLT 99.0% and NMT 101.0% of zinc oxide (ZnO).

Description Zinc Oxide occurs as a white, amorphous powder. It is odorless and tasteless.
It is practically insoluble in water, acetic acid(100), ethanol(95) or ether.
It dissolves in dilute hydrochloric acid or in sodium hydroxide TS.
It slowly absorbs carbon dioxide in the air.

Identification (1) Zinc Oxide exhibits a yellow color when ignited and exhibits its original color when cooled.

(2) A solution of Zinc Oxide in dilute hydrochloric acid (1 in 10) responds to the Qualitative Analysis for zinc salt.

Purity (1) ***Carbonate, and clarity and color of solution***—To 2.0 g of Zinc Oxide, add 10 mL of water, shake for mixing, add 30 mL of dilute sulfuric acid, and heat on a steam bath with stirring for mixing. The solution does not exhibit bubbles. Also, the solution is colorless and clear.

(2) ***Alkalinity***—To 1.0 g of Zinc Oxide, add 10 mL of water, boil for 2 minutes and cool. Filter with a glass

filter (G 3). To the filtrate, add 2 drops of phenolphthalein TS and 0.20 mL of 0.1 mol/L hydrochloric acid VS. The solution is colorless.

(3) ***Sulfate*—**To 0.5 g of Zinc Oxide, add 40 mL of water, shake for mixing, and filter. To 20 mL of the filtrate, add 1 mL of dilute hydrochloric acid, and add water to make 50 mL. Use this as the test solution and perform the test. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid VS (NMT 0.096%).

(4) ***Iron*—**Dissolve 1.0 g of Zinc Oxide in 50 mL of diluted hydrochloric acid (1 in 2), dissolve in 0.1 g of ammonium peroxydisulfate, and perform extraction with 20 mL of 4-methyl-2-pentanone. To the 4-methyl-2-pentanone layer, add 30 mL of pH 4.5 acetic acid-sodium acetate buffer for iron test for extraction. Use the pH 4.5 acetic acid-sodium acetate buffer layer as the test solution. Separately, proceed in the same manner with 1.0 mL of iron standard solution, and use this solution as the control solution. Add 2 mL of a solution of ascorbic acid for iron test (1 in 100) to each of the test solution and the control solution for mixing, and allow to stand for 30 minutes. To each of the solutions, add 5 mL of a solution of α,α'-dipyridyl in ethanol(95) (1 in 200), add water to make 50 mL, and allow to stand for 30 minutes. Compare the colors of the respective resulting solutions in the white background; the color of the test solution is not more intense than that of the control solution (NMT 10 ppm).

(5) ***Cadmium*—**Dissolve 2.0 g of Zinc Oxide in 14 mL of diluted dilute nitric acid (1 in 2), boil for 1 minute, cool, and add water to make exactly 100 mL. Use this solution as the test solution. Separately, prepare the standard solution by mixing cadmium standard solution and 3.5% nitric acid. Perform the test with the test solution and the standard solution as directed under the Atomic Absorption Spectroscopy according to the following conditions; the absorbance of the test solution is NMT that of the standard solution (NMT 10 ppm).

Gas: Air–acetylene or propane
Lamp: Cadmium hollow-cathode lamp
Wavelength: 228.8 nm

(6) ***Lead*—**To 2.0 g of Zinc Oxide, add 20 mL of water. While shaking for mixing, add 5 mL of acetic acid(100), and heat on a steam bath to dissolve. After cooling, add 5 drops of potassium chromate TS. The solution is not turbid.

(7) ***Arsenic*—**Dissolve 0.5 g of Zinc Oxide in 5 mL of dilute hydrochloric acid. Use this as the test solution and perform the test (NMT 4 ppm).

Loss on ignition NMT 1.0% (1 g, 850 ℃, 1 hour).

Assay Weigh accurately about 0.8 g of Zinc Oxide, previously ignited at 850 ℃ for 1 hour, dissolve in 2 mL of water and 3 mL of hydrochloric acid, and add water to make exactly 100 mL. Pipet 10 mL of this solution, add 80 mL of water and add sodium hydroxide solution (1 in 50) until a little of precipitate is produced. Add 5 mL of pH 10.7 ammonia-ammonium chloride buffer solution, and titrate with 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 40 mg of eryochrome black T-sodium chloride indicator).

Each mL of 0.05 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 4.069 mg of ZnO

Packaging and storage Preserve in tight containers.

Zinc Sulfate Hydrate
황산아연수화물

$ZnSO_4 \cdot 7H_2O$: 287.58
Zinc Sulfate Heptahydrate [*7446-20-0*]

Zinc Sulfate Hydrate contains NLT 99.0% and NMT 102.0% of zinc sulfate ($ZnSO_4 \cdot 7H_2O$).

Description Zinc Sulfate Hydrate occurs as colorless crystals or a white crystalline powder.
It is very soluble in water and practically insoluble in ethanol(99.5).
It effloresces in dry air.

Identification (1) An aqueous solution of Zinc Sulfate Hydrate (1 in 20) responds to the Qualitative Analysis for zinc salt.

(2) An aqueous solution of Zinc Sulfate Hydrate (1 in 20) responds to the Qualitative Analysis for sulfate.

pH Dissolve 1.0 g of Zinc Sulfate Hydrate in 20 mL of water; the pH of this solution is between 4.4 and 6.0.

Purity (1) ***Clarity and color of solution***—Dissolve 0.25 g of Zinc Sulfate Hydrate in 5 mL of water; the solution is clear and colorless.

(2) ***Heavy metals***—Transfer 1.0 g of Zinc Sulfate Hydrate into a Nessler tube, dissolve in 10 mL of water, add 20 mL of potassium cyanide TS, and shake well to mix. Add 2 drops of sodium sulfide TS, and after 5 minutes, observe from the above using diffuse light against a white background; it is not more intense than the following control solution.

Control solution—To 1.0 mL of lead standard solution, add 10 mL of water and 20 mL of potassium cyanide TS, mix well, and add 2 drops of potassium cyanide TS (NMT 10 ppm).

(3) ***Alkaline earth metals and alkali metals***—Dissolve 2.0 g of Zinc Sulfate Hydrate in 150 mL of water, add ammonium sulfide TS to complete the precipitation, add water to make exactly 200 mL, and shake well to mix. Then, filter with a dry filter paper. Discard the first 20 mL of the filtrate, pipet the subsequent 100 mL of the filtrate, evaporate to dryness, and ignite as directed under the Residue on ignition; the residue is NMT 5.0

mg.

(4) ***Arsenic***—Prepare the test solution with 1.0 g of Zinc Sulfate Hydrate according to Method 1, and perform the test (NMT 2 ppm).

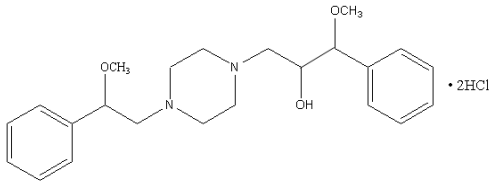
Loss on drying Between 35.5% and 38.5% (1.0 g, 105 ℃, 3 hours).

Assay Weigh accurately about 0.3 g of Zinc Sulfate Hydrate, and dissolve in water to make 100 mL exactly. Pipet 25 mL of this solution, add 100 mL of water and 2 mL of pH 10.7 ammonia-ammonium chloride buffer solution, and titrate with 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS (indicator: 40 mg of eryochrome black T-sodium chloride indicator).

Each mL of 0.01 mol/L ethylenediaminetetraacetic acid disodium salt VS
= 2.8756 mg of $ZnSO_4 \cdot 7H_2O$

Packaging and storage Preserve in tight containers.

Zipeprol Dihydrochloride
지페프롤염산염



$C_{23}H_{32}N_2O_3 \cdot 2HCl$: 457.43
4-(2-Methoxy-2-phenylethyl)-α-(methoxyphenylmethyl)-1-piperazineethanol dihydrochloride, [*34758-84-4*]

Zipeprol Dihydrochloride contains NLT 98.5% and NMT 101.0% of zolpidem tartrate (C42H48N6O8), calculated on the anhydrous basis.

Description Zipeprol Dihydrochloride occurs as a white fine powder.
It is soluble in water, sparingly soluble in ethanol(95) and chloroform and insoluble in petroleum ether and ether.

Melting point—Between 227 and 231 °C.

Identification (1) An aqueous solution of Zipeprol Dihydrochloride responds to the Qualitative Analysis for chloride.

(2) 0.5% ethanol solutions of Zipeprol Dihydrochloride and zipeprol dihydrochloride RS are used as the test solution and the standard solution, respectively. With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot the test solution and the standard solution on the thin-layer chromatographic plate made of silica gel for thin-layer chromatography. Develop the plate with a mixture of water, 1-butanol, and acetic acid(100) (5 : 4 : 1) as the developing solvent, and air-dry the plate. Spray Dragendorff's TS evenly onto the plate; the R_f value and the color of the spots obtained from the test and the standard solutions are the same.

Purity (1) ***Heavy metals***—Proceed with 1.0 g of Zipeprol Dihydrochloride according to Method 1 and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 20 ppm).

(2) ***Related substances***—To about 0.1 g of Zipeprol Dihydrochloride, add ethanol(95) to make exactly 10 mL, and use this solution as the test solution. Separately, weigh about 10 mg of 2-phenyl-(2-methoxyethyl)piperazine, dissolve in ethanol(95) to make exactly 100 mL, and use this solution as the standard solution. Spot 5 μL each of the test solution and the standard solution on two thin-layer chromatographic plates made of silica gel for thin-layer chromatography, develop the plates with a mixture of water, 1-butanol, and acetic acid(100) (5 : 4 : 1) and a mixture of water, 1-butanol, and ammonia water (5 : 4 : 1), respectively, and air-dry the plates. Spray Dragendorff's TS and 0.1 mol/L sodium nitrate solution evenly onto the plate in this order; the spots other than the principal spot obtained from the test solution are not greater or more intense than the spots obtained from the standard solution (NMT 1.0%).

Loss on drying NMT 1.0% (1.0 g, 105 °C, 4 hours).

Residue on ignition NMT 0.1% (2.0 g).

Assay Weigh accurately about 0.4 g of Zipeprol Dihydrochloride, put into an Erlenmeyer flask, add 40 mL of acetic acid(100) for non-aqueous titration, and warm the flask slightly to dissolve. Cool to room temperature, slowly add 10 mL of mercury(II) acetic acid for non-aqueous titration TS, and titrate with 0.1 mol/L perchloric acid VS. However, the endpoint is when the color of the solution changes to bluish green (indicator: 3 drops of methylrosaniline chloride TS) Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 22.87 mg of $C_{23}H_{32}N_2O_3 \cdot 2HCl$

Packaging and storage Preserve in tight containers.

Zipeprol Dihydrochloride Syrup
지페프롤염산염 시럽

Zipeprol Dihydrochloride Syrup contains NLT 95.0% and NMT 105.0% of the labelled amount of zipeprol dihydrochloride ($C_{23}H_{32}N_2O_3 \cdot 2HCl$: 457.43).

Method of preparation Prepare as directed under Syrups, with Zipeprol Dihydrochloride.

Identification The retention times of the major peaks from the test solution and the standard solution prepared

as directed under the Assay are the same.

pH Between 4.3 and 6.3.

Uniformity of dosage units (distribution) Meets the requirements.

Assay Weigh accurately an amount of Zipeprol Dihydrochloride Syrup, equivalent to 0.1 g of zipeprol dihydrochloride ($C_{23}H_{32}N_2O_3 \cdot 2HCl$) according to the labeled amount, add 50 mL of water and 4 mL of 1 mol/L sodium hydroxide TS, extract 3 times with each 50 mL of chloroform. Combine the chloroform extracts, pass through anhydrous sodium sulfate to remove water, filter, and evaporate the filtrate to dryness. Add the mobile phase to the residue and use the solution as the test solution. Separately, weigh accurately about 0.1 g of zipeprol dihydrochloride RS, add the mobile phase to make 250 mL, and use the solution as the standard solution. Perform the test with each 10 μL of the test solution and the standard solution as directed under the Liquid Chromatography according to the following operating conditions and determine the peak areas, A_T and A_S, of zipeprol dihydrochloride from each solution.

$$\text{Amount (mg) of zipeprol dihydrochloride } (C_{23}H_{32}N_2O_3 \cdot 2HCl) = \text{Amount (mg) of zipeprol dihydrochloride RS} \times \frac{A_T}{A_S}$$

Operating conditions

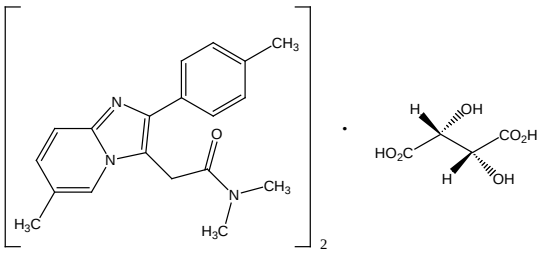
Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4 mm in internal diameter and about 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm to 10 μm in particle diameter).

Mobile phase: A mixture of 0.1 mol/L potassium dihydrogen phosphate, acetonitrile and phosphoric acid (60 : 40 : 0.5).

Packaging and storage Preserve in well-closed containers.

Zolpidem Tartrate
졸피뎀타르타르산염



$C_{42}H_{48}N_6O_8$: 764.87

2,3-Dihydroxybutanedioic acid; *N*,*N*-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetamide [*99294-93-6*]

Zolpidem Tartrate contains NLT 98.5% and NMT 101.0% of zolpidem tartrate ($C_{42}H_{48}N_6O_8$), calculated on the anhydrous basis.

Description Zolpidem Tartrate occurs as a white crystalline powder.
It is sparingly soluble in methanol, slightly soluble in water, and practically insoluble in dichloromethane.
It is hygroscopic.

Identification (1) Dissolve 0.10 g each of Zolpidem Tartrate and zolpidem tartrate RS in 10 mL of 0.1 mol/L hydrochloric acid TS, add 10 mL of water, then add dropwise 1 mL of 3.4 w/v% ammonia water while stirring. Filter the resulting precipitate, wash the precipitate with water, and then dry at 100 to 105 °C for 2 hours. Determine the infrared spectra of the precipitates as directed in the potassium bromide disk method under the Mid-infrared Spectroscopy: both spectra exhibit similar intensities of absorption at the same wavenumbers.

(2) Dissolve 50 mg of Zolpidem Tartrate in 5 mL of methanol, add 0.1 mL of diethylamine and methanol to make 10 mL, and use this solution as the test solution. Separately, dissolve 50 mg of zolpidem tartrate RS in 5 mL of methanol, add 0.1 mL of diethylamine and methanol to make 10 mL, and use this solution as the standard solution (1). Also, dissolve 50 mg of flunitrazepam RS in dichloromethane to make 10 mL. Mix 1 mL of the solution with 1 ml of the standard solution (1), and use this solution as the standard solution (2). With these solutions, perform the test as directed under the Thin Layer Chromatography. Spot 5 μL each of the test solution, the standard solution (1) and (2) on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, cyclohexane and diethylamine (45 : 45 : 10) as the developing solvent to a distance of about 12 cm and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); the R_f value of the principal spot obtained from the test solution is the same as that of the principal spot from the standard solution (1). The test is valid when the chromatogram from the standard solution (2) shows two clearly separated spots.

(3) Dissolve about 0.1 g of Zolpidem Tartrate in 1 mL of warm methanol. 0.1 mL of this solution responds to the Chemical identification reaction 3) for tartrate.

Purity (1) ***Clarity and color of solution solution***—Mix 0.25 g of Zolpidem Tartrate with 0.125 g of L-tartaric acid, dissolve the mixture in 20 mL of water, and add to make 25 mL; the solution is clear.

(2) ***Heavy metals***—Proceed with 2.0 g of Zolpidem Tartrate according to Method 4 under the Heavy Metals, and perform the test. Prepare the control solution with 2.0 mL of lead standard solution (NMT 10 ppm).

(3) ***Related substances***—Dissolve 10 mg of Zolpidem Tartrate in 20 mL of methanol, and use this solution as the test solution. Pipet 1 mL of this solution

and add methanol to make exactly 100 mL. Pipet 2 mL of this solution, add methanol to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of each solution by the automatic integration method; the total area of the peaks other than zolpidem from the test solution is not greater than the peak area of zolpidem from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 7.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of a solution prepared by adding 1000 mL of water to 4.9 g of phosphoric acid and adjusting the pH to 5.5 with triethylamine, methanol, and acetonitrile (11 : 5 : 4).

Flow rate: Adjust the flow rate so that the retention time of zolpidem is about 5 minutes.

System suitability

System performance: Dissolve 10 mg each of Zolpidem Tartrate and benzyl p-hydroxybenzoate in 100 mL of methanol. Proceed with 5 μL of this solution according to the above operating conditions; zolpidem and benzyl p-hydroxybenzoate are eluted in this order with the resolution being NLT 9.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution under the above operating conditions; the relative standard deviation of the peak areas of zolpidem is NMT 5.0%.

Time span of measurement: About 5 times the retention time of zolpidem.

Water NMT 3.0% (0.5 g, volumetric titration, direct titration).

Residue on ignition NMT 0.1% (1 g).

Assay Weigh accurately about 0.30 g of Zolpidem Tartrate, dissolve in a mixture of 20 mL of acetic anhydride and 20 mL of acetic acid(100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration under the Titrimetry). Perform a blank test in the same manner and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 38.24 mg of $C_{42}H_{48}N_6O_8$

Packaging and storage Preserve in light-resistant, tight containers.

Zolpidem Tartrate Tablets
졸피뎀타르타르산염 정

Zolpidem Tartrate Tablets contains NLT 95.0% and NMT 105.0% of the labeled amount of zolpidem tartrate (C42H48N6O8 : 764.87).

Method of preparation Prepare as directed under Tablets, with Zolpidem Tartrate.

Identification Take 1 tablet of Zolpidem Tartrate Tablets, add 100 mL of 0.1 mol/L hydrochloric acid TS, shake to mix well for 30 minutes, and then filter. Discard the first 20 mL of filtrate, weigh an amount of the subsequent filtrate, equivalent to 1 mg of zolpidem tartrate according to the labeled amount, and add 0.1 mol/L hydrochloric acid TS to make 100 mL. Determine the absorption spectra of this solution as directed under the Ultraviolet-visible Spectroscopy; it exhibits maxima at wavelengths of 235 nm to 239 nm and 292 nm to 296 nm.

Dissolution Perform the test with 1 tablet of Zolpidem Tartrate Tablets at 50 revolutions per minute according to Method 2 under the Dissolution, using 900 mL of water as the dissolution solution. Take NLT 20 mL of the dissolved solution after 15 minutes from the start of the dissolution test, and filter through a membrane filter with a pore size of NMT 0.45 μm. Discard the first 10 mL of the filtrate, pipet *V* mL of the subsequent filtrate, add the solution 2 for the dissolution test to make exactly *V′* mL so that each mL contains about 2.8 μg of zolpidem tartrate according to the labeled amount, and use this solution as the test solution. Separately, weigh accurately about 22 mg of the zolpidem tartrate RS (previously determined the water content in the same manner as for Zolpidem Tartrate Tablets), dissolve with water to make exactly 100 mL. Take 5 mL of this solution and add water to make exactly 200 mL. Pipet 25 mL of this solution, add the solution 2 for the dissolution test to make exactly 50 mL, and use this solution as the standard solution. Determine the absorbances, A_T and A_S, of the test solution and the standard solution, at the wavelength of 242 nm as directed under the Ultraviolet-visible Spectroscopy, using diluted solution 2 for the dissolution test (1 in 2) as a control solution. Meets the requirements if the dissolution rate of Zolpidem Tartrate Tablets in 15 minutes is NLT 80%.

Dissolution rate (%) for the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$)
= Amount (mg) of zolpidem tartrate RS, as calculated on the anhydrous basis $\times \frac{A_T}{A_S} \times \frac{V'}{V} \times \frac{1}{C} \times \frac{45}{4}$

C: Amount (mg) of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) in 1 tablet

Uniformity of dosage units It meets the requirements when the Content uniformity test is performed according

to following method.

Take 1 tablet of Zolpidem Tartrate Tablets, add *V* / 10 mL of 0.1 mol/L hydrochloric acid TS and shake to mix well for 15 minutes to disintegrate. Add *2V* / 5 mL of methanol, add exactly *V* / 10 mL of internal standard solution, shake to mix well for 15 minutes, and add methanol make it *V* mL so that each mL contains about 0.1 mg of zolpidem tartrate ($C_{42}H_{48}N_6O_8$). Centrifuge this solution, and use the clear supernatant as the test solution. Separately, weigh accurately about 25 mg of zolpidem tartrate RS (previously determined water content in the same manner as for Zolpidem Tartrate Tablets), dissolve in 25 mL of 0.1 mol/L hydrochloric acid TS, add exactly 25 mL of internal standard solution, add methanol to make 250 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions.

Amount (mg) zolpidem tartrate ($C_{42}H_{48}N_6O_8$)
= Amount (mg) of zolpidem tartrate RS, as calculated on the anhydrous basis$\times \frac{Q_T}{Q_S} \times \frac{V}{500}$

Internal standard solution—A solution of benzyl p-hydroxybenzoate in methanol (1 in 1000).

Assay Take NLT 20 tablets of Zolpidem Tartrate Tablets, add *V* / 10 mL of 0.1 mol/L hydrochloric acid TS, and shake to mix well for 15 minutes to disintegrate. Add exactly *2V* / 5 mL of methanol and *V* / 10 mL of internal standard solution, shake to mix well for 15 minutes, and add methanol to make *V* mL so that each mL contains about 1 mg of zolpidem tartrate. After centrifuging this solution, add a mixture of methanol and 0.1 mol/L hydrochloric acid TS (9 : 1) to 1 mL of the clear supernatant to make 10 mL, and use this solution as the test solution. Separately, weigh accurately about 25 mg of zolpidem tartrate RS (separately, determined water content in the same manner as for Zolpidem Tartrate Tablets), dissolve in 0.1 mol/L hydrochloric acid TS, add exactly 2.5 mL of the internal standard solution, add methanol to make 250 mL, and use this solution as the standard solution. Perform the test with 5 μL each of the test solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, Q_T and Q_S of the zolpidem to the peak area of the internal standard.

C: Labeled amount (mg) of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) in 1 tablet
= Amount (mg) of zolpidem tartrate RS, as calculated on the anhydrous basis$\times \frac{Q_T}{Q_S} \times \frac{V}{500}$

Internal standard solution—A solution of benzyl p-hydroxybenzoate in methanol (1 in 100).

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column about 4.6 mm in internal diameter and about 7.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25 °C.

Mobile phase: A mixture of a solution prepared by adding 1000 mL of water to 4.9 g of phosphoric acid and then adding triethylamine to adjust the pH to 5.5, methanol and acetonitrile (55: 25 : 20).

Flow rate: Adjust the flow rate so that the retention time of zolpidem is about 5 minutes.

System suitability

System performance: Proceed with 5 μL of the standard solution according to the above conditions; zolpidem and the internal standard are eluted in this order with the resolution being NLT 9.

System repeatability: Repeat the test 6 times with 5 μL each of the standard solution according to the above conditions; the relative standard deviation of ratios of the peak area of zolpidem to that of the internal standard is NMT 1.0%.

Packaging and storage Preserve in well-closed containers.